Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

SUBGROUP REPORT ON THE LOWERMOOR WATER POLLUTION INCIDENT

February 2013

CONTENTS

Chapter 6: Toxicological and epidemiological data on contaminants from the scientific literature

Appendices

Appendix 1: Membership of the Lowermoor subgroup
Appendix 2: Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Appendix 3: Health and other professionals who provided information
Appendix 4: Discussion of the quality and reliability of scientific data
Appendix 5: Responses received as a result of the consultation exercise
Appendix 6: Lowermoor Subgroup's response to the consultation exercise
Appendix 7: Drinking water quality – the legislative framework for public drinking water supplies
Appendix 8: Water quality data for the parishes of Camelford, Davidstow, Advent, St Minver Lowlands and St Minver Highlands
Appendix 9: Water quality data for the parishes of Camelford and Davidstow, 1989
Appendix 10:Water quality data for the parishes of St Teath, Tintagel and Trevalga
Appendix 11:Water quality data for the parishes of St Endellion, Forrabury & Minster and St Juliot
Appendix 12: Lowermoor water quality modelling report. Black & Veatch Ltd, 2004.
Appendix 13: Lowermoor water quality modelling report, Phase 2. Black & Veatch Ltd. August 2006.
Appendix 14: Other water pollution incidents involving aluminium sulphate
Appendix 15: Report on the estimated consumption of aluminium, sulphate, copper, zinc, lead and pH following the contamination incident on 6th July 1988. Crowther Clayton Associates. Report no. 91/2737.
Appendix 16: Extract from "The Health of the Population", Department of Public Health Medicine, Cornwall and Isles of Scilly Health Authority, 1988.
Appendix 17: Letter from DHSS to Dr CR Grainger, 24 August 1988
Appendix 18: Summary and critique of epidemiological studies of the North Cornwall population
Appendix 19: Report of the North Cornwall Homeopathic Project
Appendix 20: Summing-up by the West Somerset Coroner
Appendix 21: Review of the scientific literature on aluminium (1994 to April 2002) prepared for the Lowermoor subgroup
Appendix 22: Review of the scientific literature on aluminium (January 2002 to October 2003), prepared for the Lowermoor Subgroup
Appendix 23: Review of the scientific literature on aluminium (November 2003 to April 2005), prepared for the Lowermoor Subgroup
Appendix 24: Review of the scientific literature on aluminium (May 2005 to July 2006), prepared for the Lowermoor Subgroup
Appendix 25: Review of the scientific literature on aluminium (August 2006 to December 2006), prepared for the Lowermoor Subgroup
Appendix 26: Review of the scientific literature on aluminium (January 2007 to September 2011), prepared for the Lowermoor Subgroup
Appendix 27: Review of the scientific literature on aluminium (October 2011 to September 2012), prepared for the Lowermoor Subgroup

Appendix 28: First review paper on metal-metal interactions prepared for the Lowermoor subgroup (January 1970 to February 2003)
Appendix 29: Second review paper on metal-metal interactions prepared for the Lowermoor subgroup (March 2003 to April 2012)
Appendix 30: Recommendations for neuropsychological and neuropathological investigations on the population potentially exposed to the contaminated water
Appendix 31: Current procedures for the management of chemical incidents
Appendix 32: Declaration of LSG members' interests

1. Executive Summary

1.1 This report of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) considers the human health effects of the chemical exposure resulting from the water pollution incident which occurred in July 1988 at the Lowermoor Water Treatment Works, near Camelford, North Cornwall. The report was written by a specially convened Subgroup of the Committee. Two local representatives served as members of the Subgroup until 16 October 2012 when they resigned and stated that they did not wish their names to be associated with the report.

1.2 The Subgroup was asked to address the following terms of reference:

"To advise on whether the exposure to chemicals resulting from the 1988 Lowermoor water pollution incident has caused, or is expected to cause, delayed or persistent harm to human health; and

" To advise whether the existing programme of monitoring and research into the human health effects of the incident should be augmented and, if so, to make recommendations."

Background

1.3 The Lowermoor water pollution incident occurred when a relief tanker driver discharged 20 tonnes of aluminium sulphate solution into the wrong tank at the unmanned water treatment works, subsequently contaminating water supplies to a large area of North Cornwall. An independent expert group, the Lowermoor Incident Health Advisory Group (LIHAG), was subsequently convened by the Government to advise on the public health implications of the pollution incident. It produced two reports, in 1989 and in 1991, which included recommendations for further work. In 2001, in response to representations from members of the local community that the long-term health consequences of the incident had not been properly addressed, Health and Environment Ministers asked the COT to carry out the investigation reported here.

Structure of the report

1.4 The Subgroup held a total of twenty-six meetings between October 2001 and October 2012. In addition, a public meeting was held in Camelford in April 2002. The chairman and members of the committee and secretariat made four visits to Camelford between July 2002 and October 2003 to collect evidence from people in the area affected by the pollution incident. A draft report was published for consultation in January 2005 and was discussed at a public consultation meeting in Camelford in February 2005. During the final stages of our investigation, we were made aware of an inquest by the West Somerset coroner into the death of an individual who was resident in Camelford at the time of the contamination incident and who had died in 2004 after a short illness with symptoms of dementia (see below). Following correspondence with the Coroner, and receipt of legal advice, completion and publication of our report was deferred until the Coroner's proceedings were completed. The inquest ended in March 2012.

1.5 The information assessed by the Subgroup included:

- Personal evidence submitted in meetings with members of the committee or in writing.
- Evidence and expert opinion from medical practitioners and other experts.
- Detailed reviews of the scientific literature on the health effects of the chemicals whose concentrations in the water supply were increased as a result of the incident.
- A visit to the Lowermoor Water Treatment Works.
- Additional work commissioned by the Subgroup from outside experts.

1.6 Full details of the background to the establishment of the Subgroup, its composition and methods of working are given in Chapter 2 of the report.

1.7 Chapter 3 describes the Lowermoor water pollution incident. The contaminated mains water was sufficiently acidic to cause corrosion of some metallic plumbing materials. Flushing of the mains distribution system to remove the contaminated water also resulted in the disturbance of existing mains sediments, mainly deposits of iron and manganese oxides. Thus, a number of contaminants could have been present at increased concentrations in the water at the end-user's tap. The chapter also describes the structure of the works, the distribution of contaminated water, the nature of the contamination of the water supply, water quality data on the concentrations of the contaminants from before the incident to the end of 1990, and modelling of the aluminium sulphate concentrations in the treatment works and mains system.

1.8 Chapter 4 discusses the potential exposures to the contaminants the concentrations of which were increased in tap water as a result of the incident i.e. aluminium, sulphate, copper, zinc, lead, manganese and iron. Worst-case exposures have been estimated for three groups: adults, toddlers and bottle-fed infants. The chapter also describes the modelling of exposure estimates carried out for South West Water Ltd in 1991.

1.9 Chapter 5 considers the evidence provided to the Subgroup by individuals who received contaminated water, and the population studies carried out in the North Cornwall area. The value and the limitations of both types of data are discussed. The personal evidence provided by individuals was of three types: general observations; observations on water quality, usage and consumption; and health effects. Information from local health professionals is summarised. Chapter 5 then describes and critically appraises studies of the North Cornwall population since the incident. These include epidemiological studies of six outcomes: self-reported symptoms, pregnancy outcomes, the growth of children, hospital discharge rates, mortality rates, and cancer incidence and mortality. Neuropsychological testing which was carried out after the incident is also described. Other subjects covered in this chapter are: children with special education needs; homeopathic data; a case of severe congophilic angiopathy in a resident of Camelford; tissue analyses and effects on livestock and domestic animals.

1.10 Chapter 6 consists of summaries of the toxicological and epidemiological data, from the scientific literature, on the contaminants of relevance. In the case of

aluminium, the main contaminant, the following sources were used: a published review of the scientific literature to 1997 by a group of international experts, and detailed, fully-referenced updates of the literature between 1995 and 2012 which were commissioned by the Subgroup. For lead, the main source of information was an international review published in 1997, updated by important new information from the literature. For all other metals, the Subgroup used the extensive, fully-referenced reviews of research and the risk assessments published by the Food Standard Agency's Expert Group on Vitamins and Minerals in 2003 updated, if necessary, by important new information from the literature. Chapter 6 also includes an assessment of the information in the scientific literature on biological interactions between the metals of concern and a summary of the radiological and chemical toxicities of uranium.

1.11 Two chapters discuss the Subgroup's conclusions. Chapter 7 presents an assessment of the health implications of each contaminant at the estimated worst-case exposures given in Chapter 4. Chapter 8 addresses the question of whether exposure to the contaminants has caused, or is expected to cause, delayed or persistent harm to human health, in the context of the symptoms and illnesses which were either reported by individuals or were identified from epidemiological studies. In Chapter 9, recommendations are made both for future monitoring and research on health and for the future handling of similar incidents.

1.12 At the end of each chapter, the reader will find a series of Key Points, which summarise the information in that chapter.

Conclusions

Preamble

1.13 This report contains the most comprehensive account of the information relating to the Lowermoor pollution incident that is available currently. Nevertheless, the data available to the Subgroup from which conclusions were drawn were often sparse, and limited in quality. In particular, the length of time which had elapsed since the incident occurred presented many problems. During the investigation, all the evidence made available was addressed carefully and systematically in order that the Subgroup could advise on whether the Lowermoor pollution incident "has caused, or is expected to cause, delayed or persistent harm to health". The immediate and persistent health effects of the incident were addressed. In the course of the investigation, a great deal of new information was discovered which was not available at the time of the previous investigations.

1.14 The establishment of a link between exposure to contaminants and the occurrence of health effects, whether immediate or long-term, requires accurate and representative information about:

- The exposure of individuals: how much and for how long,
- Scientific and toxicological data relating to the known effects of the contaminants to which individuals were exposed,
- Any symptoms experienced at the time, or months or years after the event, and
- The pattern of health outcomes in the population as a whole.

These matters are explored further below.

Question 1: The exposure of individuals. Who received contaminated water and how long was the water supply contaminated after the pollution incident?

1.15 The extent and severity of the contamination can only be determined by the analysis of samples of water taken at a particular place and time. The contaminated water would have reached different points on the network at different times and peak contaminant concentrations would also have been experienced at different times, because it takes time for the water to move from the treatment works through the distribution system. With the exception of those locations for which monitoring data exist or where individuals experienced discoloured or unpalatable water, it is not possible to determine whether any particular point on the Lowermoor distribution network did or did not receive contaminated water because of a large scale flushing exercise which was carried out by the water supplier at different points in the distribution network. Sequential water quality data are not available and thus description of the progress of the aluminium sulphate as it travelled through the distribution system is not possible.

1.16 The initial period of contamination with high concentrations of contaminants lasted about a week. Both water quality data and modelling of the passage of aluminium in the trunk mains indicate that the concentrations of this metal in the water supply reached a high, initial peak and then fell rapidly. However, thirty per cent of samples taken up to the end of 1988 and 6% in 1989 remained above the 1984 WHO Guideline Value for Drinking Water Quality for aluminium. This WHO Guideline Value was set to avoid deposits in the distribution system and discolouration of water, not because of a risk of adverse health effects above this concentration. Concentrations of copper and lead were high for approximately a week after the contamination incident and sporadically thereafter. Less than 0.5% of samples exceeded the 1984 WHO Guideline Value for zinc.

1.17 Water quality data on contaminants during the flushing exercises indicated that the proportion of samples with concentrations of manganese above the relevant 1984 WHO Guideline Value increased in the month after the incident but fell markedly thereafter, although sporadic high concentrations were recorded. The proportion of iron concentrations exceeding the relevant 1984 WHO Guideline Value rose in the month after the incident and remained high until the end of 1990.

Question 2: Scientific and toxicological data relating to known effects of contaminants. On the basis of the toxicity data in the scientific literature and the estimated exposures, would the contaminants be expected to cause delayed or persistent harm to human health?

1.18 This question is considered separately for each contaminant in Chapter 7. The possibility of additive or synergistic interactions is also addressed. For each contaminant, the implications for health of the worst-case estimated intakes are considered in the context of the toxicological and epidemiological data in the scientific literature on each contaminant. The chapter also discusses the uncertainty involved in making these assessments, which arise from incomplete data on water quality and exposure, an incomplete scientific literature on the chemicals concerned and the unusual short term but high level of the exposure.

Aluminium

1.19 For aluminium, a No Observed Adverse Effect Level[1] for functional neurological effects was derived from the scientific literature from a study in which aluminium was administered for 90 days. This was used to calculate a Margin of Exposure[2] for adults, toddlers and those who were bottle-fed infants at the time of the incident (i.e. below one year of age). Immediately after the incident, there were very low Margins of Exposure but they rose to pre-incident levels within one month. Taking into account the fact that the Margins of Exposure were below pre-incident levels for only a short period, on the basis of the current evidence, it is unlikely that the short period of increased exposure to aluminium would have caused, or would be expected to cause, delayed or persistent harm to health. However, infants are a potentially vulnerable group and, therefore, the possibility of delayed or persistent harm to health should be explored further in those who were infants at the time of the incident (i.e. below one year of age). Consumption of the contaminated water by pregnant women may have led to exposure of the developing fetus. Although the period of exposure to increased levels of aluminium was short, in view of the neurodevelopmental effects seen with aluminium in animal studies, we consider that the possibility of delayed or persistent harm to health should be explored also in those who were *in utero* at the time of the incident.

Copper

1.20 The increased concentrations of copper in drinking water in the first week or so after the incident probably contributed to acute, adverse gastrointestinal symptoms. It is not anticipated that they would have caused, or would be expected to cause, delayed or persistent harm to health because of the homeostatic control of copper balance in man.

Zinc

1.21 The occasional high concentrations of zinc which occurred after the incident could have contributed to acute, adverse gastrointestinal symptoms. However, it can be concluded from the current evidence that estimated exposures to zinc were not high enough nor prolonged enough to have caused, or be expected to cause, delayed or persistent harm to health.

Lead

1.22 Children are the most vulnerable group when considering exposure to lead but it is difficult to assess the impact on health of a short-term increased exposure to lead in the absence of information on blood lead concentrations. No cases of acute lead poisoning were reported after the incident. Nevertheless, any additional exposure of young children to lead is undesirable and recommendations have been made for monitoring of the cognitive, behavioural and educational development of this age

[1] The No Observed Adverse Effect Level is the lowest administered dose of a substance at which no adverse effect has been observed in studies in animals or humans.

[2] The Margin of Exposure is the margin between the No or Lowest Observed (Adverse) Effect Level and the daily intake of a chemical. The higher the Margin of Exposure, the more reassurance there is that the intake of chemical was not high enough to have harmed health. In general, a Margin of Exposure of 100 is considered acceptable when the NOAEL is derived from a study entailing prolonged exposure.

group. Consumption of the contaminated water by pregnant women could have led to exposure of the developing fetus to lead. We therefore recommend that those who were *in utero* at the time of the incident are included in the cohort to be monitored. There is limited evidence that individuals exposed to high levels of inorganic lead compounds over a long period have a higher risk of cancer than usual but any increased risk of cancer at the small additional exposures to lead which occurred following the incident is likely to be negligible.

Manganese

1.23 Most of the manganese in drinking water would have been in the form of insoluble particles from which absorption of manganese would be low. For adults, it is not anticipated that concentrations of manganese in drinking water after the incident would have exceeded the acceptable total intakes of manganese recommended by the Food Standards Agency's Expert Group on Vitamins and Minerals for the general population. Therefore, on the basis of current evidence, it is not anticipated that the period of increased exposure to manganese would have caused, or would be expected to cause, delayed or persistent harm to health in those who were adults or toddlers at the time of the incident. Although, on the basis of current evidence, it is not anticipated that the sporadic high concentrations of manganese after the incident would have caused, or be expected to cause, delayed or persistent harm to health in infants, recommendations have been made for further monitoring of this age group.

Iron

1.24 It is not anticipated that the sporadic increases in the concentration of iron in drinking water after the incident would have caused or would be expected to cause, any adverse health consequences because of the homeostatic control of iron by the body.

Sulphate

1.25 The sporadic high concentrations of sulphat**e** in drinking water after the incident may have caused acute, adverse gastrointestinal symptoms. There is no evidence in the literature of delayed or persistent harm to health.

Uranium

1.26 In the absence of water quality data on uranium after the incident, it is not possible to assess the risk of uranium concentrations based on its chemical toxicity. The National Radiological Protection Board advised in 1996 that levels of uranium in water from the Lowermoor reservoir were most unlikely to present a significant radiation dose or subsequent risk to health.

Additive effects

1.27 There may have been an additive effect of those contaminants with the potential to cause adverse gastrointestinal effects even when the concentration of individual contaminants alone was not high enough to cause such a response; this may have led to an unpleasant, acute gastrointestinal response among those who drank the water. The recorded pH values of the water after the incident were not low enough to

cause the cases of sore throat and skin irritation which are reported. It may be that high concentrations of sulphate and metal salts rendered the water more irritant than would be anticipated from its pH alone.

1.28 The available data do not provide any evidence which indicates that the combination of metals which occurred as a result of the pollution incident would have caused, or would be expected to cause, delayed or persistent additive or synergistic effects.

Question 3: Symptoms experienced and the pattern of health outcomes observed. Are the symptoms or illnesses reported by individuals or identified from epidemiological studies considered to have been caused by delayed or persistent effects of the contaminants?

1.29 The symptoms reported as possible health effects of the incident were identified from a number of sources including personal testimony and population studies. The types of chronic symptoms and diseases which were most commonly reported to the Subgroup in interviews with, and written submissions from, individuals fell into the categories of neuropsychological effects, joint pains and/or swelling, nail problems, cancer and thyroid disease. These were similar to those reported by 70 people in the report of a homeopathic project in 1992 which also reported malaise, tiredness and exhaustion, a dry thirst, and a sensitivity to tapwater. The Subgroup recognised that this water contamination incident was unique and that there was a recognisable pattern of symptoms and diagnoses among the individuals who provided personal evidence. The Subgroup also recognised, through contact with the local population, the considerable concern and distress expressed about the possible health consequences of the incident in relation both to individuals and the community as a whole.

1.30 In Chapter 8, each symptom (or symptom complex) and each disease is considered in the context of the evidence relating to the potential exposures to the contaminants, known toxic effects of the contaminants, and the results of epidemiological studies on the exposed population. The likelihood that the reported health effects were caused by the contaminants is assessed.

1.31 The data on the contaminants in the scientific literature indicate that estimated exposures were not sufficient to have caused neurotoxic effects in adults nor in those who were children at the time of the incident. However, the Subgroup was advised that the overall pattern of results in one of the neuropsychological studies indicated subtle effects in the individuals tested but that it was not possible to determine whether these effects were due to the contaminated water because of deficiencies in the design of the studies. Therefore, further work is recommended on this endpoint.

1.32 The Subgroup became aware during the course of its work of a rare case of severe cerebral amyloid angiopathy in an individual who was resident in Camelford at the time of the contamination incident. This case was the subject of an inquiry by the West Somerset coroner between 2010 and 2012. An investigation had shown higher than usual concentrations of aluminium in the individual's brain, although samples from the brain of an individual with similar neuropathology, but of unknown aluminium exposure, also showed higher than usual concentrations. Research commissioned by the Coroner showed no significant correlations between aluminium

or iron concentrations and the level of congophilic angiopathy or senile plaques in 60 postmortem brains donated to the Medical Research Council (MRC) study on Cognitive Function and Aging. This case is clearly an important observation but there are a number of uncertainties which make it impossible to conclude whether it is causally associated with the contamination incident or not. Further work is recommended.

1.33 There is no indication from the toxicological data that the estimated exposures to the contaminants which occurred after the incident can cause effects on joints and it is not possible to conclude that there is a causal relationship between the joint pains and/or swelling reported and exposure to the contaminants. Arthritis and related problems occur commonly in the population. Nevertheless, the Subgroup recognised that many individuals with whom they spoke were concerned about joint problems. Therefore, further work is recommended on this endpoint.

1.34 Two years after the incident, a consultant dermatologist examined individuals suffering from nail and skin problems. The dermatologist concluded that there was unlikely to be a public health problem affecting the skin of the population in the Camelford area. In his experience, the type of problems reported were common in the general population. He advised that further metabolic investigation of the patients' nails was not required. There is no relevant information in the epidemiological studies nor from the toxicological data on possible effects of the contaminants on nails which can add to this opinion.

1.35 The results of a study of cancer incidence and mortality between 1988 and 1998 in the population living in the area which received contaminated water provide no evidence of an increased overall cancer risk arising from the incident.

1.36 The occurrence of three cases of acute leukaemia in children attending a secondary school in the area which had received contaminated water was examined in a study which looked at child health events, especially infections. Infection is thought to be associated with increased rates and clusters of leukaemia. The study showed that there was an increased rate of infectious illness in children living in the Lowermoor supply area compared to those living in other parts of Cornwall and that this higher rate of infection occurred before the pollution incident.

1.37 One reference was found in the scientific literature showing an effect of aluminium on the thyroid gland. Thyroid disease is common in the population but recommendations have been made for further work.

1.38 A homeopathic report cited a sensitivity to tap water as a common finding after the incident but, from the symptoms described, this does not appear to be the immune condition termed "sensitisation". It has been proposed that it may be a manifestation of the non-immune condition termed "chemical sensitivity". It is difficult to assess the potential significance of this process in the context of the Lowermoor incident in view of the lack of firm mechanistic evidence and of robust means of diagnosis. Therefore, at this stage, it is not possible to draw conclusions or make recommendations in relation to these symptoms.

1.39 The Subgroup was informed that there was a higher proportion of children with a statement of Special Educational Needs (SEN) ("Statements") in North

Cornwall than in the rest of Cornwall and concern was expressed that this might be related to the pollution incident. The Subgroup received expert advice that the determination of SEN status is influenced by many different factors and that no conclusions could be drawn from SEN figures about the long-term impact of the incident on health. In addition, a detailed investigation did not find there to be any consistent difference between the numbers of children with Statements in the secondary school which was likely to have had the highest proportion of children from the affected area and those in other schools in Cornwall.

Recommendations

1.40 It should be noted that it is not within the Subgroup's terms of reference to carry out further research. Any research could be commissioned by the Government or other research funding bodies and placed with a research group which has the necessary specialist expertise to carry out that particular study.

Further studies on the population potentially exposed to the contaminated water

A. Neuropsychological and neuropathological investigations

1.41 We recommend that further studies are conducted to determine whether consumption of the contaminated water is associated with an increased risk of abnormal neuropsychological status or any abnormal pattern of neuropathology. Expert advice is provided on the design of a suitable study or studies and expert input will be required on their conduct (see Chapter 9 for a summary of the research recommendations).

1.42 In Chapter 5 we report on a published case of severe cerebral amyloid angiopathy in an individual who was resident in Camelford at the time of the contamination incident and who was found to have high concentrations of aluminium in the brain *post mortem*. We consider that the observation merits further research. Expert advice is provided on the design of a suitable study or studies and expert input will be required on their conduct (see Chapter 9 for a summary of the research recommendations).

B. Investigations of the cognitive, behavioural and educational development of children

1.43 Investigations should be conducted into the cognitive, behavioural and educational development of all children who were under 1 year of age at this time of the incident and children who were *in utero* at the time of the incident to determine whether exposure to the contaminated water may have adversely affected such development. Expert advice on the design of a suitable study or studies and expert input will be required on their conduct.

C. Analysis of routine health statistics

1.44 We are informed that data on cancer incidence and mortality are available from 1998 to the present day for the previously established cohort which was potentially exposed to contaminated water after the Lowermoor pollution incident. Therefore, further analyses could be carried out. We consider that the burden of this work should be removed from the local primary care trust and should, in future, be carried out by an academic department familiar with the analysis of routine health statistics. The monitoring should include analysis of overall rates of relevant health outcomes, and analysis of all relevant disease subgroups. If possible, the assessment

of the exposed population should be refined to take account of the fact that some areas experienced a higher level of contamination than others. If such a refinement is possible, it could also be applied retrospectively.

D. Joint pains and/or swelling

1.45 Routine health statistics cannot be used to monitor the prevalence of joint pains and/or swellings. We recommend that a study should be carried out to assess whether the prevalence of joint pains and/or swelling in the population receiving contaminated water is higher than normal.

1.46 In view of the long time which has elapsed since the incident, we ask that these recommendations are considered promptly.

Toxicological studies

1.47 The toxicological data on aluminium, although extensive, is insufficient to make a definitive hazard assessment. There is a need for further work on the toxicity of aluminium to assist in the risk assessment of exposure of humans to different aluminium salts, including:

- studies to identify No Observed Adverse Effect Levels for aluminium salts to which humans may be exposed using both acute and chronic exposure and a range of salts of different bioavailabilities. Specific endpoints to be investigated include neurotoxicity, reproductive toxicity and developmental toxicity.
- mechanistic data on the neurotoxicity of aluminium and of its potential role in neurological disease, including abnormalities of neurodevelopment, and other disorders.
- further investigations of the bioavailability of aluminium in humans, including the extent of and the reasons for the reported interindividual variation.
- studies which mimic the exposure conditions experienced by individuals who drank the contaminated water i.e. a short, high initial exposure to aluminium, with a long period of follow-up.

Future management and evaluation of similar incidents

1.48 There have been considerable improvements in contingency arrangements for and the management of any future chemical incidents since 1988. However, a few areas have been identified as a result of the Subgroup's work which may require particular consideration in the management of a future incident of the type:

- Identification of the exposed population. It is vital that the population and subpopulations that may need to be monitored in any later epidemiological studies are identified as early as possible after the incident. If identification of these populations is delayed, exposed individuals may move out of the area and be lost to follow-up.
- Subgroups of the exposed population. If the exposed population includes a large number of transient residents e.g. holiday makers who are in the area temporarily at the time of the incident, consideration must be given as to how this subpopulation can be identified for inclusion in any future monitoring programme.
- Information and advice. Rapid, widespread dissemination of clear and accurate advice is essential. Individuals should be informed about what has happened, the

likely consequences and any action they may need to take as promptly as possible. An information point, such as an enquiry line or drop-in centre, should be set up and should continue to operate for some time after the incident so that individuals can seek advice if and when new concerns arise; this could also act as a gathering point for information.

- Possible contamination of food. Consideration of the effect of contamination upon the intake of chemicals from food when there are either direct or indirect routes for the contamination of food.

2. Introduction

Historical Perspective

2.1 The Lowermoor water pollution incident occurred on 6 July 1988 at the South West Water Authority's (SWWA) water treatment works at Lowermoor, near Camelford, Cornwall. A relief tanker driver discharged 20 tonnes of aluminium sulphate solution into the wrong tank at the unmanned works, subsequently contaminating water supplies to a large area of North Cornwall. The incident is described in detail in Chapter 3 of this report.

2.2 In 1989, in response to concern about the public health implications of the pollution incident, the Government established an independent expert group, the Lowermoor Incident Health Advisory Group (LIHAG), to provide advice to the Cornwall and Isles of Scilly District Health Authority "on the implications for the health of the population in the Camelford area following the contamination of their drinking water in July 1988". The first LIHAG report, published in July 1989, concluded that:

> **"Early symptoms, which were mostly gastrointestinal disturbances, rashes and mouth ulcers, can most probably be attributed to the incident. It would appear that symptoms were mostly mild and short lived, as general practitioners experienced no increase in consultation rates at the time and in the subsequent month…**
>
> **"A substantial number of residents and holiday makers are known to have complained later of continuing or new symptoms following the incident. These symptoms have included joint and muscle pains, memory loss, hypersensitivity and gastrointestinal disorders. We consider it unlikely in the extreme that long-term effects from copper, sulphate, zinc or lead would result from exposures of the degree and short duration that occurred after this incident. Although the possibility of effects due to the interaction of these chemicals cannot be wholly excluded, we can find no supportive evidence. Increased absorption of aluminium may have occurred in some individuals who persisted in drinking the heavily contaminated water. However, all the available evidence suggests that such increases would have been transient, with most of the aluminium being excreted rapidly and only trace amounts being deposited in tissue, chiefly bone. All the known toxic effects of aluminium are associated with chronically elevated exposure and we have concluded therefore that delayed or persistent effects following such brief exposures are unlikely. In our view it is not possible to attribute the very real current health complaints to the toxic effects of the incident, except insofar as they are a consequence of the sustained anxiety naturally felt by many people."**

2.3 The report also made a series of recommendations about the future handling and follow-up of similar incidents (Lowermoor Incident Health Advisory Group, 1989).

2.4 In October 1990, following representations from the local community, some of whom continued to attribute health problems to the incident, LIHAG was reconvened with the following terms of reference:

> **"To assess reports which have become available since July 1989 of persistent symptoms and clinicopathological findings amongst people who were resident in the Camelford area at the time of the Lowermoor incident; and to advise the Department of Health and the Cornwall and Isles of Scilly District Health Authority on the implications of its findings."**

2.5 The second report, which was published in November 1991, concluded that:

> **"The research reported to us does not provide convincing evidence that harmful accumulation of aluminium has occurred, nor that there is a greater prevalence of organic abnormalities in the exposed population. We do not expect lasting physical harm from the toxicity of the contaminated water itself... Nevertheless, the incident was unique, and the actual doses of aluminium and other contaminants received by the residents are unknown; therefore, although we have no reason to predict any late consequences, we cannot exclude them categorically.**
>
> **We still have no doubt that the accident itself and subseqent events have led to real mental and physical suffering in the community. We emphasize that we do not believe that people in the Lowermoor area are imagining symptoms. The physical problems associated with all the worry and concern and the psychological harm could last a long time for some people. Such a situation is well recognised following major accidents."**

2.6 This report also recommended a number of further actions and research, some of which are continuing (Lowermoor Incident Health Advisory Group, 1991):

(a) **monitoring of hospital discharge rates (general and psychiatric) for a period of 5 years.** A review of hospital discharge rates from 1987 to 1993 has been published (Owen and Miles, 1995). This study is discussed in Chapter 5 of our report.

(b) **regular contact with local general practitioners and community leaders.** Regular contact was maintained in the early years after the incident between the Cornwall and Isles of Scilly Health Authority and the Lowermoor Liaison Group, which included members of the local community, representatives of South West Water Authority (SWWA) and officers of the North Cornwall District Council. Thereafter, informal contact occurred between the Health Authority, general practitioners and council officers. The occurrence of 3 cases of leukaemia in Camelford in 1996, and the investigation of possible causes led to a further round of consultation with the local community and general practitioners. Since then, contact has been informal and *ad hoc*.

(c) **Lowermoor residents should be 'flagged' in the NHS Central Registry, so that long-term reports can be received on their mortality experience.** A retrospective study of mortality from 1988 to 1997 has been published (Owen *et al*, 2002), and a study of cancer incidence and mortality has been completed (Owen *et al*, undated

report). Both studies are discussed in Chapter 5 of our report. Monitoring of mortality rates and cancer incidence continues.

2.7 Finally, the report stated:

> **"We recommend that any subsequent studies relating to this incident which appear to have implications for public health policy be open to peer review and scientific scrutiny in the usual manner. Where it appears appropriate, further assessment should be performed by the various expert Committees which advise the Government on matters of public health. Follow-up of individuals remains a matter for general practitioners and the District Health Authority."** (Lowermoor Incident Health Advisory Group, 1991).

2.8 In 2001, in response to representations from members of the local community that the health consequences of the incident had not been properly addressed, Health and Environment Ministers asked the Chief Medical Officer's independent expert advisory committee, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), to advise on whether the pollution incident had resulted in delayed or persistent health effects, and on the need for additional monitoring and research (Department of Environment, Food and Rural Affairs, 2001). The COT set up a subgroup, the Lowermoor Subgroup (LSG), under the Chairmanship of Professor HF Woods CBE, to undertake this task. The subgroup held its first meeting on 16 October 2001. However, due to delays in the appointment of the secretariat and of the local representatives, the subgroup could not begin substantive work until January 2002.

Terms of Reference of the COT Lowermoor Subgroup

2.9 The subgroup had the following terms of reference:

> ***"To advise on whether the exposure to chemicals resulting from the 1988 Lowermoor water pollution incident has caused, or is expected to cause, delayed or persistent harm to human health; and***
>
> ***To advise whether the existing programme of monitoring and research into the human health effects of the incident should be augmented and, if so, to make recommendations"***

Membership of the Subgroup

2.10 The membership of the subgroup is given in Appendix 1. Professor Woods, a clinical pharmacologist and chairman of the COT between 1992 and 2002, chaired the subgroup. Members of the subgroup were appointed by the Department of Health and comprised a public interest representative, a consultant physician, a consultant paediatrician, and scientists with expertise in toxicology and epidemiology. Two local representatives were also appointed to the subgroup. They resigned at the final meeting on 16 October 2012 before discussion of any of the agenda items and stated that they do not wish their names to be associated with the report.

2.11 The subgroup was supported by a secretariat from the Department of Health and, from January 2006, the Health Protection Agency.

2.12 The membership of the Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment is given in Appendix 2.

Methods of Working

2.13 Our investigation comprised:

- A reassessment of evidence previously seen by the Lowermoor Incident Health Advisory Group (LIHAG).

- A reassessment of the data on water quality with particular attention to the concentrations of, and the exposures to, aluminium, copper, lead, zinc, manganese, iron, sulphate and hydrogen ions.

- A consideration of background information on the prevalence and causes of symptoms and diseases linked to the incident. We adopted a broad and comprehensive approach considering all possible health outcomes.

- Five visits to the Lowermoor area. These visits included interviews with local people including professionals. A guided tour of the Lowermoor Water Treatment Works took place on 4 April 2002 when we were able to inspect the works, view the components relevant to the incident, and ask questions of staff present.

- The collection and assessment of evidence from people in the affected area. We advertised locally and nationally in an attempt to ensure that all interested individuals were offered the opportunity to contribute. One hundred and fourteen individuals provided evidence in total, including 9 who were children at the time of the incident. These individuals provided information on the appearance of the water, the amount that different individuals had consumed, on health effects, and on how the incident was handled. We invited additional information from interested parties and placed advertisements in The Times on 30 May 2002, The Guardian on 5 June 2002 and The Daily Mirror on 18 June 2002. Activities of the subgroup were made known locally through the local representatives, a support newsletter, the local press and by word of mouth.

- The collection and assessment of evidence from public health doctors, clinicians, and other experts. These included experts in the chemistry, and in the bioavailability and metabolism of aluminium; in water chemistry; in analytical chemistry; and in neuroendocrinology. We also consulted those who had carried out neuropsychological investigations on individuals exposed to the contaminated water. Some of this information was provided in writing. In other cases, experts attended our meetings to give presentations and answer questions. Some individuals were invited to talk to us and others offered spontaneously. We had no powers to compel any individual to talk to us. A list of health and other professionals who provided information to the subgroup is given in Appendix 3.

- Our secretariat, assisted by the Department of Health Toxicology Unit at the Imperial College London, prepared detailed reviews of the scientific literature on the health effects associated with the contaminants released into the water at the time of the incident. We also consulted evaluations of the relevant toxicology and epidemiology made by authoritative groups such as the World Health Organization (WHO) and the Expert Group on Vitamins and Minerals (EVM).

- The commissioning of studies from outside contractors to increase our understanding of the water contamination incident and the passage of contaminants in the water distribution system.

- A three-month consultation on the draft report in which individuals were invited to submit responses. Twenty-six written responses were received. Further comments were made at a public consultation meeting in the Lowermoor area.

2.14 All of the information received has been of value to us. However, it must be recognised that the degree of scientific rigour with which the different types of information were collected and analysed affects the confidence with which conclusions can be drawn. We have laid out, in the introductions to the relevant chapters, the strengths and weaknesses of the information received in the course of our investigation and the ways in which different data have been used. We have also considered the strengths and weaknesses of study design and conduct when assessing the quality and reliability of particular scientific data and papers, and have discussed these aspects in this report (see Appendix 4 for a detailed discussion of the principles we have followed in assessing information). The review methodology used has depended upon the nature of the data under consideration.

Dates of meetings and visits

2.15 We convened 26 committee meetings on the following dates: 16 October 2001, 22 January 2002, 3 April 2002, 29 May 2002, 16 July 2002, 30 September 2002, 19 November 2002, 27 January 2003, 10 March 2003, 19 May 2003, 7 July 2003, 15 September 2003, 24 November 2003, 9 February 2004, 29 March 2004, 7 June 2004, 26 July 2004, 6 September 2004, 14 December 2004, 14 June 2005, 10 October 2005, 19 January 2007, 4 May 2007, 8 December 2011, 2 July 2012 and 16 October 2012.

2.16 We held a public meeting in Camelford on 3 April 2002, at North Cornwall District Council Offices, in order to introduce the work of the subgroup to the local population. The visit to the Lowermoor Water Treatment Works and discussion with local individuals took place on 4th April 2002. Subsequently, visits to Camelford to take evidence from local individuals were made by the Chairman and members of the subgroup and secretariat on 19 July 2002, 6 and 7 May 2003, 22 July 2003, and 27 and 28 October 2003.

2.17 The subgroup agreed to a request by the Department of Health that the agendas and minutes of meetings, once cleared by the Chairman, would be placed on the Subgroup's website (http:// http://cot.food.gov.uk/cotwg/lowermoorsub/).

However, where evidence was submitted 'in confidence' from interested parties and groups, confidentiality was observed.

2.18 A draft report was published for consultation in January 2005. The consultation period ran from 26 January to 20 May 2005, during which the committee held a public consultation meeting in Camelford on 17 February 2005. Twenty-six written responses were received to the consultation. We discussed these at our meetings in June and October 2005. The responses are attached at Appendix 5 and our response to the consultation exercise is attached at Appendix 6.

2.19 During the final stages of our investigation, we were made aware of an inquest by the West Somerset coroner into the death of an individual who lived in Camelford at the time of the Lowermoor incident and who had died in 2004 after a short illness with symptoms of dementia. The Coroner initially intended to hold the inquest before a jury and explained in a letter to our secretariat that he had "requested the Chief Constable of the Devon and Cornwall Constabulary to let me have the papers relating to the investigations into the original incident and also allegations that there had been a cover-up (MR Rose, personal communication, 16th January 2008)." He went on to say that "if your committee was to publish a report commenting on these allegations it might be alleged that they were attempting to bias the jury". Although the Subgroup's remit did not include an investigation of allegations of a "cover-up", advice was sought from DH lawyers as to whether our report should be published before the inquest had concluded. The advice received stated that, in view of the above statement by the Coroner, "it is possible that it would be alleged that other material in the Committee's report also amounts to an attempt to bias the jury. There are likely to be issues in common. You should not publish if there is any risk that publishing could compromise the Coroner's proceedings." (SH Dyer, personal communication, 8 April 2008). It was further advised that publication of our report should be deferred until the Coroner's proceedings were completed. In the event, the inquest ended in March 2012. We held two further meetings in July and October 2012 to discuss new scientific information presented at the inquest, updates of the scientific literature on aluminium and on metal-metal interactions, and to finalise the report.

3. The Lowermoor water pollution incident: water supply and contamination

Introduction

3.1 This chapter gives an overview of the Lowermoor water pollution incident, describes the distribution of contaminated water and summarises the monitoring data collected by the water supplier on the concentrations of contaminants in the water after the incident.

Lowermoor Water Treatment Works

3.2 The Lowermoor Water Treatment Works supplies water to the North Cornwall water distribution network (see Figure 1). The works derive raw water from Crowdy Reservoir which is approximately ¾ of a mile away. The water in the reservoir derives from run-off and drainage from surrounding moorland. The reservoir is typical of upland water containing relatively low concentrations of dissolved material and has a relatively intense brown colour caused by the organic compounds which are characteristics of upland/moorland waters. Such waters also tend to be acidic i.e. they have a low pH and waters of this type have a low buffering capacity. The raw water supplied to the Lowermoor Water Treatment Works has a pH in the range 5.1 to 7.1 (Crowther Clayton Associates, 1993).

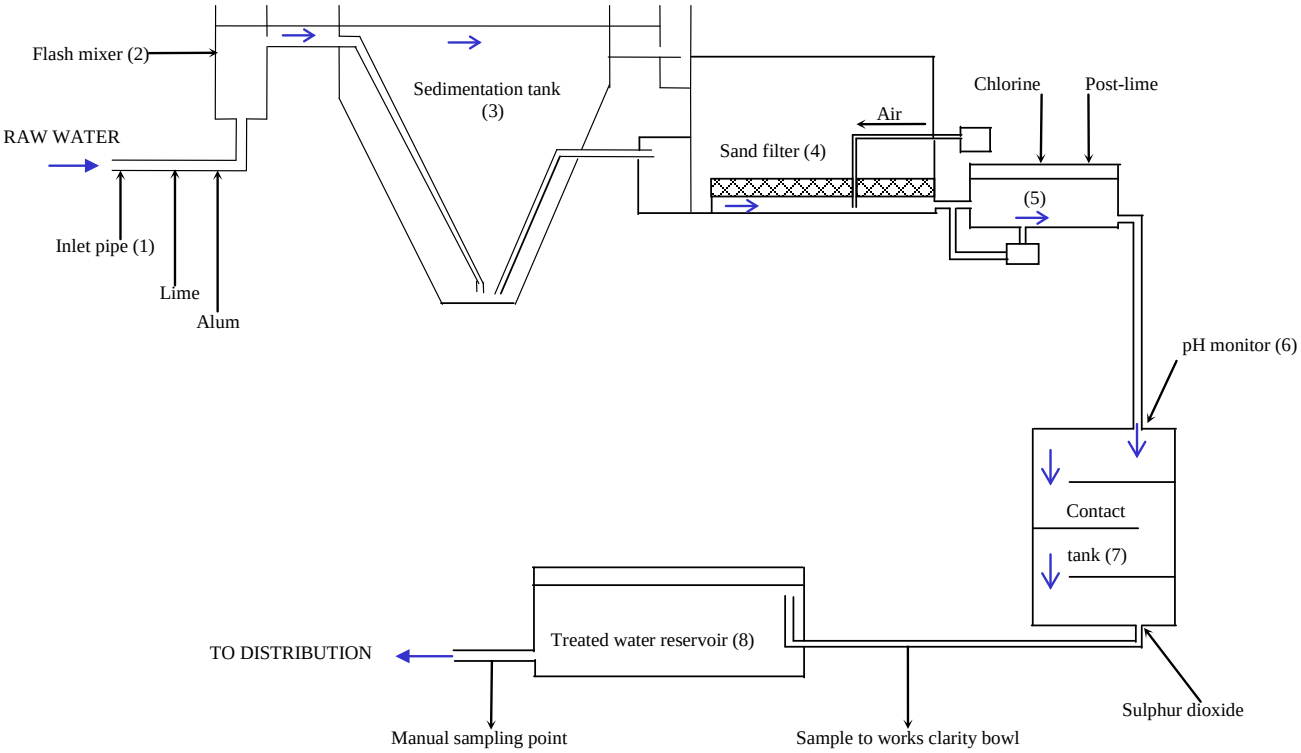
3.3 The Lowermoor Water Treatment Works was built in 1973 and at the time of the incident the works throughput was 255 cubic metres per hour (m^3/hour) (Lowermoor Incident Health Advisory Group, 1989). At that time the plant was operated by South West Water Authority (SWWA) and since privatisation of the water industry, in 1988-1989, has been operated by South West Water Ltd.

3.4 A schematic diagram of the works, with a description of the main components of the treatment plant, is given in Figure 2. At the time of the incident, the Lowermoor Water Treatment Works consisted of the following main items of plant:

- **An inlet pipe** (1): Raw water flowed from the Crowdy reservoir and was controlled by a valve in the inlet pipe. The maximum design flow was 6,800 m^3/day. Chemicals needed for water treatment were added in a controlled manner into the supply line. The main chemicals added were aluminium sulphate (to remove suspended solid matter and dissolved organic acids in a process called coagulation) and slaked lime (to adjust the pH of the water).

- **Flash-mixer** (2): This is a small concrete tank where the added chemicals were mixed thoroughly, in order that the coagulation process took place and a floc was formed. At this stage, a polyelectrolyte was added to bind the small floc particles into larger ones, enabling them to settle more rapidly in the sedimentation tanks.

Figure 2: Schematic layout of Lowermoor Water Treatment Works at the time of the incident (after Lawrence[3], 1988).



- **Sedimentation tanks** (3) **and sand filters** (4): There were four tanks in which the solid floc particles settled slowly to form a sludge blanket, which was drawn off periodically. Clear water was then fed through sand filters, to remove solid floc which may have remained.

- **Filtered-water outlet channel** (5): The filtered water was discharged into an outlet channel into which further lime was added, via the post-lime dosing plant, to raise the pH from approximately 6 to over 8. Chlorine gas was added at this point.

- **pH monitor** (6).

- **Contact tank** (7): Chlorine disinfection took place in this baffled tank which had an estimated capacity of about 415m^3. The flow rate was regulated through the contact tank to ensure efficient mixing and to allow a minimum contact time with chlorine of at least 30 minutes. When the water approached the end of the contact tank, sulphur dioxide was added to lower the chlorine concentration to a level which ensured disinfection at the consumers' tap. Phosphate was also added to remove traces of dissolved iron salts. This produced a precipitate of iron phosphate which deposits in trace quantities in the treated water reservoir or as a lining in the

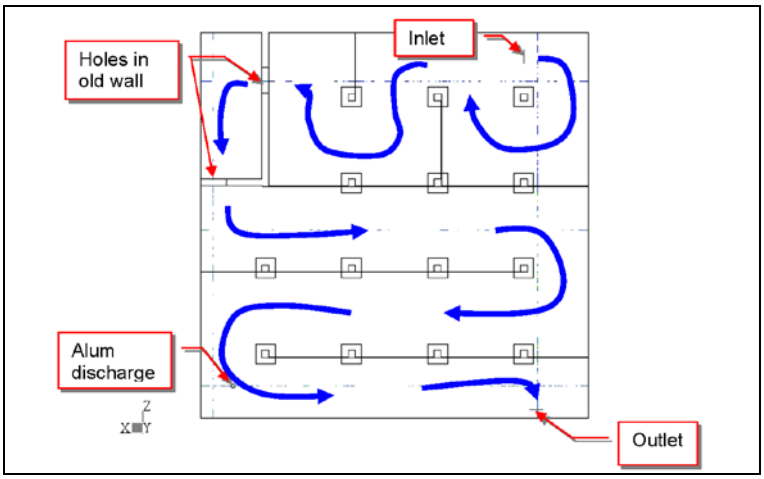
[3] On 13 July 1988, the Board of SWWA asked Dr John Lawrence, a Board Member and Director of ICI Brixham Laboratory, to conduct an inquiry into the events at the Lowermoor Water Treatment Works on and after 6 July and on the consequences. He reported on 12 August 1988.

pipework of the distribution system. Figures 3a and 3b provide a plan and 3-dimensional representation of the contact tank.

- **Treated water reservoir (clear water reservoir)** (8): This is a storage reservoir with a capacity of about 2,300m^3. The treated water enters the reservoir through a bellmouth about the top water level. It leaves the reservoir, and the works, under gravity to areas to the south, or is pumped up to the north (see Figure 1).

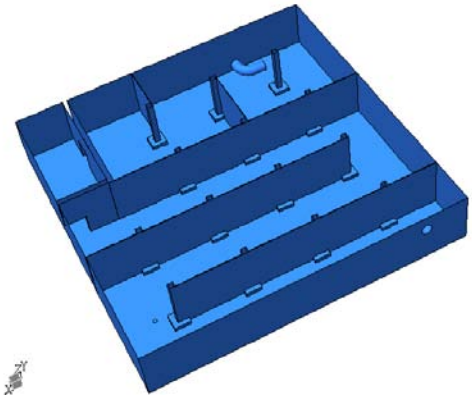
A pH monitor (6), at the point where water enters the contact tank, provided a technical signal for the control devices and also an emergency signal to the control rooms at Exeter and Bodmin when pH was outside the specified limits[4]. The Lowermoor Water Treatment Works was designed to be largely automatic and for much of the time was unmanned (Lawrence, 1988).

Figure 3a: Contact tank: Plan (from Black & Veatch Ltd, 2004)



[4] The pH value for drinking water in distribution recommended by the WHO Guidelines extant at the time of the incident was in the range 6.5-8.5 (see Table 2).

Figure 3b: Contact Tank: 3-dimensional representation (from Black & Veatch Ltd, 2004)



The pollution incident

3.5 As stated above, aluminium sulphate solution is routinely used as a coagulant and flocculant in drinking water treatment. Aluminium sulphate is added early in the treatment process to cause suspended solid matter to coagulate (see Figure 2), enabling removal by sedimentation and filtration. This process also removes most of the aluminium ions as the hydroxide.

3.6 On the afternoon of Wednesday July 6 1988, a delivery of aluminium sulphate solution was made to the unmanned works. This was discharged into the wrong tank i.e. into the chlorine contact tank (point 7 in Figure 2) instead of into a storage tank. The start of the discharge was 5.03pm and it finished at 5.40pm (Crowther Clayton Associates, personal communication, November 2003). This tank is immediately upstream of the treated water reservoir for water awaiting distribution through the mains (point 8 in Figure 2). Water contaminated with high concentrations of aluminium sulphate therefore moved into the treated water reservoir and then entered the distribution system. We were informed by South West Water Ltd that all the aluminium derived from the mistaken delivery had entered the distribution system within two days of the incident (Buckingham, personal communication, July 2002).

3.7 Later on in the evening of 6 July, from about 8.00pm onwards, customers began to complain to SWWA that the water had an unpleasant taste and a sticky feel to the touch. These properties are consistent with water of low pH (acidic) and the presence of aluminium sulphate (Lawrence, 1988; Crowther Clayton Associates, 2003). The acidity was incorrectly attributed to problems with the lime treatment plant. At about 11.00pm on 6 July 1988 SWWA began to flush out the acid water from the distribution pipes, with the water being emptied into rivers and waterways (Lawrence, 1988). The primary flush was into the river Camel upstream of Camelford with the secondary flush into the river Allen (Cross, personal communication, February 2004). This drew much of the aluminium sulphate in the chlorine contact tank and the treated water reservoir into the distribution system and local waterways. The process of flushing caused the death of fish in the Allen and Camel rivers, before the full extent of the contamination was recognised. The flushing

programme later involved sites which drained directly to the sea, in order that river water quality would not be affected (Lawrence, 1988).

3.8 At some time on the morning of Friday 8 July it was noticed that the level in the aluminium storage tank was low and the misdelivery and source of contamination was discovered (Lawrence, 1988). We have not been able to ascertain the time when this occurred.

3.9 The contaminated water entered the distribution system and, as a result, properties in the water supply area received acidic water containing higher than normal concentrations of aluminium and sulphate. As a consequence, other metals such as copper and lead dissolved from pipes and storage tanks resulting in a secondary source of contamination. The extent and severity of contamination is discussed in detail below.

3.10 Subsequently, work was carried out by SWWA over a period of 1 to 2 years to clean service reservoirs, and to cleanse and flush the mains.

The distribution of contaminated water

3.11 The Lowermoor Water Treatment Works supplies treated water to the North Cornwall distribution network. The main towns in the area served by the works are Boscastle, Camelford, Davidstow, Delabole, Helstone, Michaelstow, Otterham, St Teath and Tintagel (see Figure 1). The St Endellion service reservoir receives water from the Lowermoor Water Treatment Works and also from the De Lank Works which is about 5½ miles south-east of Lowermoor. The St Endellion service reservoir supplies the Port Isaac - St Endellion - Polzeath area.

3.12 The area covered by the Lowermoor distribution system contained approximately 7,000 properties, although some of these properties were served by long service pipes from the De Lank distribution system. It has been estimated that the summer population of the area was about 20,000, approximately 12,000 of whom were resident, although not all of these individuals would necessarily have consumed contaminated water. Because it takes time for the water to move from the treatment works through the distribution system, the contaminated water would have reached different points on the network at different times and peak contaminant concentrations would also have been experienced at different times. As a consequence of the large scale flushing exercise at different points in the distribution network, it is not possible to determine whether any particular point on the Lowermoor distribution network did or did not receive contaminated water (Buckingham, personal communication, July 2003). The extent and severity of the contamination can only be determined by the analysis of samples of water taken at a particular place and time. We present and discuss the analytical data below.

The nature of the contamination of the water supply

3.13 The aluminium sulphate solution discharged into the supply at the Lowermoor Water Treatment Works is referred to in the water industry as '8% Alum' (i.e. 8% w/w as aluminium oxide). It comprised twenty tonnes (15,150 litres) of a solution of hydrated aluminium sulphate ($Al_2(SO_4)_3.14H_2O$) with a specific gravity of 1.32 kilograms per litre (kg/l) (Lawrence, 1988). An aluminium sulphate solution of this

specific gravity contains 42.5 grams (g) aluminium/kg solution. The delivery therefore resulted in 850 kg of aluminium being deposited into the chlorine contact tank.

3.14 Aluminium sulphate is the salt of a strong acid (sulphuric acid) and a weaker base (aluminium hydroxide). Therefore, when it dissolves in water it forms an acidic solution of aluminium hydroxide, hydrogen ions and sulphate ions according to the following equation:

$$Al_2(SO_4)_3 + 6H_2O \Leftrightarrow 2Al(OH)_3 + 6H^+ + 3(SO_4)^{2-}$$

3.15 In the water treatment process, a solution of aluminium sulphate is added in a controlled way to water. The addition of an excess of aluminium sulphate, as occurred in this incident will result in water of low pH. When the water from the mains supply entered domestic pipework, the acidity of the water would have been sufficient to cause corrosion of the metallic plumbing materials. Under normal circumstances, a protective layer of copper compounds develops on the inside of copper water pipes and tanks preventing copper dissolving into the water supply. The acidic conditions recorded in the incident could have partially or wholly stripped away this protective layer, resulting in corrosion of the pipework until such time as the protective layer had reformed. This could have occurred in both hot and cold water copper pipework and in copper hot water cylinders (Drinking Water Inspectorate, personal communication, September 2003). We have seen physical evidence, during the public meeting on 4 April 2002, of such effects on pipework.

3.16 Service pipes connecting the mains supply to the domestic pipework can be made of galvanised iron (iron coated with zinc). In such cases, the acidic conditions could have stripped the zinc galvanise, leaving exposed and unprotected cast iron pipes. Likewise, galvanised cold water storage tanks or any brass fittings containing zinc would have been vulnerable to corrosion. The interiors of hot water storage systems, such as tea urns or vending machines, may also have been affected depending on type and the quality of the metals used in the lining. Events of this type have been reported to us during our collection of personal testimony.

3.17 Service pipes in houses built before 1970 may be made of lead. Older properties may also have lead piping within the house. In such properties the acidic water could have dissolved lead from the pipes, leading to increased concentrations in the water in the domestic system.

3.18 Flushing of the mains distribution system to remove the contaminated water resulted in the disturbance of old mains sediments, mainly deposits of iron and manganese oxides, and contributed to the discolouration of water. In the case of lead service pipes, the flushing exercises could also have dislodged deposits containing lead and lead salts which had built up in the pipes.

Calculated theoretical values for the aluminium sulphate concentration in the Lowermoor Water Treatment Works

3.19 As stated above, the 20 tonnes of aluminium sulphate solution was added to the chlorine contact tank (point 7 in Figure 2). We have received conflicting information about the state of the tank at the time of the incident. An employee of

SWWA at the time of the incident, at a meeting of the Lowermoor Liaison Group on 22 December 1988, stated that the bottom of the tank was filled to the level of the outlet pipe with a solid, compacted deposit of sludge (Cross, 1990a). However, Mr Buckingham of South West Water Ltd informed us in May 2002 that he was certain that the base of the tank was clean (Buckingham, personal communication, 2002). Nevertheless, South West Water Ltd noted that the large volume of liquid comprising the aluminium sulphate solution would have taken up a great deal of space at the base of the tank. Mixing would have taken place at the interface between the concentrated aluminium sulphate solution and the water in the tank.

3.20 The capacity of the treated water reservoir is approximately 2,300 cubic metres (m^3) (Crowther Clayton Associates, 1993) but it was believed at the time to be about 60% full (Crowther Clayton Associates, 2003) i.e. to have held approximately 1,380 m^3 water (1,380,000 litres). Therefore, if all the added aluminium sulphate was completely mixed into this volume, the maximum concentration in the reservoir would have been approximately 3,900 milligrams aluminium sulphate/l water (mg/l) (equivalent to approximately 600 mg aluminium/l and 3,300 mg sulphate/l) (see Table 1). This is an over simplification because of the uncertainty about the rate and extent of mixing in both in the contact tank and the treated water reservoir (Crowther Clayton Associates, 2003). South West Water has previously stated that laboratory investigation indicated that concentrations of aluminium and sulphate in the mains water could have reached 1,200 mg aluminium/l and 6,000 mg sulphate/l (Lowermoor Incident Health Advisory Group, 1989). This is twice the concentration calculated above. Thus it is apparent that there is considerable uncertainty as to the concentration of aluminium and sulphate that entered the mains water supply.

Table 1: Theoretical concentrations of aluminium, aluminium sulphate and sulphate in the treated water reservoir[a], if mixing had been complete.

	Weight added (mg x 10^6)	Volume of reservoir (litres)	Theoretical concentration in reservoir (mg/l)
Aluminium sulphate	5,383	1,380,000	3,901
Aluminium	850	1,380,000	616
Sulphate	4,533	1,380,000	3,285

a: point 8 in Figure 2

Collection of water samples

3.21 It is standard practice, when analysing for contaminants in water, that samples are taken into a prepared vessel in order to minimise contamination from environmental sources. When sampling in domestic premises, drinking water should be drawn from the cold tap in the kitchen which is fed directly from the mains. A sample taken immediately after turning on this tap will collect water already in the domestic plumbing system, and therefore is used to measure levels of copper, lead or zinc. As described above, these contaminants can be dissolved from the domestic plumbing system. A representative sample of mains water can be obtained from the kitchen cold tap if this is left running for at least 2 minutes (Drinking Water Inspectorate, personal communication, July 2003).

3.22 Water from hot water taps will usually be drawn from the domestic hot water tank. Such tanks are usually made of copper and, if the water is sufficiently acidic to

dissolve copper, heating of the system above 60°C tends to increase the rate of corrosion. It is therefore inadvisable to use water from hot water taps for drinking purposes, as it will tend to contain higher concentrations of copper than water from the cold water taps. Some individuals indicated, during the course of this enquiry, that they filled a kettle from the kitchen hot water tap (see Chapter 5).

Sampling techniques used by SWWA

3.23 South West Water Ltd was asked for details of the method by which water samples were taken after the Lowermoor incident. Information was provided by individuals who were employed at the relevant time within the potable water and sampling functions of the SWWA although these employees were not involved in the Lowermoor sampling programme (Buckingham, personal communication, June 2003). These enquiries indicated that there were three types of sample taken at the time of the incident: a) random daytime samples, b) 2 minute flush samples and c) 30 minute standing samples.

a) Random daytime samples are taken by collecting the first flow of water from the tap. The term random is used because the water will have been standing in the pipe for an unknown length of time. Such samples represent water received by customers through domestic taps.

b) The two minute flush samples are taken after water has been flowing for two minutes and are therefore considered representative of water in the mains.

c) For 30 minute standing samples, the tap being sampled is turned on and allowed to flush for 2 minutes. The tap is closed and the water is then left to stand in the pipe for 30 minutes, after which the sample is taken. These samples give a more standardised representation of the water at an individual's property so that any effects caused by the nature of the private pipework are more readily assessed.

3.24 South West Water Ltd informed us that each of these types of sample would have been used during the monitoring programme. However, one of the employees had indicated that the samples would most commonly have been the 2 minute flush sample as an indication of the water in the mains (Buckingham, personal communication, June 2003). In the case of the 2 minute flush sample, most of the contaminants from the domestic pipework (copper, lead or zinc) will have been flushed away before the sample was taken. Therefore, the monitoring data for these metals for water from the cold tap may not have revealed the highest concentrations which occurred after the incident. Individual sample data are presented below. No information is available about the sampling method used for any individual sample.

3.25 South West Water Ltd also informed us that samples were taken from cold water taps in a wide variety of locations and situations and from hot water taps. Hydrants were sampled during flushing and when tap water could not be sampled. Hydrants are installed at the end of spur mains to provide a point to flush out the ends of the water mains and thus samples drawn from hydrants are taken from the ends of the distribution system.

Water quality data from SWWA and South West Water Ltd

Introduction

3.26 We discuss below the monitoring results for four successive periods: 6 January 1988 to 5 July 1988 (pre-incident), 7 July to 4 August 1988, 5 August to 31 December 1988, and 1 January to 31 December 1989[5]. We reviewed data up to the end of 1989 in order to assess the long-term impact of the incident on the water supply. For the first, third and fourth periods, we were provided with results from specific locations within most of the parishes which are entirely served by the Lowermoor Water Treatment Works, subject to the following provisions:

- Firstly, while it is possible to ascertain where the water mains were located at the time, the area is rural. There are many long service pipes, some of which may cross a parish boundary from a mains served by one water treatment works into a parish which appears only to have water mains coming from another treatment works. It is possible to identify some of the cross border pipes from records but, as there are no records of service pipes and these can be in excess of a mile in length, it is possible that some samples are not from the expected water treatment works.

- Secondly, some of the addresses where samples were taken were not complete.

3.27 Nevertheless, South West Water Ltd advised us that they had no reason to believe that the locations were not substantially, if not entirely, correct. We were informed that, so far as South West Water Ltd was able to ascertain, these data were the results of the company's sampling of potable water supplied throughout the distribution system of the parishes in question (Buckingham, 2004). The exact location of the sampling sites was not supplied to us because South West Water Ltd consider that they cannot supply the names of customers at the address from which the sample was taken nor information which could identify the customers e.g. the house number or name (Buckingham, September 2004). The locations of the parishes are shown in Figure 4.

3.28 For the second period, the immediate post-incident period, the samples were provided from named locations, on a daily or two-daily basis, for all major contaminants except manganese and iron.

3.29 In discussing the results of analyses for contaminants in water samples, we refer to 'WHO Guideline Values'. These are guidelines for drinking water quality recommended by the World Health Organization. In the case of chemical contaminants, the guidelines take the form of a maximum recommended concentration for a contaminant in drinking water. In the case of acidity, the Guideline Value is a recommended range within which the pH of drinking water should lie. The guidelines are intended to be used as a basis for the development of national standards but are not mandatory limits[6].

[5] Sampling of the water supply up to and including 30 August 1988 was underaken by SWWA and thereafter sampling was by South West Water Services Ltd, which subsequently changed its name to South West Water Ltd.

[6] WHO states: " In order to define such limits, it is necessary to consider the Guideline Values in the context of local or national environmental, social, economic, and cultural considerations" (WHO, 1984).

3.30 All Guideline Values are set to ensure protection of public health but Guideline Values may not necessarily be set on health grounds. Guideline Values may be set because, if exceeded, water would be unpalatable or discoloured rather than because the water might be hazardous to health. The basis on which a particular Guideline Value has been set is indicated below.

3.31 The first WHO Guideline Values were published in 1984 and were revised in 1993, 1998, 2004 and 2011 (WHO, 1984, 1993, 1998, 2004 and 2011). In this report, we have mostly compared contaminant concentrations with the 1984 Guideline Values as these were relevant in 1988 and 1989, when the water samples analyses discussed below were taken. There were no national standards for drinking water quality until The Water Supply (Water Quality) Regulations 1989, which came fully into force on 1 January 1990. The standards and guidelines for the quality of public drinking water supplies[7] since 1984 are set out in Table 2, which shows that several guidelines/standards have changed since 1988. This is discussed further below.

3.32 A summary of the legislative framework for the quality of public drinking water supplies is given in Appendix 7.

Pre-incident monitoring data

3.33 We considered monitoring results from the area supplied by the SWWA before the pollution incident so that we could estimate pre-incident water quality and thus place later monitoring results in context. Unfortunately, only limited data are available for the time before the incident. Prior to the Water Supply (Water Quality) Regulations 1989, which came fully into force on 1 January 1990, there were no obligatory reporting requirements on water authorities in regard to water quality. In particular, there was no routine sampling for chemical contaminants at the customer's tap. Sampling for quality control was usually carried out at the point where the treated water enters the water distribution system and, therefore, would not be representative of concentrations at the tap for parameters such as copper and lead which arise largely from domestic plumbing.

3.34 Summary drinking water quality data from the South West Water Authority area for the period 1970-1984 to 1988 indicate that concentrations of aluminium ranged from below the limit of detection to 2.44 mg/l. Out of 35 supply areas, the highest mean concentration was 0.34 mg/l. pH values ranged from 5.0 to 11.2, with a lowest mean value of 7.5 (Foster, personal communication, 2004).

[7] Water supplied by a water company.

Table 2: Standards and guidelines for drinking water quality

Parameter	1984 Guideline Value (WHO, 1984)	Standard 1990 - 2003 (1989 Regs)	Current Standard (2000 Regs)	Basis of standard
Aluminium (Al)	200 µg/l	200 µg/l	200 µg/l	Avoidance of depositions in the distribution system and discolouration of the water. Included only as an indicator parameter[a] in EU Directive 98/83/EC.
Copper (Cu)	1000 µg/l	3000 µg/l	2000 µg/l	Staining of laundry and plumbing fixtures formed basis of 1984 WHO GDWQ[b]. EU Directive 80/778/EEC indicated a non-statutory Guide Level of 3000 µg/l (water sampled after it had been standing for 12 hours in the piping). Probably based on astringent taste, discolouration and corrosion at concentrations above this level. Implemented as PGV in 1989 regulations. WHO GDWQ was revised to 2000 µg/l (provisional) in 1993, using 1982 JECFA[c] TDI[d] based on liver toxicity in old study in dogs. Most recent WHO GDWQ (2011) states that this level should permit consumption of 2 or 3 litres of water per day, use of a nutritional supplement and copper from foods without exceeding the tolerable upper intake level of 10 mg/day (IOM, 2001) or eliciting an adverse gastrointestinal response.
Lead (Pb)	50 µg/l	50 µg/l	25 µg/l 10 µg/l from 25 December 2013	Standards based on the protection of health, particularly neurological and behavioural development of infants and children. GDWQ revised in 1996 due to revised (lower) JECFA PTWI[e] (to prevent accumulation of lead) and basing calculation on infants (who are most sensitive to the effects of lead). 2011 GDWQ set on the basis of treatment performance and analytical achievability.
Zinc (Zn)	5000 µg/l	5000 µg/l	No standard	WHO 1984 GDWQ based on taste considerations. WHO GDWQ (1996) revised to 3000µg/l based on taste and appearance. Not included in EU Directive 98/83/EC or 2000 Regulations as rarely occurs in drinking water at levels of concern.
Iron (Fe)	300 µg/l	200 µg/l	200 µg/l	Early WHO GDWQs based on staining of laundry and sanitary ware, and taste. Lower standard in EU Directive 98/83/EC possibly because turbidity and colour can occur at concentrations lower than 300 µg/l. Included only as an indicator[a] parameter in EU Directive 98/83/EC. No WHO GDWQ set in 2011 as considered not of health concern at levels found in drinking-water.
Manganese (Mn)	100 µg/l	50 µg/l	50 µg/l	WHO GDWQ based on staining of plumbing fixtures and laundry. Lower standard in EU Directive 80/778/EEC possibly because coating of pipes and discolouration can occur at lower concentrations. Included only as an indicator parameter[a] in EU Directive 98/83/EC. No WHO GDWQ set in 2011 as considered not of health concern at levels found in drinking-water.
Hydrogen Ion (pH)	6.5 - 8.5	5.5 - 9.5	6.5 - 10.0[f]	Corrosion of pipes occurs at low pH and taste and a soapy feel at high pH. Included only as an indicator parameter[a] in EU Directive 98/83/EC
Sulphate	400 mg/l	250 mg/l	250 mg/l	WHO 1984 GDWQ based on taste considerations. Lower taste threshold of 250 mg/l reported by

(SO_4)				WHO (1996). Corrosion may also occur at higher concentrations. Included only as an indicator parameter[a] in both EU Directive 98/83/EC and 2000 Regulations. No WHO GDWQ set in 2011 as considered not of health concern at levels found in drinking-water.

Notes:

a: The EU Directive on the Quality of Water intended for Human Consumption differentiates between "Chemical parameters" and "Indicator parameters." In the event of non-compliance with a parameter that has an indicator function, the Member State concerned must consider whether that non-compliance poses any risk to human health in deciding whether remedial action to restore the quality of the water is necessary.

b: WHO GDWQ - World Health Organization Guidelines for Drinking Water Quality

c: JECFA - Joint FAO/WHO Expert Committee on Food Additives

d: TDI - Tolerable Daily Intake

e: PTWI – Provisional Tolerable Weekly Intake

f: Amended in the Water Supply (Water Quality) (Amendment) Regulations 2001 to 6.5 – 9.5

3.35 South West Water Ltd also provided data on individual samples taken from sites in parishes within the Lowermoor water treatment area before the incident. The data available, which come from the parishes of Camelford, Davidstow, St Minver Lowlands, St Minver Highlands, St Teath, Tintagel, St Endellion and Forrabury and Minster, are summarised in Table 3.

Table 3: Water quality data from SWWA for the North Cornwall area, 6 January 1988 to 5 July 1988 – a summary

Contaminant	No. samples	Minimum (mg/l)	Maximum (mg/l)	No. (%) exceeding GV[a]
Aluminium	179	0.02	0.55	8 (5)
Sulphate	8	12.5	21.3	0 (0)
pH	130	5.9	9.8	50[b] (39)
Copper	32	<0.005	16.0	3 (9)
Zinc	14	0.003	0.016	0 (0)
Lead	7	<0.005	0.060	1(14)
Manganese	172	0.006	0.046	0 (0)
Iron	172	<0.010	0.880	2 (1)

a: relevant WHO Guideline Value (WHO, 1984)
b: 2 samples had a pH less than 6.5 and 48 samples had a pH greater than 8.5

Results of monitoring - 7 July to 4 August 1988

3.36 SWWA began to measure contaminant concentrations at sites in the distribution system on 7 July - the day after the contamination incident occurred. The monitoring data from the distribution area were obtained from a number of sites (reservoir points, residential properties, shops, public toilets, finished water from the treatment works) at many different locations in the supply zone: Rock, Polzeath, Port Isaac, Boscastle, Camelford, St Teath, Delabole, Trewetha, Pendogget, Marshgate, Tintagel, Michaelstow, Treveighan, Otterham, Rockhead and Churchtown. Sampling parameters comprised pH, aluminium, copper, zinc, lead and sulphate (South West Water, personal communication, 2002). Some of these locations were sampled on more than one occasion during this time, while at others a single sample was taken.

3.37 South West Water Ltd informed us that, unless specified as a hot water sample, the source was likely to be the cold water system (Buckingham, personal communication, July 2003).

Aluminium

3.38 The SWWA monitoring data for the period 7 July to 4 August 1988, with the locations from which they were taken, are presented in Table 4. A graphical representation of these results is given in Figure 5, with the exception of 'in-works' samples from the Lowermoor Water Treatment Works because these do not represent the concentrations in the distribution system. Concentrations in hot water samples are excluded, because the source of aluminium was the mains water. Each point on the graph indicates a concentration measured in a sample of water on the date indicated. The results for 197 samples are plotted. In some cases, results were labelled as referring to a 2-day period (e.g. 9-10 July 1988) and we have plotted these between the two dates. When the concentration of a contaminant was recorded as less than a certain value (e.g. <0.01 mg/l), we have plotted it as that value. It should be noted

that, when there are two or more samples containing the same concentrations on the same day, the results will appear as a single point on the graph (full data are given in Table 4).

3.39 The data show that concentrations varied during this period but sequential data are not available to allow us to describe the progress of the aluminium sulphate as it travelled through the distribution system. Figure 5 demonstrates that, initially, high concentrations of aluminium occurred in water samples. The highest concentration was 109 mg aluminium/l measured in a sample from the Boscastle service reservoir inlet on 7 July 1988. The aluminium concentrations fell in samples taken over the next few days and, after 10 July 1988, only 5.5% of samples contained more than 1 mg aluminium/l. However, on 4 August 1988, 58% of the concentrations remained above the 1984 WHO Guideline Value of 0.2 mg/l.

3.40 Table 5 shows the changes of aluminium concentration with time in samples taken from 2 locations where sampling started on 9 July 1988 and continued at intervals until 2 August 1988. Concentrations reached 6.93 and 11.97 mg aluminium/l, respectively, on 9 July but then fell rapidly, although they still exceeded the 1984 Guideline Value at the end of the period.

Table 4 Drinking water quality data from SWWA for the period 7 July 1988 to 4 August 1988

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
7 July 1988						
Sycamore Avenue Rock	0.10	N/A	N/A	N/A	N/A	7.6
Blue Hills, Higher Triscon, Polzeath	0.06	N/A	N/A	N/A	N/A	8.2
St. Endellion Service Reservoir	0.19	N/A	N/A	N/A	N/A	8.8
2 Mayfield Drive, Port Isaac (West)	9.00	N/A	N/A	N/A	N/A	4.7
Camelford	41.00	N/A	N/A	N/A	N/A	4.3
Slaughterbridge	50.00	N/A	N/A	N/A	N/A	4.3
Trevalsa	<.01	N/A	N/A	N/A	N/A	7.1
Boscastle Service Reservoir	109.00	N/A	N/A	N/A	N/A	4.1
Boscastle Service Reservoir	7.90	N/A	N/A	N/A	N/A	4.7
Rockhead Service Reservoir	32.00	N/A	N/A	N/A	N/A	4.4
8 July 1988						
26 St. Verse Road, Port Isaac	32.50	0.57	0.85	0.04	N/A	4.0
Pendoggett	27.50	0.45	0.41	0.03	N/A	5.0
St Teath	20.50	0.77	3.0	0.06	N/A	5.0
Delabole Inlet	2.26	0.06	0.11	0.04	N/A	6.0
Delabole S R Outlet	4.39	0.28	0.68	0.04	N/A	6.0
Michaelstow	34.50	1.2	2.1	0.12	N/A	4.8
Camelford	1.80	0.20	0.09	<0.01	N/A	8.1
Davidstow Inlet	6.00	0.03	0.15	<0.01	N/A	5.4
Davidstow Outlet	<0.01	<0.01	0.04	<0.01	N/A	7.5
Hallworthy	21.00	1.7	0.34	0.09	N/A	5.4
Boscastle Inlet	5.58	0.01	0.11	<0.01	N/A	4.4
Rockhead Inlet	2.17	0.01	0.06	<0.01	N/A	8.3

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
9 July 1988						
Trewetha Cottage, Trewetha	6.93	8.8	1.2	<0.01	115	4.6
Trewetha Farm, Trewetha	7.70	0.06	0.57	<0.01	N/A	4.7
Spar Shop, Port Isaac	10.08	0.57	0.73	<0.01	110	4.8
Port Isaac Fishermen Ltd	0.60	<0.01	<0.02	<0.01	N/A	8.8
Pengavne, Pendogget	6.20	0.77	0.13	<0.01	83	4.6
5 Longfield Road, Camelford	2.71	0.09	0.11	<0.01	82	4.6
8 Roughtor Drive, Camelford	1.87	0.01	0.08	<0.01	N/A	8.4
Vine Cottage, Boscastle	5.29	<0.01	0.12	<0.01	N/A	7.0
Hillside Cottage, High Street, Boscastle	1.95	0.09	0.11	0.20	60	5.9
Cottage High Street, Boscastle	1.93	0.04	0.10	0.06	N/A	6.0
Treven, Marshgate	11.97	<0.01	0.25	<0.01	139	5.6
34, Rock Road, Delabole	0.75	0.10	0.06	<0.01	N/A	8.8
Polkerr, Tintagel	0.49	0.14	0.06	<0.01	N/A	7.8
9 or 10 July 1988						
Vale View, Trewannan Lane, St. Teath	2.96	1.8	1.9	0.03	N/A	4.6
Rockmead Rock Road, Delabole	0.99	0.10	0.08	<0.01	N/A	8.2
Grange Cottage, Bossinor	0.91	0.02	0.06	<0.01	N/A	8.3
Bruallan Nursery, St. Teath	3.98	0.28	0.13	<0.01	67	4.4
2 Westwinds, Otterham Station Hot Water	0.07	7.0	1.6	<0.03	132	5.8
Treven "A" Marshgate Hot Water	4.86	20.0	0.82	0.46	146	5.1
5 Woodbine Cottage, Michaelstow	0.81	0.01	0.12	<0.01	N/A	8.6
ESSO Garage, Otterham Station	10.26	0.04	0.26	<0.01	130	4.8
Glebe View Bungalow, Michaelstow	0.98	0.03	0.08	<0.03	27	7.2

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
Woodbine Cottage, Michaelstow	1.00	<0.01	0.9	<0.03	26	7.2
Bruallan Nursery, St. Teath	0.58	0.06	0.05	<0.03	30	6.6
Vale View Bungalow Trewennan, St. Teath	0.97	0.12	0.12	<0.03	31	6.5
10 July 1988						
Vine Cottage, Boscastle	0.82	<0.01	0.06	<0.03	57	9.0
Vine Cottage, Boscastle Hot Water	0.33	0.01	0.04	<0.03	24	9.5
Orchard House, Boscastle Cold Water	1.68	0.03	0.08	<0.03	52	8.5
Orchard House, Boscastle Hot Water	0.18	0.03	0.69	0.03	72	7.8
Fairfield Fore Street, Boscastle Cold Water	0.90	0.01	0.06	0.03	47	6.6
Fairfield Fore Street, Boscastle Hot Water	0.58	1.5	1.7	0.07	64	6.1
Hillside Boscastle Cold Water	0.90	0.12	1.7	0.07	47	7.0
Hillside Boscastle Hot Water	0.23	0.12	0.10	0.22	18	8.0
Grange Cottage Bossiney	0.80	0.02	0.05	<0.03	28	10.0
Grange Cottage, Bossiney Hot Water	1.32	16	2.8	0.08	77	5.1
Tintagel Cold Water	0.39	0.04	0.11	<0.03	30	9.1
Tintagel Hot Water	0.68	5.2	0.39	0.05	53	6.0
Trewetha Cottage, Nr. Port Isaac	1.00	0.39	0.09	<0.03	37	4.8
Trewetha Farm, Trewetha, Nr. Port Isaac	0.80	0.03	0.18	<0.03	35	5.0
The Spar Shop, Port Isaac	0.43	<0.01	0.02	<0.03	16	6.8
84 Fore Street, Port Isaac	0.60	0.01	0.02	<0.03	16	6.8
Pengawne Bungalow, Pendoggett	0.96	0.18	0.08	<0.03	33	6.1
142 High Street, Delabole	0.47	0.05	0.07	<0.03	28	6.7
33 Rock Head Road, Delabole	1.02	<0.01	0.05	<0.03	27	7.2
Rockmead Rock Head Street, Delabole	1.00	<0.01	0.04	<0.03	27	7.0
5 Longfield Drive, Camelford	1.07	0.03	0.07	<0.03	62	4.6
8 Rough Tor Drive, Camelford	1.37	<0.01	0.05	<0.03	27	8.4

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
11 July 1988						
Mayfield Drive, Port Isaac	0.69	0.05	<0.05	<0.05	29.0	7.5
2 Chapel Cane, Treveighan, St. Teath Hot Water	0.31	13.0	2.75	<0.05	97.0	6.5
2 Chapel Cane, Treveighan, St. Teath Cold Water	0.45	<0.05	0.057	<0.05	29.0	7.5
Orchard House, Boscastle	0.46	<0.05	<0.05	<0.05	36.0	7.5
Heigh-Ho Boscastle Hillside	0.61	<0.05	<0.05	<0.05	33.0	7.5
14 July 1988						
Roseleigh, Trewetha, Port Isaac Cold	0.98	<0.005	<0.005	<0.005	N/A	7.8
Roseleigh, Trewetha Hot	0.25	0.04	0.016	<0.005	N/A	5.8
Ceriale, Marshgate Cold	2.00	<0.005	<0.005	<0.005	N/A	7.8
Ceriale, Marshgate Hot	0.65	0.018	0.007	<0.005	N/A	6.7
Fairfield, Boscastle	1.00	<0.005	<0.005	<0.005	N/A	7.4
Orchard Lodge, Boscastle Cold	1.50	<0.005	<0.005	<0.005	N/A	7.5
Orchard Lodge, Boscastle	0.54	0.019	0.009	<0.005	N/A	6.7
5 Longfield Road, Camelford Cold	0.86	<0.005	<0.005	<0.005	N/A	8.5
5 Longfield Road, Camelford	1.60	0.009	<0.005	<0.005	N/A	7.1
18 July 1988						
Toilets Port Isaac	0.53	<0.005	0.011	<0.005	23.6	8.0
Garage St. Teath	0.49	<0.005	0.011	<0.005	24.8	9.0
Garage Delabole	0.77	<0.005	0.010	<0.005	25.3	8.2
Toilets Tintagel	0.59	0.007	0.015	0.009	25.0	7.9
Vine Cottage, Boscastle	1.00	<0.005	0.017	<0.005	25.2	9.1
Treven Marshgate	0.89	<0.005	0.021	0.006	25.3	9.4
Garage Camelford	0.59	<0.005	0.011	<0.005	26.3	8.0
Sunnydale, Michaelstow	0.57	<0.005	0.016	<0.005	25.9	8.3

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
19 July 1988						
From Cold Tap, 2 Chapel Hill, Treveighan	0.48	0.005	0.013	0.005	34.0	8.7
Hot Tap, 2 Chapel Hill, Treveighan	0.65	0.098	0.045	0.008	30.2	7.8
CoId Tap at Trewetha Cottage, Trewetha	0.46	0.013	0.010	0.005	31.2	7.9
From Hot Water Tap at Trewetha Cottage, Trewetha	3.00	1.12	7.83	0.009	63.3	3.7
CoId Water Tap at Trevena Marshgate	0.68	0.008	0.005	0.006	29.3	9.5
Hot Water Tap Trevena Marshgate	1.20	0.043	0.005	0.021	29.6	8.8
20 July 1988						
Toilets, Port Isaac	0.48	N/A	N/A	N/A	27.0	8.4
Garage St. Teath	0.29	N/A	N/A	N/A	30.3	9.3
Garage Delabole	0.68	N/A	N/A	32.6	7.6	
Toilets Tintagel	0.50	N/A	N/A	28.8	8.1	
Vine Cottage, Boscastle	0.73	N/A	N/A	N/A	29.9	9.1
Treven Marshgate	0.56	N/A	N/A	N/A	30.0	9.4
Garage Camelford	0.54	N/A	N/A	N/A	23.1	8.2
Sunnydale Michaelstow	0.37	N/A	N/A	N/A	26.2	9.2
21 July 1988						
Public Toilets, Port Isaac	0.53	<0.05	<0.05	<0.05	22.1	7.6
The Garage, St. Teath	0.29	<0.05	<0.05	<0.05	20.5	9.0
Delabole Depot, Delabole	2.20	<0.05	<0.05	<0.05	19.4	8.5
The Toilets, Tintagel	0.56	<0.05	<0.05	<0.05	25.9	8.0
The Toilets, Boscastle	0.56	<0.05	0.05	<0.05	26.3	7.9
The Toilets, Camelford	0.37	<0.05	<0.05	<0.05	18.7	7.4
Campsite, Michaelstow	0.39	<0.05	<0.05	<0.05	18.5	7.5
The Garage, Otterham Station	0.62	<0.05	<0.05	<0.05	25.7	8.4

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
Lowermoor W.T.W. In-works samples	0.07	<0.05	<0.05	<0.05	15.7	5.7
Lowermoor W.T.W. Final Water	0.12	<0.05	<0.05	<0.05	17.8	9.2
23 July 1988						
Lowermoor Dis 1 Edam Cottage, Michaelstow	0.44	<0.05	<0.05	<0.05	16.5	7.9
Lowermoor Dis 23 Victoria Road, Camelford	0.39	<0.05	<0.05	<0.05	17.7	8.6
Lowermoor W.T.W. Final Water	0.10	<0.05	<0.05	<0.05	18.1	8.8
Lowermoor W.T.W. In-works samples	0.03	<0.05	<0.05	<0.05	18.5	5.6
Lowermoor W.T.W. In-works samples	0.06	<0.05	<0.05	<0.05	18.7	5.8
Lowernoor Dis Carleton Farm, Marshgate	0.57	<0.05	<0.05	<0.05	23.5	9.0
Lowermoor Dis Pencliffe, Boscastle	0.65	<0.05	<0.05	<0.05	17.5	8.4
Lowermoor Dis Brocks Cottage, Church Lane	0.27	<0.05	0.098	<0.05	19.1	7.9
Lowermoor Dis 24 Roce Road, Delabole	0.41	<0.05	<0.05	<0.05	18.3	8.7
Lowermoor Dis Bruallen. St. Teath	0.41	<0.05	<0.05	<0.05	18.8	9.0
Port Isaac Windrush	0.37	<0.05	<0.05	<0.05	19.7	7.7
Tre-Chy Michaelstow Lowermoor Survey Taste	0.35	<0.05	<0.05	<0.05	17.5	8.2
59 Mount Camel, Camelford	1.00	<0.05	<0.05	<0.05	19.1	8.8
Lowermoor W.T.W. In-works samples	0.19	<0.05	<0.05	<0.05	15.4	5.9
Lowermoor W.T.W. In-works samples	0.02	<0.05	<0.05	<0.05	15.6	5.9
23 or 24 July 1988						
Lowermoor W.T.W. Final Water	0.07	<0.05	<0.05	<0.05	18.4	9.3
Ottervale, Otterham, Churchtown	0.70	<0.05	<0.05	<0.05	23.2	8.3
Rose Cottage Marshgate	0.59	<0.05	<0.05	<0.05	19.6	8.9
Flat 19 Tethadene, St. Teath	0.41	<0.05	<0.05	<0.05	19.2	9.7
24 July 1988						
18 Langfords Meadow, Boscastle	0.61	<0.05	<0.05	<0.05	17.8	8.3

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
Harlyn Castle View, Tintagel	0.33	<0.05	0.87	<0.05	18.9	7.8
High Street, Delabole	0.43	<0.05	<0.05	<0.05	19.2	8.4
8 Hartland Road, Port Isaac (East)	0.36	<0.05	<0.05	<0.05	19.1	8.0
26 July 1988						
Toilets, Port Isaac	0.51	<0.05	<0.05	<0.05	19.1	7.8
Garage, St. Teath	0.58	<0.05	<0.05	<0.05	18.3	8.2
Garage, Delabole	0.72	<0.05	<0.05	<0.05	19.6	8.3
Garage, Tintagel	0.44	<0.05	<0.05	<0.05	19.5	8.0
Toilets, Boscastle	0.45	<0.05	<0.05	<0.05	18.8	8.0
Toilets, Camelford	0.53	<0.05	<0.05	<0.05	21.0	8.8
Garage, Otterham Station	0.53	<0.05	<0.05	<0.05	19.1	8.1
Michaelstow Holiday Park	0.60	<0.05	<0.05	<0.05	20.8	7.9
Lowermoor W.T.W. In-works samples	0.12	<0.05	<0.05	<0.05	23.8	6.3
Lowermoor W.T.W. Final Water	0.12	<0.05	<0.05	<0.05	24.9	10.2
27 July 1988						
Toilets, Port Isaac	0.56	<0.05	<0.05	<0.05	21.8	7.9
Garage, St. Teath	0.44	<0.05	<0.05	<0.05	21.7	9.3
Garage, Delabole	0.61	<0.05	<0.05	<0.05	22.6	9.2
Toilets, Tintagel	0.60	<0.05	<0.05	<0.05	22.6	8.3
Toilets, Boscastle	0.51	<0.05	<0.05	<0.05	19.9	8.0
Treven Marshgate	0.45	<0.05	<0.05	<0.05	19.9	9.1
Lowermoor W.T.W. -In-works sample	0.07	<0.05	<0.05	<0.05	19.9	9.4
Lowermoor W.T.W. -Final water	0.13	<0.05	<0.05	<0.05	25.6	8.9
Sunnydale, Michaelstow	0.43	<0.05	<0.05	<0.05	23.4	9.3
Delabole Service Reservoir	0.40	<0.05	<0.05	<0.05	22.0	7.8
Delabole Service Reservoir	0.24	<0.05	<0.05	<0.05	23.0	9.1

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
Rockhead Service Reservoir	0.20	<0.05	<0.05	<0.05	23.0	8.8
Lowermoor W.T.W - Final Water	0.20	<0.05	<0.05	<0.05	26.0	9.5
Cold Water Tap at Trewetha Cottage, Port Isaac	0.62	N/A	N/A	<0.05	21.6	8.0
Hot Water Tap at Trewetha Cottage, Port Isaac	0.31	0.153	N/A	<0.05	23.4	7.2
27 or 28 July 1988						
Garage, St. Teath	0.42	<0.05	N/A	<0.05	23.2	9.1
Garage, Otterham	0.40	<0.05	N/A	<0.05	21.7	8.1
Lowermoor W.T.W. -In-works samples	0.28	<0.05	N/A	<0.05	17.2	5.1
Lowermoor W .T.W. -Final water	0.23	<0.05	N/A	<0.05	20.6	7.8
Cold Water Tap, 2 Chapel Hill Treveighan, St. Teath	0.60	<0.05	N/A	<0.05	21.1	8.2
Hot Water Tap, 2 Chapel Hill Treveighan, St. Teath	0.36	0.108	N/A	<0.05	21.1	7.9
Cold Water Tap at Trevone, Marshgate	0.44	<0.05	N/A	<0.05	20.2	9.0
Hot Water Tap at Trevone, Marshgate	0.39	0.090	N/A	<0.05	23.1	8.4
28 July 1988						
Toilets, Port Isaac	0.64	<0.05	N/A	<0.05	22.5	7.7
Delabole Depot	0.48	<0.05	N/A	<0.05	22.4	8.6
Garage, Tintagel	0.86	<0.05	N/A	<0.05	23.8	8.6
Toilets, Boscastle	0.47	<0.05	N/A	<0.05	21.7	8.9
Toilets, Camelford	0.40	<0.05	N/A	<0.05	21.2	7.1
29 July 1988						
Tre-Chy Lowermoor Survey	0.38	<0.05	N/A	<0.05	20.3	7.2
17 Chapel Street, Camelford	0.27	<0.05	N/A	<0.05	24.4	6.8
Lowermoor W.T .W. -In-works samples	0.19	<0.05	N/A	<0.05	19.2	6.4
Lowermoor W.T .W. -In-works samples	0.08	<0.05	N/A	<0.05	20.1	5.3

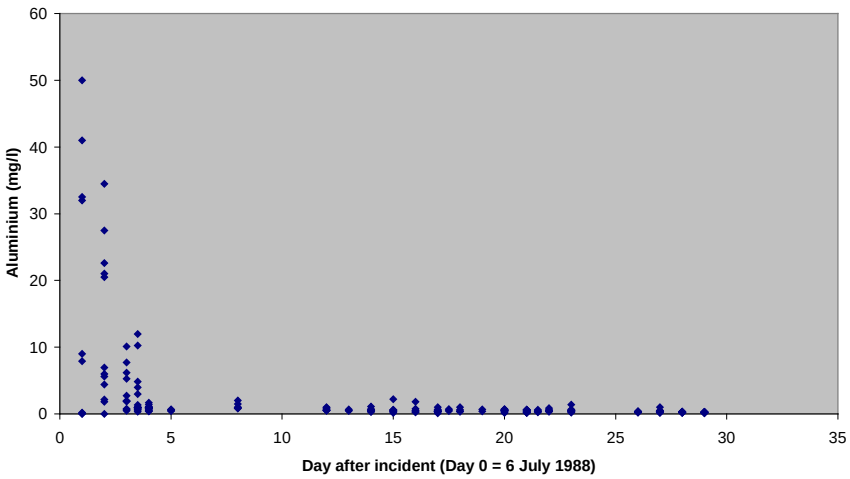
Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
Lowermoor W.T.W. Final water	0.17	<0.05	N/A	<0.05	24.3	7.0
1 Ottervale, Churchtown	0.65	<0.05	N/A	<0.05	20.2	7.9
Montana Marshgate Lowermoor Survey	0.42	<0.05	N/A	<0.05	21.3	9.1
Sharrocks Cottage, Fore Street, Boscastle	0.49	<0.05	N/A	<0.05	21.7	8.7
30 The Botts, Bossiney, Tintagel	0.52	<0.05	N/A	<0.05	21.0	8.2
11 Penmead Road, Delabole	0.49	<0.05	N/A	<0.05	21.8	8.3
Chy-Lees, Plot No. 4, Eglos Court, St. Teath	1.40	<0.05	N/A	<0.05	22.8	9.6
Coristin, Christian Guest House	0.57	<0.05	N/A	<0.05	20.7	8.2
Chy-Lees, Plot No. 4, Eglos Court, St. Teath	0.44	<0.05	N/A	<0.05	30.9	7.2
1 August 1988						
Port Isaac Toilets	0.36	<0.05	N/A	<0.05	22.7	7.8
St. Teath Garage	0.29	<0.05	N/A	<0.05	22.1	7.6
Toilets, Delabole	0.23	<0.05	N/A	<0.05	20.0	7.6
Toilets, Tintagel	0.30	<0.05	N/A	<0.05	22.5	7.7
Toilets, Boscastle	0.37	<0.05	N/A	<0.05	21.6	7.7
Camelford, Toilets	0.17	<0.05	N/A	<0.05	18.5	7.7
Garage, Otterham Station	0.30	0.827	N/A	<0.05	4.5	5.2
Michaelstow Holiday Village	0.29	<0.05	N/A	<0.05	21.5	7.6
Tre-Chy, Michaelstow	N/A	N/A	N/A	N/A	N/A	7.7
3 West Winds Otterham Station	N/A	N/A	N/A	N/A	N/A	8.6
2 August 1988						
Toilets, Port Isaac	0.32	<0.05	N/A	<0.05	18.9	7.7
St. Teath Garage	0.36	<0.05	N/A	<0.05	19.5	7.6
Garage, Delabole	0.55	<0.05	N/A	<0.05	18.5	8.2
Toilets, Tintagel	0.41	<0.05	N/A	<0.05	19.0	7.9
Vins Cottage, Boscastle	0.39	<0.05	N/A	<0.05	20.7	9.2

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
Trevan Marshgate	0.36	<0.05	N/A	<0.05	20.5	8.9
13A Fore Street, Camelford	0.27	<0.05	N/A	<0.05	20.4	8.6
Sunnydale, Michaelstow	0.44	<0.05	N/A	<0.05	18.3	8.3
Lowermoor W.T.W. -In-works samples	0.11	<0.05	N/A	<0.05	16.9	6.1
Lowermoor W.T.W. -Final Water	0.13	<0.05	N/A	<0.05	19.6	8.9
3 August 1988						
Port Isaac, Toilets	0.34	<0.05	N/A	<0.05	20.2	7.8
St. Teath, Garage	0.24	<0.05	N/A	<0.05	20.2	7.4
Delabole, Toilets	0.22	<0.05	N/A	<0.05	20.4	7.9
Boscastle, Toilets	0.30	<0.05	N/A	<0.05	21.6	7.9
Tintagel, Toilets	0.29	<0.05	N/A	<0.05	20.5	8.0
Camelford, Toilets	0.24	<0.05	N/A	<0.05	18.6	7.5
Otterham Station, Garage	0.25	<0.05	N/A	<0.05	18.7	7.4
Michaelstow Caravan Park	0.20	<0.05	N/A	<0.05	20.0	7.7
Lowermoor W.T.W. -In-works samples	0.07	<0.05	N/A	<0.05	17.7	5.8
Lowermoor W.T.W. -Final water	0.15	<0.05	N/A	<0.05	18.8	7.5
4 August 1988						
Planet Park, Delabole	0.20	<0.005	N/A	<0.005	18.3	7.6
Villet View, Trevillet Lane, St. Teath	0.27	0.007	N/A	<0.005	18.2	7.8
Mount Pleasant, Treligga	0.19	<0.05	N/A	<0.05	N/A	8.2
Toilets, Port Isaac	0.27	<0.05	N/A	<0.05	N/A	7.9
Garage, St. Teath	0.29	<0.05	N/A	<0.05	N/A	7.8
Garage, Delabole	0.19	<0.05	N/A	<0.05	N/A	8.0
Toilets, Tintagel	0.21	<0.05	N/A	<0.05	19.3	7.6
Toilets, Boscastle	0.29	<0.05	N/A	<0.05	19.8	7.8
Treven, Marshgate	0.28	<0.05	N/A	<0.05	20.0	8.8

Sampling location	Aluminium (mg/l)	Copper (mg/l)	Zinc (mg/l)	Lead (mg/l)	Sulphate (mg/l)	pH
Garage, Camelford	0.22	<0.05	N/A	<0.05	19.5	7.9
Churchtown, Michaelstow	0.16	<0.05	N/A	<0.05	19.2	7.9
Lowermoor W.T.W - Final Water	0.08	<0.05	N/A	<0.05	19.1	9.2

N/A: not available

Figure 5: Aluminium concentrations plotted from SWWA data (7July to 4 August 1988)



3.41 As noted in Table 2, the 1984 WHO Guideline Value of 0.2 mg aluminium/l was set to avoid deposits in the distribution system and discolouration of water, not because of a risk of adverse health effects above this concentration. The current standard for aluminium is also 0.2 mg/l (SI No 3184, 2000) and is set on the same basis.

Table 5: Aluminium concentrations in samples taken from two locations at intervals from 9 July 1988 to 2 August 1988

Location	Sampling date	Aluminium (mg/l) – (cold water)	Aluminium (mg/l) – (hot water)
Trewetha Cottage, Port Isaac	9/7/88	6.93	-
	10/7/88	1.00	-
	19/7/88	0.46	3.0
	27/7/88	0.62	0.31
Treven, Marshgate	9/7/88	11.97	4.86
	19/7/88	0.68	1.2
	20/7/88	0.56	-
	27/7/88	0.45	-
	2/8/88	0.36	-

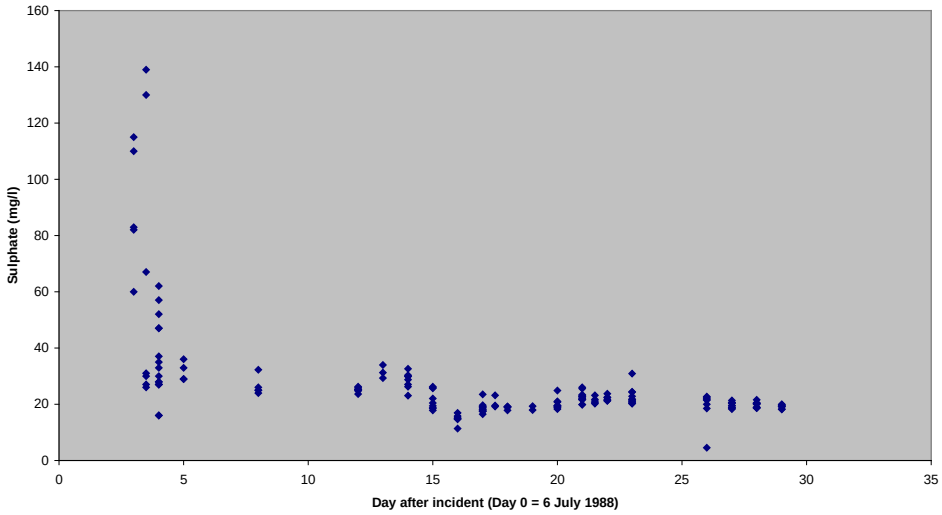
3.42 In the consultation exercise, one correspondent noted that there were discrepancies between the concentrations recorded for aluminium and those recorded for sulphate, compared to those expected from their stoichiometric equivalents. These discrepancies are particularly marked shortly after the incident. We are advised that the chemistry occurring at the time was likely to have been complex and that there are a number of mechanisms which could have influenced the ratio of aluminium to sulphate (Drinking Water Inspectorate, personal communication, March 2005; South West Water, personal communication, May 2005). We note that discrepancies also occurred in samples taken by private individuals and analysed by another laboratory (see paragraph 3.66). We therefore see no reason to disregard these analytical results.

Sulphate

3.43 Measurement of sulphate concentrations in both hot and cold water samples began on 9 July 1988. The results for the first 4 weeks after the incident are shown in Figure 6. Only results for cold water samples are included because the source of sulphate was the mains water; these comprised a total of 160 samples. Sulphate concentrations were below the 1984 WHO Guideline Value of 400 mg/l in all samples. After 11 July, the concentrations fell and on 4 August they lay in the range 18.2 to 20.0 mg sulphate/l.

3.44 The 1984 WHO Guideline Value for sulphate was set on taste considerations. The current standard for sulphate is 250 mg sulphate/l (SI No 3184, 2000).

Figure 6: Sulphate concentrations plotted from SWWA data (9 July to 4 August 1988)

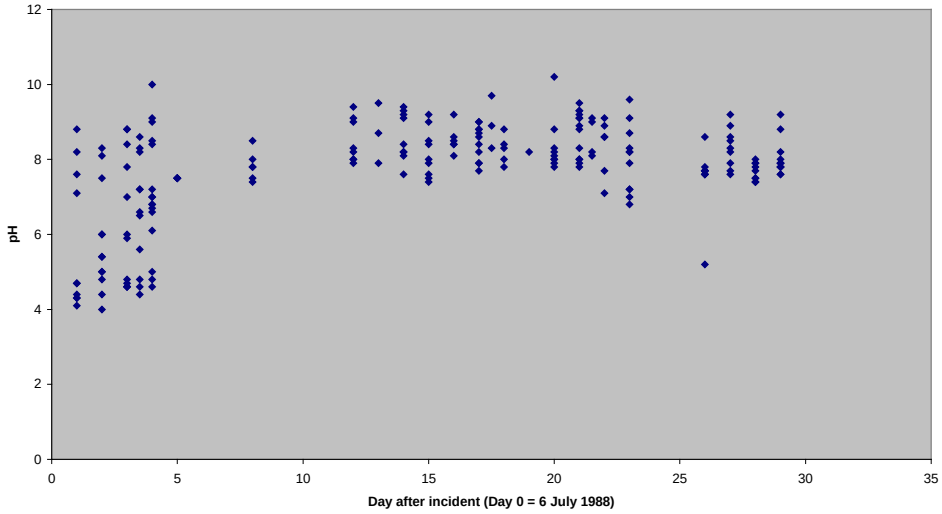


Acidity (pH)

3.45 The monitoring of pH levels in the water began on 7 July 1988. Figure 7[8] shows the results for all domestic cold water samples (199 samples) in the first four weeks after the incident. There was no consistent difference between hot and cold water samples (see Table 4). The 1984 Guideline Value for pH was between 6.5 and 8.5. Figure 7 shows that pH values lay outside this range in the first 4 weeks after the incident on 102 occasions. In the first few days, the water samples were frequently acid, with a pH below 6.5. By 4 August 1988, no sample had a pH below 6.5 and 2 samples had a pH higher than 8.5.

[8] Note that the vertical axis on the graph, the pH, is on a logarithmic scale.

Figure 7: Acidity (pH) plotted from SWWA data (7 July to 4 August 1988)

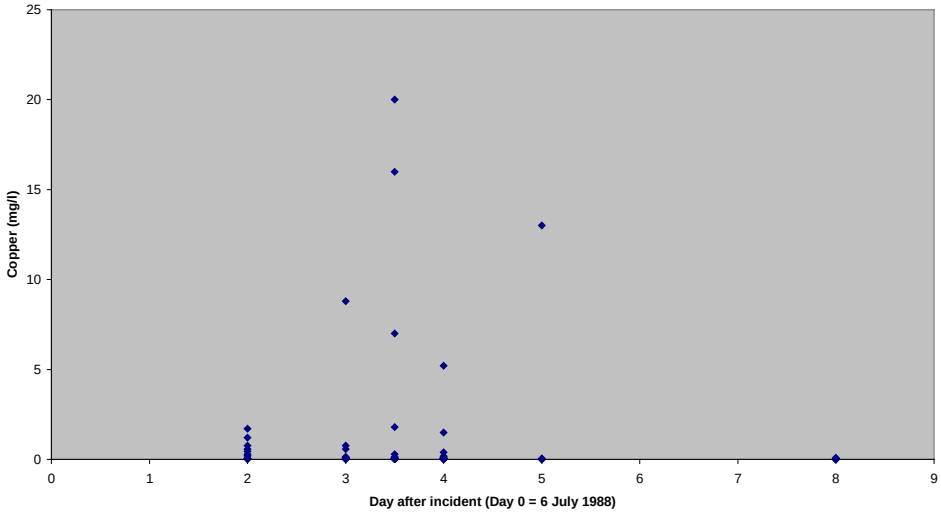


3.46 The 1984 WHO Guideline Value for acidity was set as a range of 6.5 to 8.5 to avoid excessive corrosion of the pipework at low pH and a taste and soapy feel to the water at high pH. The upper standard for optimal pH of drinking water has now increased from 8.5 to 10.0 (SI No 3184, 2000).

Copper

3.47 The measurement of concentrations of copper, zinc and lead began on 8 July 1988 in cold water samples and on 9 July in hot water samples. The results for copper, up to and including 14 July 1988 (73 samples), are presented in Figure 8. Both hot and cold water samples are included. Up to 4 August 1988, eleven samples (15%) exceeded the 1984 WHO Guideline Value of 1 mg/l. The maximum concentration in a hot water sample was 20 mg/l and in a cold water sample it was 8.8 mg/l. The Guideline Value was based on the possibility of staining of laundry and plumbing fixtures above this concentration, not because of a risk of adverse health effects. After 21 July 1988 there were no copper concentrations which exceeded the Guideline Value.

Figure 8: Copper concentrations plotted from SWWA data (8 to 14 July 1988)



3.48 The water quality standard for copper has changed since 1988 and is currently 2 mg/l, in line with the revised WHO provisional Guideline Value of 2 mg/l, which is set to protect against acute gastrointestinal effects (nausea, vomiting and diarrhoea) consequent upon consumption of higher concentrations of copper in water (SI No 3184, 2000; WHO 1998, 2003). These effects are more dependent on the concentration of copper than total dose ingested (WHO, 2003).

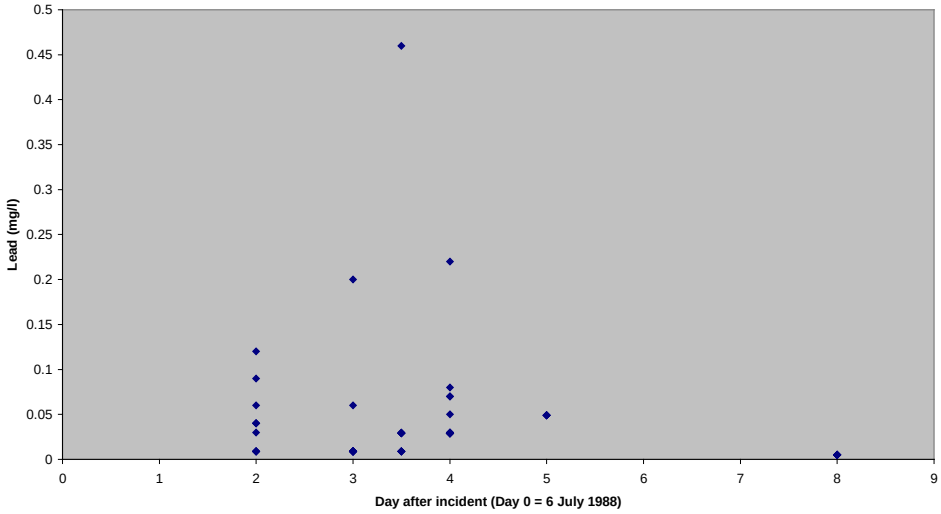
Zinc

3.49 In the first week after the incident, all results for the concentration of zinc (64 samples, from both hot and cold water systems) were below the 1984 WHO Guideline Value of 5 mg/l. After the first week, one hot water sample had a zinc concentration of 7.83 mg/l (on 19 July 1988) but no other sample exceeded the Guideline Value. The 1984 WHO Guideline Value was based on taste considerations. Currently, there is no standard for zinc in drinking water standard as zinc rarely occurs in drinking water at concentrations which cause concern (SI No 3184, 2000).

Lead

3.50 At the time of the incident, "only a small proportion" of dwellings in the supply zone had lead plumbing (South West Water, personal communication, 2002). The results for monitoring of lead up to 14 July 1988 (73 samples) are presented in Figure 9. Nine samples (12%) exceeded the 1984 WHO Guideline Value of 0.05 mg lead/l, of which two were hot water samples. The maximum concentrations were 0.46 mg/l in a hot water sample and 0.22 mg/l in a cold water sample. In no samples taken after 11 July did lead concentrations exceed the Guideline Value.

Figure 9: Lead concentrations plotted from SWWA data (8 to 14 July 1988)



3.51 The water quality standard for lead is set to minimise the risk of adverse effects on the health and development of young children by reducing exposure to the lowest practically achievable (see Chapter 6 for a discussion of the toxicity of lead). The standard for lead halved in 2000 from 0.05 to 0.025 mg/l and will be lowered further to 0.01 mg/l after 2013 (SI No 3184, 2000).

Manganese

3.52 Manganese concentrations in water samples may be raised as a result of flushing of water pipes and the subsequent disturbance of sediment in the water distribution system. Manganese would normally be present as black particles of insoluble manganese dioxide.

3.53 There are no manganese concentrations listed in the data set provided to us by SWWA from which we derived the results for aluminium and the other contaminants discussed above. The monitoring data for manganese available to us during this period were those for parishes served by the Lowermoor distribution system (see paragraph 3.58). These comprised 147 samples, of which 16 (11%) were in excess of the 1984 WHO Guideline Value of 0.1 mg manganese/l. The highest concentration of manganese recorded during this period was 1.3 mg/l on 9 July.

3.54 The WHO Guideline Value for manganese was based on the possibility of staining of sanitary ware and laundry at concentrations above 0.1 mg/l. The current standard is 0.05 mg manganese/l, again set for aesthetic reasons, not on health grounds (SI No 3184, 2000).

Iron

3.55 Iron concentrations in water samples can be raised following flushing of water pipes and the subsequent disturbance of sediment in the water distribution system. At high concentrations, it gives rise to a brown colouration of water.

3.56 There are no iron concentrations listed in the data provided to us by SWWA. The monitoring data for iron available to us during this period were those pertaining to parishes served by the Lowermoor distribution system (see paragraph 3.58). These comprised 147 samples, of which 10 (7%) were in excess of the 1984 WHO Guideline Value of 0.3 mg iron/l. The highest concentration of iron recorded during this period was 9.5 mg/l on 9 July.

3.57 The 1984 WHO Guideline Value for iron was based on the possibility of staining of laundry and sanitary ware at concentrations above 0.3 mg/l. The current standard is 0.2 mg/l, which is set only as an 'indicator parameter'[9].

Results of monitoring - 5 August to 31 December 1988

3.58 We discuss below the water quality data from the Lowermoor distribution area for the third of the time periods (5 August to 31 December 1988). The data for this period were supplied for the parishes of Camelford, Davidstow, St Minver Lowlands, St Minver Highlands, Advent, St Teath, Tintagel, Trevalga, St Endellion, Forrabury and Minster, and St Juliot (see Figure 4 for locations) and are given in full in Appendices 8 to 11.

3.59 The total number of results provided for each contaminant is given in Table 6.

[9] The EU Directive on the Quality of Water intended for Human Consumption differentiates between "Chemical parameters" and "Indicator parameters." In the event of non-compliance with a parameter that has an indicator function, the Member State concerned must consider whether that non-compliance poses any risk to human health in deciding whether remedial action to restore the quality of the water is necessary.

Table 6: Number of sample results from SWWA monitoring data provided for each contaminant, 5 August to 31 December 1988 (Source: Buckingham, January 2004 and May 2004)

Parish	Aluminium	Sulphate	Copper	Zinc	Lead	Mn[a]	Iron
Camelford	287	276	293	293	291	287	292
Davidstow	4	4	5	5	5	5	5
Advent	0	1	1	1	1	1	1
St Minver Highland	54	32	54	0	54	54	54
St Minver Lowland	44	23	44	0	44	44	44
St Teath	207	129	207	207	206	104	207
Tintagel	181	130	214	214	214	97	214
Trevalga	0	0	0	9	8	5	5
St Endellion	85	48	86	85	85	77	85
Forrabury & Minster	48	32	47	47	62	47	47
St Juliot	6	4	6	6	6	6	6
Total no. of samples	**916**	**679**	**957**	**867**	**976**	**727**	**960**

a: manganese

3.60 For aluminium, the percentage of samples with concentrations above the 1984 WHO Guideline Value of 0.2 mg/l were as shown in Table 7. Overall, 30% of samples exceeded the Guideline Value during this period. However, most samples contained less than 0.5 mg aluminium/l. The occasions when aluminium concentrations were highest are given in Table 9.

Table 7: Percentage of sample results between 5 August 1988 and 31 December 1988 containing more than 0.2 mg aluminium/l

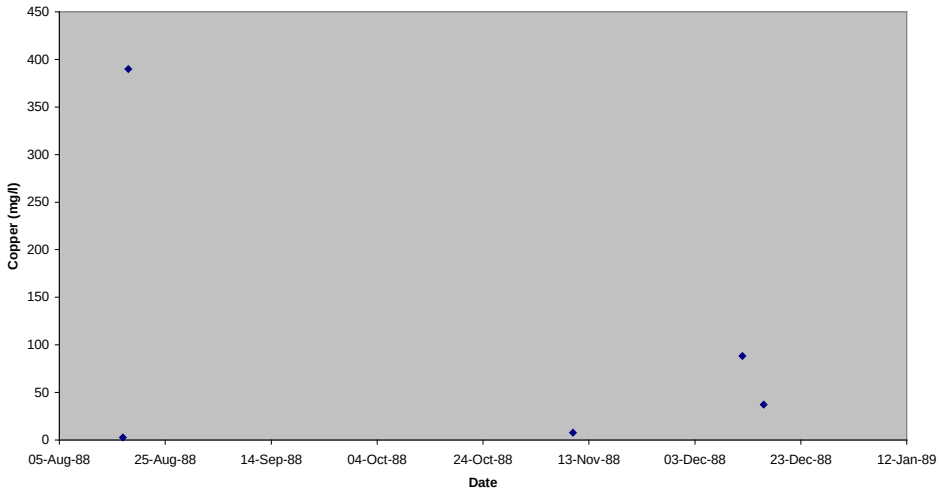
Parish	% Samples above 1984 WHO Guideline Value
Camelford	18
Davidstow	0
St Minver Highlands	17
St Minver Lowlands	5
St Teath	36
Tintagel	36
St Endellion	53
Forrabury & Minster	35
St Juliot	83

3.61 For the other parameters, the number of results which exceeded the relevant 1984 WHO Guideline Value is given in Table 8. The maximum concentration of each parameter during this time period is also given. The data are also shown in Figures 10 to 14. pH was less than 6.5 on only 4 occasions; the lowest pH recorded was 5.9.

Table 8: Number of results exceeding 1984 WHO Guideline Value, 5 August 1988 to 31 December 1988 (Source: Buckingham, January 2004 and May 2004)

Contaminant	Number (%) of results exceeding WHO 1984 Guideline Value	Maximum concentration (mg/l)
Sulphate	0	-
Copper	5 (0.5)	390
Zinc	2 (0.2)	83.4
Lead[10]	14 (1.4)	6.7
Manganese	4 (0.6)	40.6
Iron	35 (3.6)	245.8

Figure 10: SWWA samples which exceeded the 1984 WHO Guideline Value for copper (5 August 1988 to 31 December 1988)



[10] Concentrations for lead are frequently given as <0.08 mg/l as well as <0.05 mg/l. These have been regarded as within the desired limits for lead.

Figure 11: SWWA samples which exceeded the 1984 WHO Guideline Value for zinc (5 August 1988 to 31 December 1988)

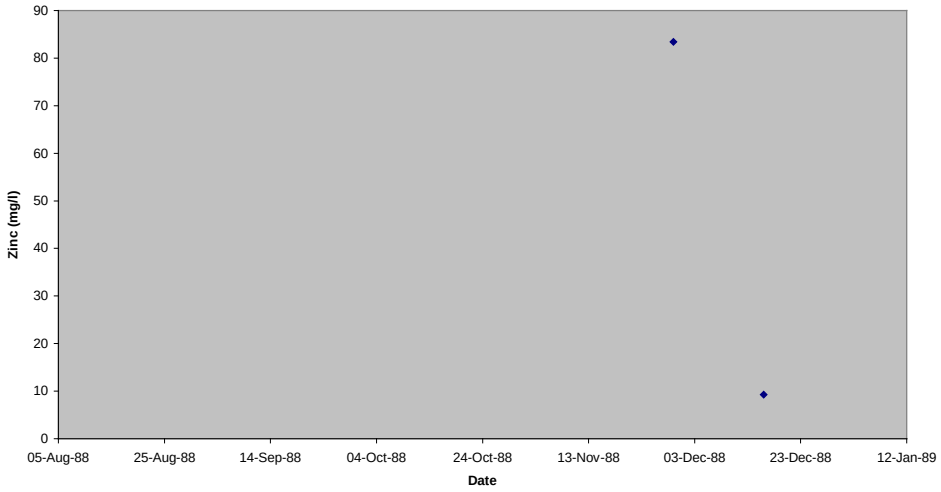


Figure 12: SWWA samples which exceeded the 1984 WHO Guideline Value for lead (5 August 1988 to 31 December 1988)

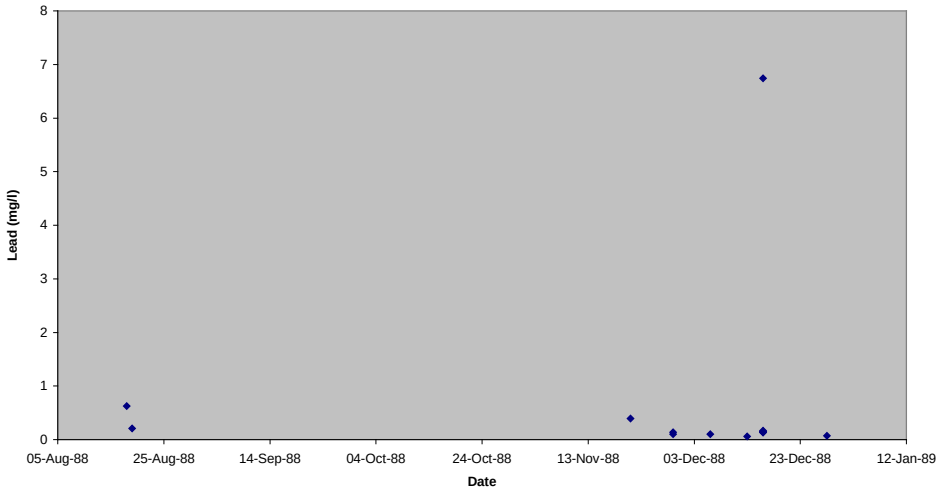


Figure 13: SWWA samples which exceded the 1984 WHO Guideline Values for manganese (5 August 1988 to 31 December 1988)

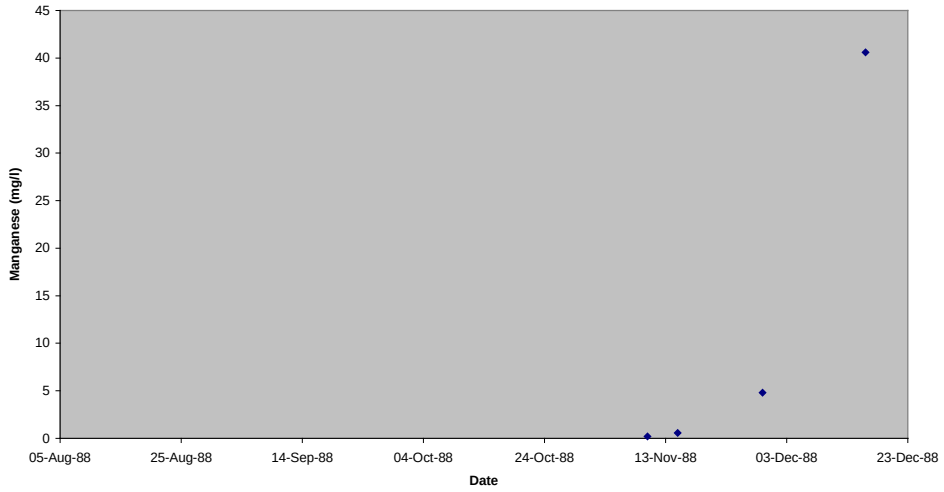
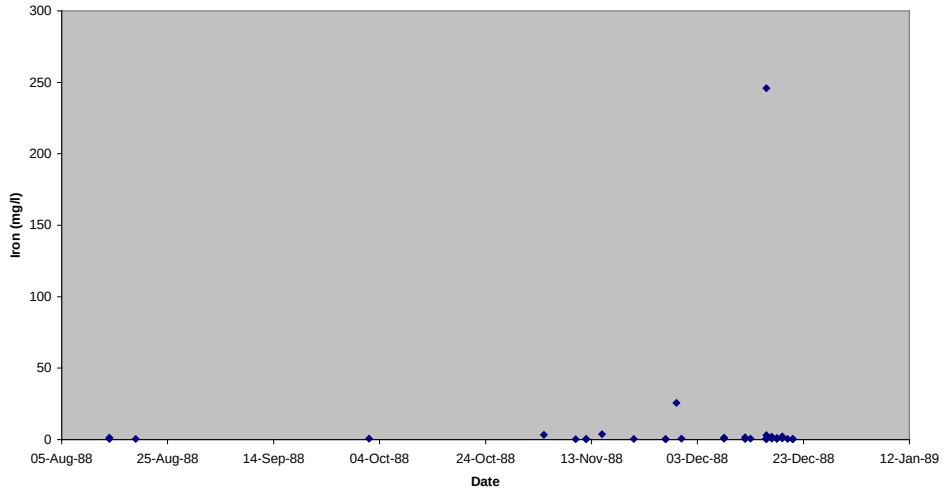


Figure 14: SWWA samples which exceeded the 1984 WHO Guideline Value for iron (5 August to 31 December 1988)



3.62 Table 9 shows the locations and dates of samples with high concentrations of contaminants.

Table 9: Locations and dates of samples where at least one parameter had high concentrations of contaminants between 5 August and 31 December 1988

Date	Parish	Concentration of contaminant (mg/l)						
		Al[a]	Sulphate	Copper	Zinc	Lead	Mn[b]	Iron
18/8/88	St Endellion	N/A	N/A	390	N/A	N/A	N/A	N/A
18/8/88	St Teath	6.9	17	<0.05	1.5	<0.05	0.04	1.04
29/11/88	Camelford	7.8	N/A	0.27	83.4	0.1	4.8	25.6
12/12/88	St Minver Lowlands	2.0	28.4	88.2	N/A	<0.03	0.03	1.5
16/12/88	Camelford	58.7	26.5	37.2	9.3	6.7	40.6	245.8

a: aluminium b: manganese N/A: not available

Results of monitoring - 1989

3.63 We were supplied with monitoring data for 1989 for the parishes of Camelford, Davidstow, St Minver Highlands, St Minver Lowlands, St Teath, Tintagel, St Endellion, Forrabury and Minster and St Juliot. The original data are given in Appendices 8 to 11. The total number of results provided for each contaminant is given in Table 10.

Table 10: Number of sample results from SWWA monitoring data provided for each contaminant in 1989 (Source: Buckingham, January 2004 and May 2004)

Parish	Al[a]	Sulphate	Copper	Zinc	Lead	pH	Mn[b]	Iron
Camelford	46	30	46	48	46	33	49	48
Davidstow	10	11	10	10	10	5	10	10
St Minver Highland	241	161	241	0	241	160	241	242
St Minver Lowland	309	187	304	0	304	190	307	309
St Teath	554	291	543	552	552	276	31	552
Tintagel	385	306	518	518	521	297	143	518
St Endellion	565	343	563	564	568	337	566	566
Forrabury & Minster	587	329	587	587	590	338	587	587
St Juliot	32	24	32	31	32	20	32	32
Total no. of samples	**2729**	**1682**	**2844**	**2310**	**2864**	**1656**	**1966**	**2864**

a: aluminium b: manganese

3.64 The number of results for each contaminant which exceeded the relevant 1984 WHO Guideline Value is given in Table 11. The maximum concentration of each parameter in 1989 is also given.

Table 11: Number of results exceeding 1984 WHO Guideline Value in 1989

Contaminant	Number (%) of results exceeding WHO 1984 Guideline Value	Maximum concentration (mg/l)
Aluminium	160 (5.9)	11.00
Sulphate	0	-
Copper	26 (0.9)	222
Zinc	1 (0.04)	5.3
Lead	40 (1.4)	7.01
Manganese	16 (0.8)	0.75
Iron	157 (5.5)	18.9

3.65 Table 12 shows the locations and dates of samples containing high concentrations of contaminants.

Table 12: Locations and dates of samples where at least one parameter had high concentrations of contaminants in 1989

		Concentration of contaminant (mg/l)						
Date	**Parish**	**Al[a]**	**Sulphate**	**Copper**	**Zinc**	**Lead**	**Mn[b]**	**Iron**
20/1/89	St Endellion	6.1	60.4	1.5	0.44	0.3	0.08	1.8
31/1/89	Camelford	11.0	NA	11.9	0.38	0.14	0.38	18.8
1/2/89	St Endellion	3.2	N/A	0.5	0.16	0.06	0.03	0.6
28/4/89	Forrabury & Minster	2.3	25.6	7	1.0	7.0	0.64	18.9
31/7/89	St Juliot	0.5	17.6	0.03	0.35	<0.003	0.75	1.2
6/10/89	St Minver Lowlands	0.5	N/A	30.9	N/A	5.9	0.05	0.7
9/10/89	St Endellion	1.2	29.0	222	5.3	<0.03	0.18	2.7
13/10/89	St Minver Lowland	0.1	20.7	39.9	N/A	<0.03	<0.01	0.2
3/11/89	St Minver Highland	1.0	14.8	155.1	N/A	0.2	0.1	1.7

a: Aluminium b: Manganese N/A: not available

Monitoring data from other sources

3.66 Some samples were taken by members of the public and analysed at laboratories other than that of SWWA (Cross, 1988, 1989). These are set out in Table 13. The highest aluminium and sulphate concentrations were recorded in a sample collected at a farm in Helstone near St Teath at 5.00am on 7 July 1988. This sample was analysed at 3 different laboratories and concentrations of 460, 620 and 720 mg aluminium/l were reported. A single analysis was reported for sulphate and gave a concentration of 4,500 mg/l and a single analysis for zinc gave a concentration of 9.0 mg/l. This was the highest concentration of zinc recorded in the immediate post-incident period. We were informed that the sample may also have contained 7 mg fluoride/l (Cross, personal communication, 2007). The sample was collected and stored in a bottle which had been washed out several times with the contaminated

water before the final sample was taken. Its reliability has been questioned by Crowther Clayton Associates (November, 2003) on the grounds that it was one of several samples collected by consumers in an available but not necessarily suitable container, and it was stored for some time between sampling and analysis. However, the maximum concentrations of aluminium and of sulphate in these samples are consistent with those previously indicated by South West Water Ltd (see paragraph 3.20). In fact, higher concentrations of aluminium would be anticipated from these samples based on the concentrations of sulphate present. The stoichiometric equivalent concentrations of aluminium calculated from the sulphate concentrations in the 6 July, 7 July (St Teath) and 11 July 1988 samples analysed by Somerset County Analyst are 412, 844 and 28 mg/l, respectively.

3.67 During the consultation exercise, we were informed by one respondent of a series of analyses carried out on water samples taken between September 1988 and July 1992 from a property in Treveighan, Michaelstow. Analyses had been carried out on the same samples by the Somerset Public Analyst for North Cornwall District Council and by South West Water Ltd. The data provided to us by the respondent indicate that there was a consistent problem with discoloured water due to high iron and, occasionally, manganese concentrations. All but one of the samples taken by South West Water Ltd or North Cornwall District Council when they visited the property contained concentrations of aluminium below the 1984 WHO Guideline Value for aluminium. High concentrations of aluminium were found in a sample taken on 29 March 1990 and retained in a bucket containing sediment, which was agitated at the time of sampling. This sample showed a marked discrepancy between the concentration of aluminium reported by South West Water Ltd (10.2 mg/l) and that reported by the Somerset Public Analyst (71.0 mg/l). Small discrepancies in concentrations of metals were found in samples taken from the tap by both South West Water Ltd and by North Cornwall District Council on 11 February 1991. A letter to the householder from North Cornwall District Council states that it is thought by each laboratory that the discrepancies are consistent with what would be expected

Table 13: Water quality data obtained from other sources (Cross, 1988 and Bridges, 1989)

Location where sample taken	Date sample taken	Analytical laboratory	Date of analysis	Results	Any further information
Sportsman Inn, Fore St, Camelford	6/7/88 (night)	Berridge Environmental Laboratories Ltd	7 or 8/8/88	Aluminium = 188 mg/l	Not recorded whether this was hot or cold water sample.
		Somerset County Analyst	8/8/88	Aluminium > 0.5 mg/l Sulphate > 1000 mg/l pH = 4.5	
		Robens Institute	Unknown	Aluminium = 251 mg/l	
		Somerset County Analyst	8/12/88	Aluminium = 190 mg/l Copper = 6 mg/l Sulphate = 2200 mg/l pH = 4.0 Lead = 0.025 mg/l Zinc = 7.1 mg/l	
Mayrose Farm, St Teath	7/7/88(05.00h)	Berridge Environmental Laboratories Ltd	7 or 8/8/88	Aluminium = 460 mg/l	Sample from cold water tap taken by owners of farm
		Somerset County Analyst	8/12/88	Aluminium = 620 mg/l Sulphate = 4500 mg/l pH = 3.9 Copper = 6.3 mg/l Lead = 0.34 mg/l Zinc = 9.0 mg/l Iron = 14.2 mg/l	

		Robens Institute	Not known	Aluminium = 720 mg/l	
Mount Camel	7/7/88 (morning)	Guy's Hospital Poisons Unit	Between 25/7/88 and 17/12/88	Copper = 0.5 mg/l Zinc = 0.5 mg/l Lead = 4 mg/l	Not recorded whether this was hot or cold water sample.
		Somerset County Analyst	8/12/88	Aluminium = 28 mg/l Sulphate = 240 mg/l pH = 4.4 Copper = 0.6 mg/l Lead = 0.025 mg/l	
Outground Mill, Camelford	11/7/88	Somerset County Analyst	8/8/88	Aluminium > 0.5 mg/l Sulphate > 108 mg/l pH = 4.6	Taken from hot water tank filled on 7/7/88.
		Somerset County Analyst	8/12/88	Aluminium = 3.1 mg/l Sulphate = 150 mg/l Copper = 22.5 mg/l pH = 4.7	

from samples of discoloured water containing suspended matter (Zorichak, personal communication, March 1991).

Modelling of pollutant concentrations in Lowermoor Water Treatment Works and in the trunk main system

3.68 In order to assist our understanding of the pollution episode, we commissioned Black & Veatch Ltd (B&V) to model the passage of aluminium sulphate through the treatment works and in the trunk mains system downstream. We recognised that this would not provide definitive answers. All modelling is an approximation of actual events and the accuracy is highly dependent on both the amount and quality of data used to construct it and the assumptions made. The model accuracy is discussed further below. We also recognised that the results produced by the model would not necessarily be correct although the more consistent the modelling results were with the analytical data, the more confidence it would be possible to have in the results. Nevertheless, we considered that it would help our understanding of both the dispersion and time course of the movement of aluminium sulphate through the treatment works and distribution system.

3.69 B&V state that the objectives of their work were:

- To investigate the extent of mixing of the alum within the treatment works.
- To predict the likely profile for concentration against time in the water leaving the works.
- To simulate the propagation of the aluminium sulphate through the network and the likely concentration received at various locations.
- To compare measured water quality data with model data and to identify any anomalies.

3.70 The primary information sources used by B&V were:

- record drawings of the contact and clear water reservoirs. It was assumed that the structure dimensions, top water levels and pipe work arrangements at the time of the incident were as shown on the drawing,
- a 1993 network model of the trunk mains, and
- chart recordings made at the time of the incident for the treatment works inflow and the level of water in the clear water reservoir.

3.71 The modelling was carried out twice: once with the assumption that there was no sludge on the base of the contact tank and the second time with the assumption that the base was covered in a layer of compacted sludge to the depth of the outlet pipe (see paragraph 3.19). The full reports of this work can be found at Appendices 12 and 13.

Modelling by Black & Veatch Ltd of aluminium in the contact tank and clear water reservoir

3.72 The mixing of aluminium sulphate in the contact tank was modelled using computational fluid dynamics (CFD) software which simulated the three dimensional hydraulics and dispersion of aluminium sulphate. The model represented the exact shape of the tank, the flow of water during the incident and the injection of the aluminium sulphate through the inspection cover at the upstream end of the final lane.

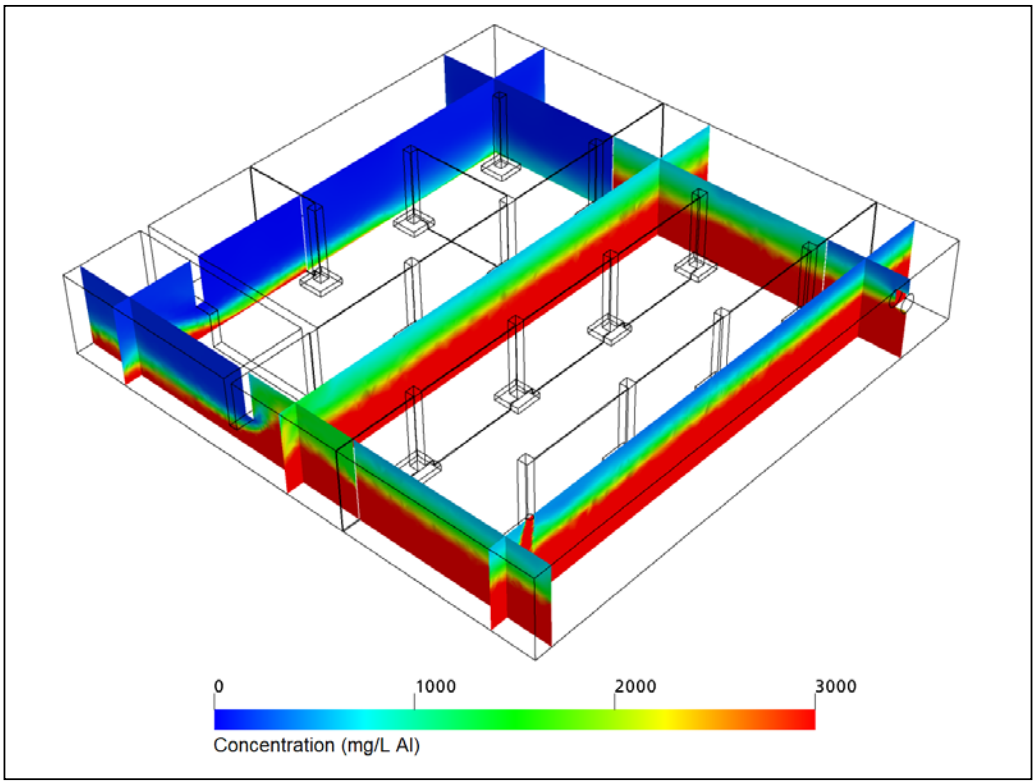
It was necessary for the model to run for two weeks before completion. Computational fluid dynamics was also used to model the three-dimensional hydraulics and dispersion of aluminium in the clear water reservoir.

3.73 Any modelling method will have sources of error and uncertainty as it is a simplified representation of what happened, not an exact record. In the current case, there are uncertainties about how well the CFD model replicates the real behaviour on the day, such as the rate of mixing of the aluminium sulphate, and factors such as the geometry of the contact tank (see Appendix 13, section 5.31 for a detailed discussion of the accuracy of CFD modelling). Nevertheless, B&V state that they have reasonable confidence in their predictions.

CFD modelling: Results without sludge

3.74 The CFD modelling of the aluminium sulphate in the contact tank showed that there was stratification of the concentration of aluminium sulphate in the tank (see Figure 15). Although the aluminium sulphate was added near the outflow of the tank, the model indicated that some aluminium sulphate travelled upstream towards the inlet. This is validated by the pH trace for the contact tank at the time of the incident (Figure 16), which shows a rapid fall in pH at around 5.00pm as the acidic aluminium sulphate reaches the pH monitor at the inlet to the tank. The model also showed that the concentration at the outlet declined rapidly after the discharge ceased. The peak concentration of aluminium at the outlet to the contact tank was predicted to be 1,470 mg/l at 37 minutes, and 82% (by mass) of the aluminium sulphate which was discharged into the contact tank was predicted to have exited the tank after 4½ hours. By extrapolation of the model, it can be estimated that more than 99% of the aluminium would have been discharged from the tank after 12 hours, but it is possible that small amounts remained in the tank for considerably longer.

Figure 15: Modelled dispersion of aluminium in the contact tank at 37 minutes if no sludge present (from Black & Veatch Ltd, 2006)



3.75 B&V state that the results of the modelling of the aluminium sulphate in the clear water reservoir showed that there was some stratification, but much less than in the contact tank. The predicted peak concentration of aluminium in the clear water reservoir was 325 mg/l after 3.7 hours. Consequently, this is the peak concentration predicted to have left the treatment works and the maximum concentration which was predicted to have entered the distribution system. It was predicted that, after 24 hours, 92% (by mass) of the aluminium sulphate which was discharged into the contact tank had left the clear water reservoir (see Figure 17).

Figure 16: Contact tank pH trace, 6 July 1988

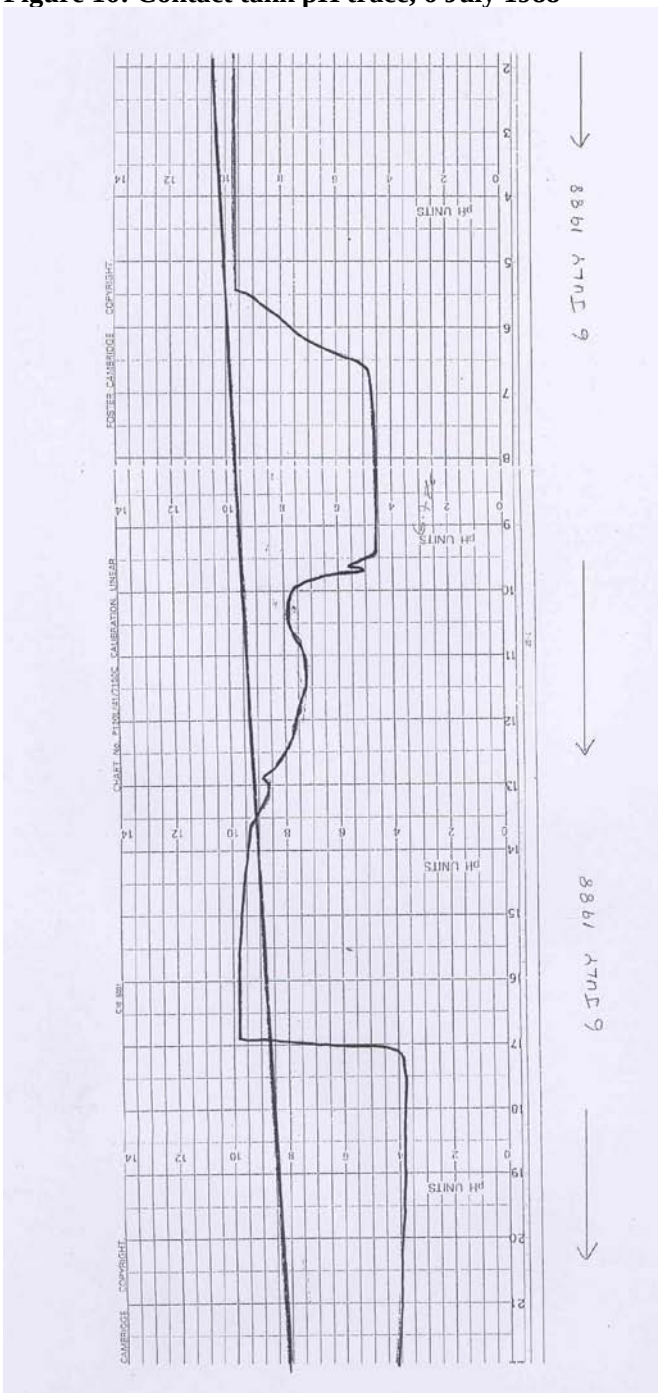
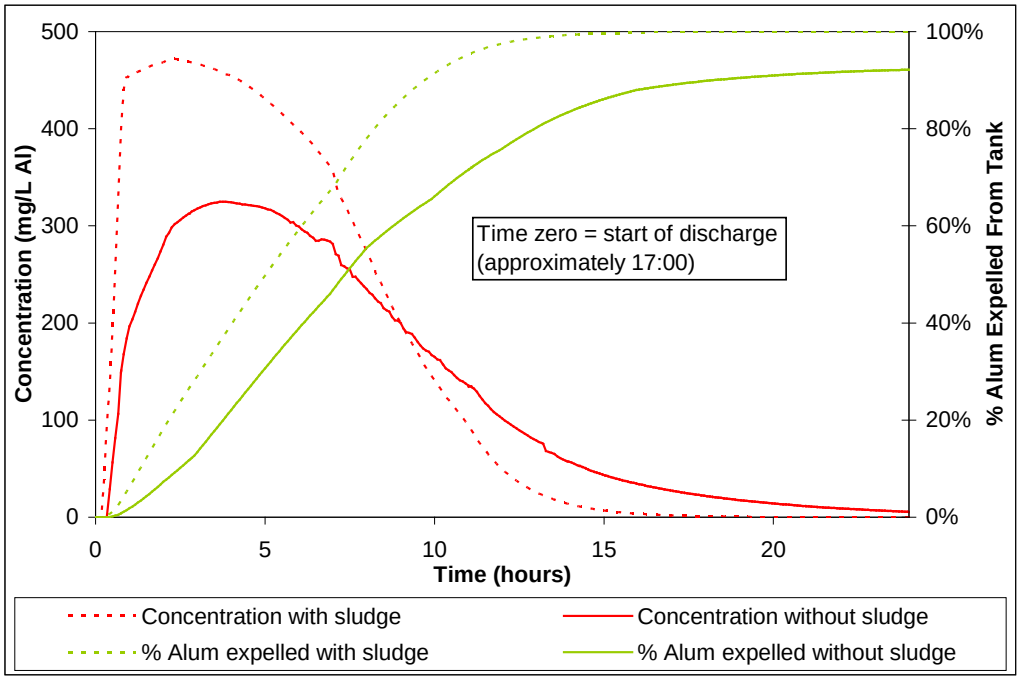


Figure 17: Modelled predicted outlet concentrations of aluminium from the clear water reservoir with and without sludge present in contact tank (from Black & Veatch Ltd, 2006)

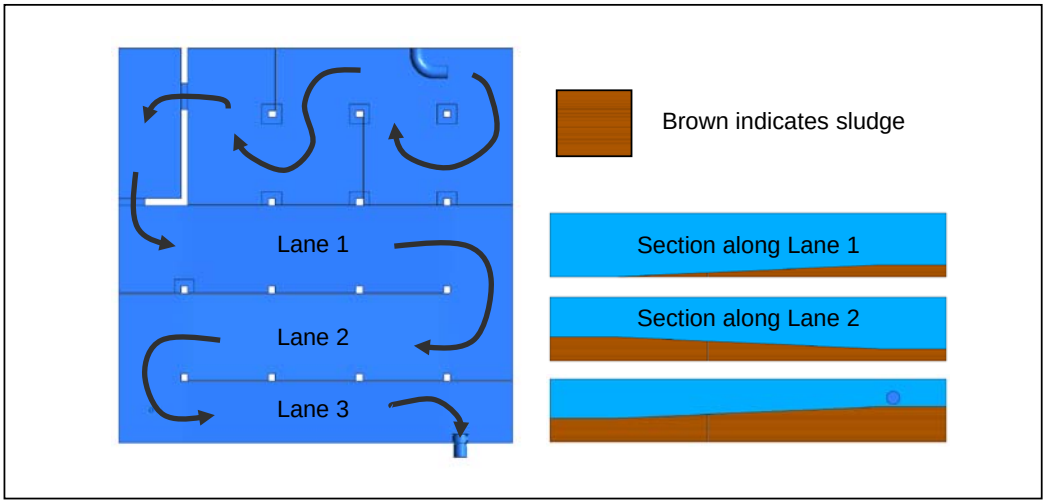


CFD modelling: Results with sludge

3.76 For purposes of the modelling, B&V assumed a constant grade of compacted sludge from zero depth near the inlet end to just below the invert of the outlet pipe (Figure 18). This ramped profile had a significant influence on the predicted aluminium concentrations. The predicted peak concentration at the outlet was higher than when the model was run without sludge present and the aluminium sulphate persisted in the tank for longer. The peak concentration of aluminium in the contact tank was predicted to be 2,730 mg/l, and approximately 75% (by mass) of the aluminium sulphate which was discharged into the contact tank was predicted to have exited the tank after 4½ hours.

3.77 It was assumed that no sludge was present in the clear water reservoir. The increased peak concentration of aluminium sulphate predicted to enter the clear water reservoir accentuated the stratification, to the extent that, although the peak concentration entering the tank was nearly double that predicted were there no sludge in the contact tank, the concentration towards the top of the tank remained lower than than that predicted were there no sludge in the contact tank (see Appendix 13, section 4.4.2). The predicted peak concentration of aluminium in the clear water reservoir was 472 mg/l after 2.5 hours (see Figure 17).

Figure 18: Assumed profile of compacted sludge in contact tank (from Black & Veatch Ltd, 2006)



pH calculations

3.78 The CFD modelling did not model pH so, in their second report (Appendix 13), B&V calculated the impact of the aluminium sulphate on the pH in the contact tank. The pH trace (Figure 16) shows that the pH value in the contact tank fell to approximately 3.8 after the incident. The concentration of aluminium sulphate required to reach this value was calculated to range from 4 to 8 mg aluminium/l, depending on the quality of the water in the contact tank prior to the incident (see Appendix 13). Both models of the contact tank (with and without sludge present) predict concentrations in excess of 8 mg aluminium/l close to the inlet to the contact tank and thus are consistent with the recorded pH value.

Effect of earlier failure of lime pump

3.79 In the early hours of Wednesday 6th July, before the aluminium sulphate contamination incident occurred, there had been a failure in the pre-lime dosing pump (see Figure 2 and paragraph 3.4). This led to a fall in the pH of the water in the contact tank from 9.7 to 4.6 between approximately 5.30am and 6.30am, as shown on the pH trace (Figure 16). The failure was detected and rectified and pH in the contact tank had returned to normal by approximately 3.00pm. We asked B&V to calculate the effect of this pump failure on the pH of the water in the clear water reservoir and the response is included as an addendum to Appendix 13. B&V found it necessary to make some major assumptions in the calculations and emphasise that the results are only indicative. The results indicate that the pH in the clear water reservoir would have fallen to approximately 5 as a result of the pump failure and that it would take 4 to 5 days for it to recover to the usual level.

Modelling by Black & Veatch Ltd of aluminium in the distribution system

3.80 The modelling of the distribution of the contaminated water in the mains was based on a computer hydraulic model, created by B&V in 1993, of the storage and

trunk main distribution systems for the Lowermoor supply zone. There were several limitations in this modelling:

- The modelling only included the Delabole and Rockhead service reservoir but not those at Boscastle, Davidstow, Michaelstow and St Endellion because these were omitted from the 1993 model (see Figure 19). The effect of this was to ignore the effect of retention time, mixing and dilution in the reservoirs omitted.
- Rockhead and Delabole reservoirs are crudely modelled. Predicted concentrations downstream of these reservoirs are unreliable, but are included because they illustrate the effect of mixing and dilution in these reservoirs.
- The smaller distribution pipework feeding Camelford, St Teath and the areas supplied from Boscastle, Davidstow and Michaelstow reservoirs were not included. These were not in the 1993 model and are likely to have undergone modification since 1988. Therefore, the modelling results did not take into account additional retention time in these smaller pipes, or local interconnections enabling local rerouting of supplies. The effect of this, and of the omission of the service reservoirs above, is to underestimate the time of travel to consumers and to reduce the accuracy of the model for locations which are remote from the trunk mains system.
- The models of the contact tank and clear water reservoir simulated a limited period only (typically covering 80% of the aluminium sulphate discharged). Therefore, modelling predictions within the network which occur well after the peak aluminium contamination has passed are based on extrapolated data and, as such, their accuracy will be low.
- It is likely that some pockets of contaminated water persisted in the system for significantly longer than predicted by the modelling, due to contaminated water being trapped in dead end pipe or consumer tanks which are not simulated by the modelling.
- Limited information was available about the location and details of the flushing of the water supply system on the night of the incident.
- All the modelling assumes that the aluminium remains in solution and does not react with other compounds. The transfer of aluminium through the system could have been more intermittent if any of the aluminium formed a precipitate or reacted with other material within the system (e.g. pipes, biological matter or sediment).

Despite these limitations, B&V considered that the modelling illustrates how the wave of contaminated water passed through an assymetric system and gives an estimate of the maximum likely concentration received and the earliest time at which different locations could have received contaminated water.

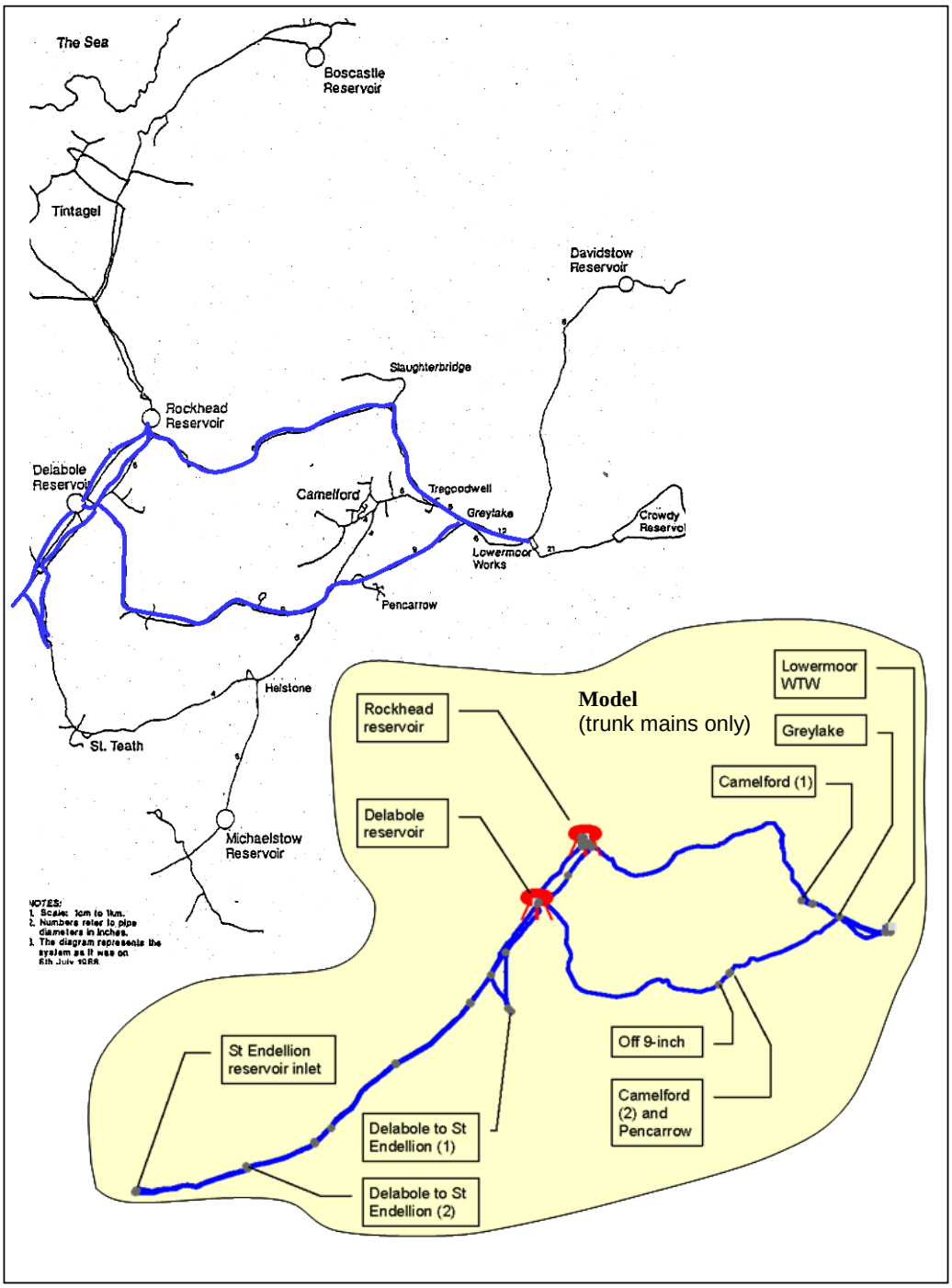
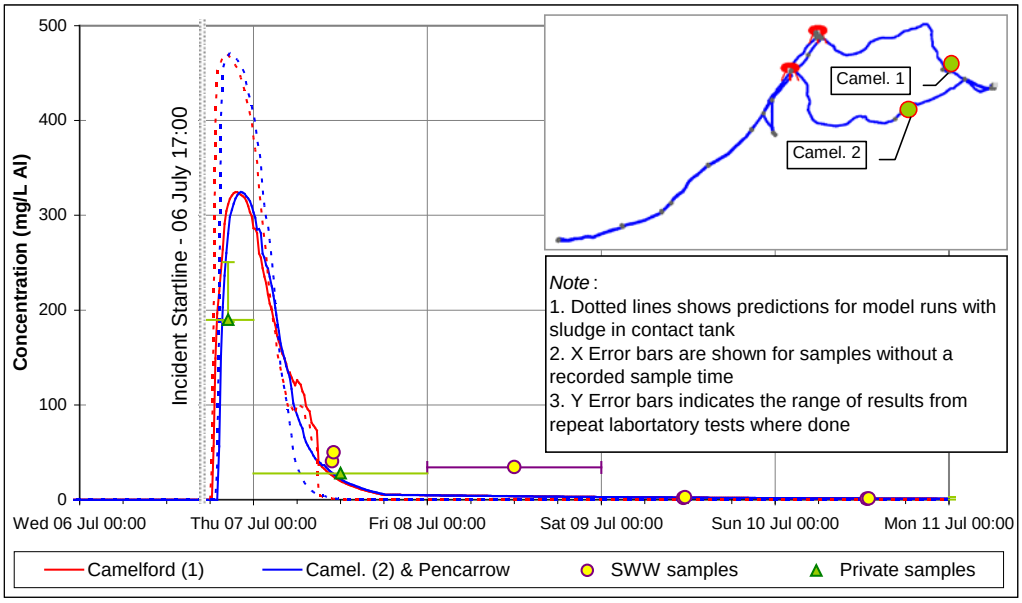


Figure 19: Map showing extent of area modelled (from Black & Veatch Ltd, 2004).

3.81 Figures 20 to 26 show the predicted concentration of aluminium at several locations on the distribution system. In the right hand upper corner of each graph is an inset showing the relevant part of the water distribution system. The predictions generated when the model was run without sludge are shown as solid lines and the predictions generated when it was run with sludge are shown as dotted lines. The

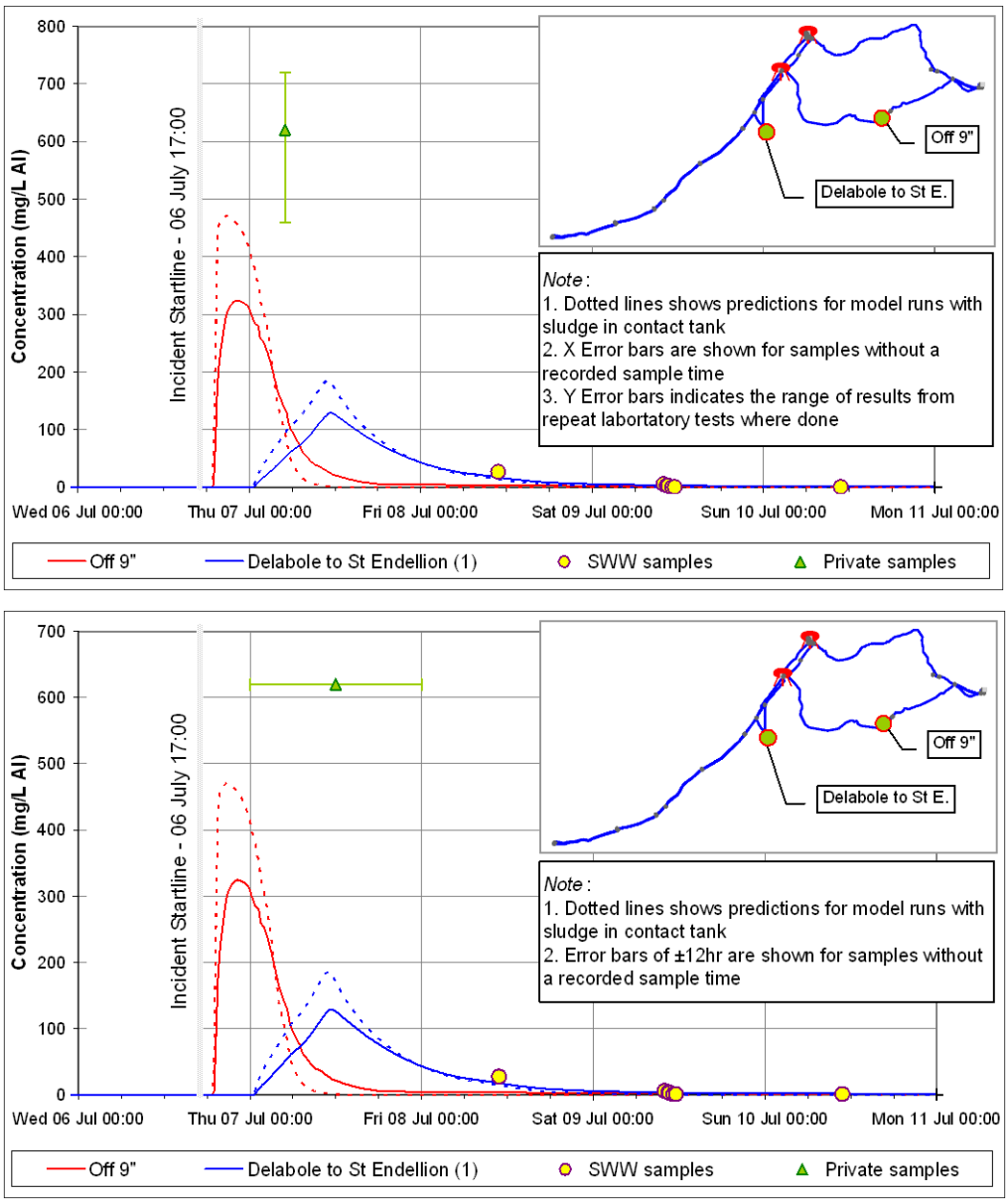
predictions are compared with water quality data from the samples taken by SWWA (yellow dots) and other sources (green triangles) on 6 to 11 July 1988. Given that the precise timing of many of the samples is unknown, the sample data are generally consistent with the model predictions.

Figure 20: Predicted aluminium concentrations in trunk mains in Camelford[a] area (from Black & Veatch Ltd, 2006)



a: Camelford is supplied by two separate feeds from the trunk main network and is therefore represented by demand from two locations in the model (Camel. 1 and Camel. 2).
Note: the vertical line above the private sample taken on the night of Wed 6 July indicates the range of analytical results obtained for this sample.

Figure 21: Predicted aluminium concentration on trunk mains in St Teath area[a] (from Black & Veatch Ltd, 2006)



a: St Teath is supplied from two directions, one from the 6-inch main feeding Helstone and Michaelstow reservoir and the second off the mains between Delabole reservoir and St Endelion

Note: the vertical line above and below the private sample taken on Thurs 7 July indicates the range of analytical results obtained for this sample.

Figure 22: Predicted aluminium concentration on trunk mains in Port Isaac and St Endellion areas (from Black & Veatch Ltd, 2006)

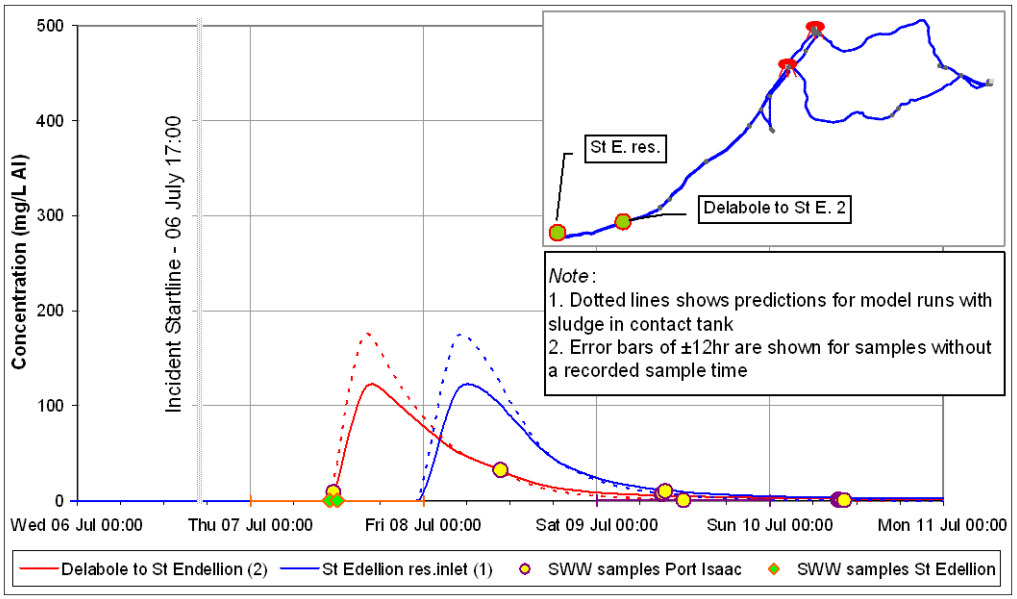
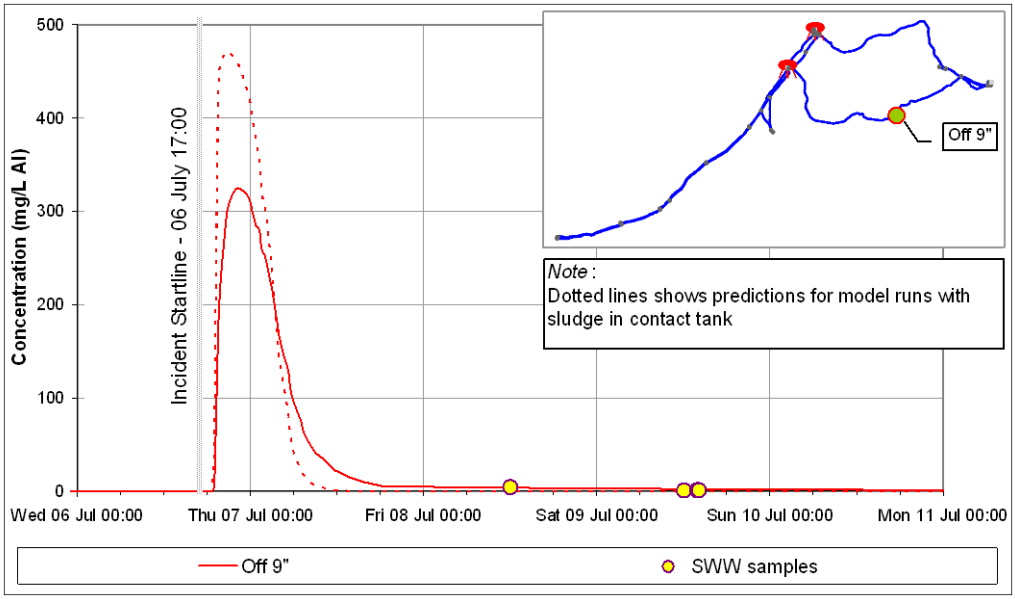


Figure 23: Predicted aluminium concentration on trunk mains in Helstone and Michaelstow reservoir area (from Black & Veatch Ltd, 2006)[a]



a: Port Isaac is supplied off the mains between Delabole reservoir and St Endellion

Figure 24: Predicted aluminium concentration on trunk mains in Delabole reservoir area (from Black & Veatch Ltd, 2006)

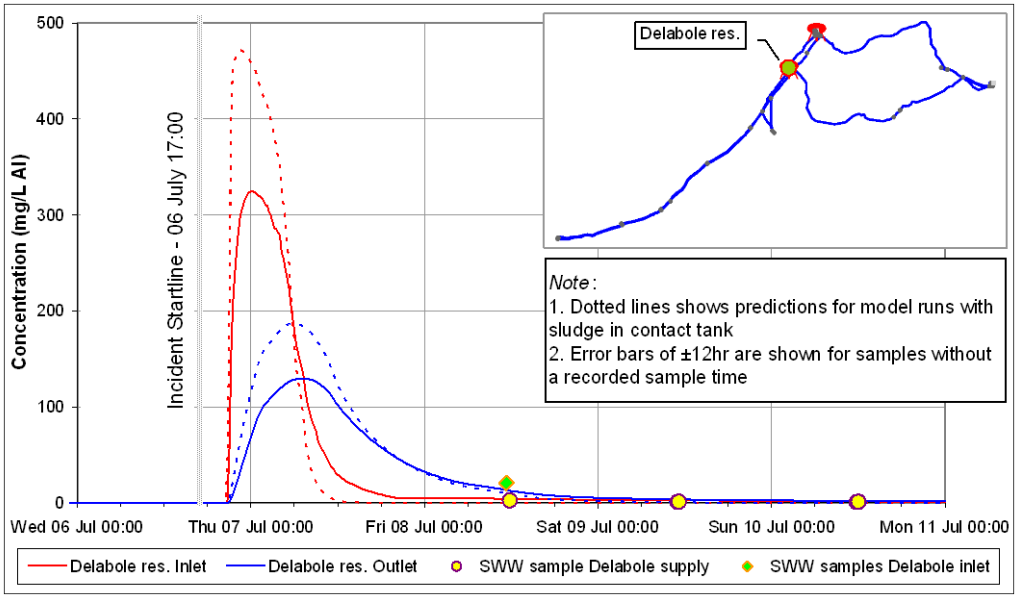


Figure 25: Predicted aluminium concentration on trunk mains in Rockhead reservoir area (from Black & Veatch Ltd, 2006)

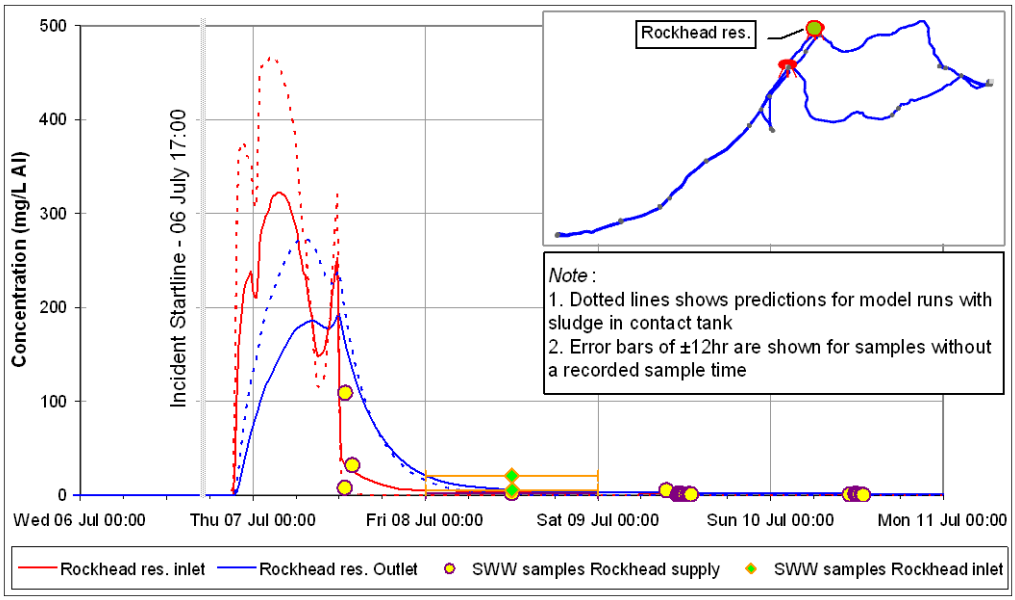
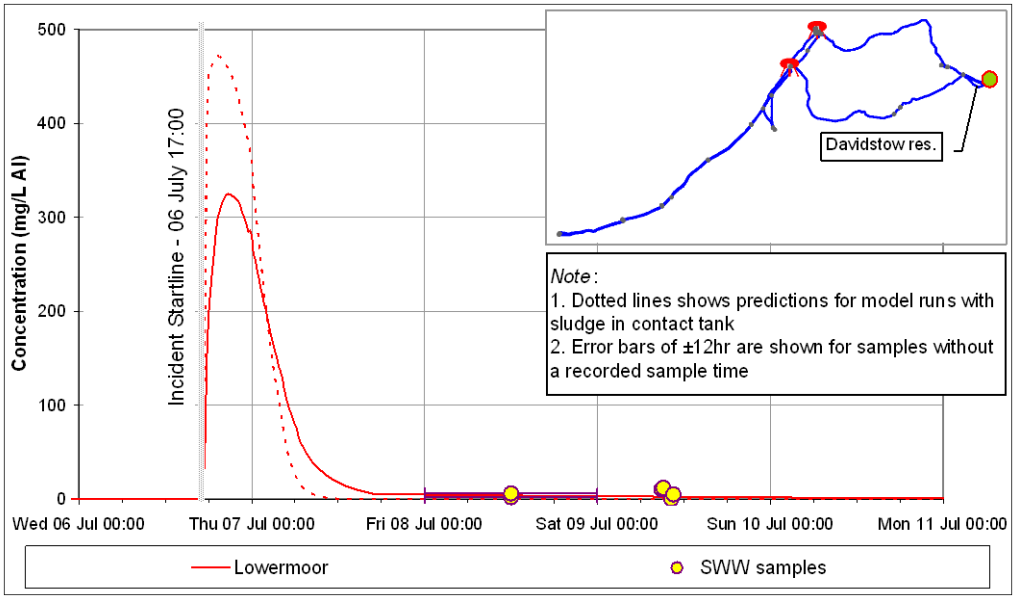


Figure 26: Predicted aluminium concentration on trunk mains in Davidstow reservoir area (from Black & Veatch Ltd, 2006)



3.82 In our discussion with B&V representatives on 6 September 2004 about their initial report (Appendix 12), it was noted that most sampling for aluminium did not begin until after the modelled peak concentrations at the various locations had been reached. The representatives were asked whether the model, and the peak concentrations in particular, could, therefore, be adequately validated. They replied that major differences in the peak concentration would affect the time course of the modelled concentration curves and noted that the water quality data on 8 to 11 July 1988 fitted the curves well. Although it would not be correct to say that the sampled values fitted the model exactly, similar patterns were observed in both the measured and modelled values.

3.83 B&V informed us that it was not possible to rely on model predictions once the peak concentration had passed through the network. Therefore, concentrations in the trunk mains later than 11 July were not reported. The maximum modelled aluminium concentrations each day from 7 to 11 July 1988 are given in Table 14.

Table 14: Maximum modelled aluminium concentration (mg/l) for specific locations (from Black & Veatch Ltd 2004, 2006)

Date	Maximum modelled concentration of aluminium (mg/l)		Location
	No sludge in contact tank	Sludge in contact tank	
6/7/88	325	472	'Off 9 inch' pipe supply St Teath, Helstone and Michaelstow; Camelford; Pencarrow; Greylake.
7/7/88	324	466	Delabole reservoir inlet Rockhead reservoir inlet
8/7/88	129	187	St Endellion reservoir inlet
9/7/88	9	5	Trewetha
10/7/88	5	2	Trewetha and Port Isaac
11/7/88	2	2	Port Isaac

Sludge

3.84 In their second report (Appendix 13), at our request, B&V provided a discussion of the causes and characteristics of sludge in water systems based on their technical knowledge of the water treatment process. This was based on a review by their water treatment specialist and takes into account the treatment processes and water chemistry at the time of the incident. It is independent of the output of the models presented in their report. The review states that raw waters containing turbidity and/or colour, when treated with a coagulant (e.g. aluminium or iron salts), produce suspended solids made up of turbidity, colour solids and aluminium or ferric hydroxide depending on the coagulant used. When lime is used for coagulation pH correction, the impurities in lime (about 4%) and some undissolved lime also contribute to the suspended solids. Over 90% of suspended solids formed in the coagulation process, and those contributed by lime, are removed in clarifiers and a very high proportion of the remainder is removed in the filters. When lime is used for final pH correction, the impurities in lime and undissolved lime usually settle in the contact tank or clear water reservoir depending on the location of the dosing point. The UK standard for turbidity of the final water before 2001 was 4 Nephelometric

Turbidity Units (NTU) and the filtered water turbidity has to be less than this because some allowance needs to be made for the contribution made by lime to turbidity. The suspended solids removed in clarifiers are evacuated from the clarifiers regularly as sludge and solids removed in the filters are cleared from the filters by regular backwashing of the filters.

3.85. B&V state that the density and nature of clarifier sludge is a function of the raw water quality and that the raw water at Lowermoor contains moderate colour and low turbidity. In their opinion, the sludge produced in the clarifier would be gelatinous as it would be made up of colour solids and aluminium hydroxide. The contribution from lime turbidity to the clarifier sludge would be small and the density of the sludge would be similar to that of water. The washwater suspended solids would be fine floculant material and the density would also be similar to that of water. However, as noted in paragraph 3.19, an employee of SWWA at the time of the incident, at a meeting of the Lowermoor Liaison Group on 22 December 1988, stated that the bottom of the tank was filled to the level of the outlet pipe with a solid, compacted deposit of sludge (Cross, 1990a).

Indications of copper concentrations in the contaminated water

3.86 Some of the individuals who spoke with the group reported that, shortly after the incident, the water from their taps was blue coloured and/or that it turned a bright blue colour on addition of soap or other detergents (see box). One Camelford resident told us that, after the incident, a member of the SWWA staff (not identified) advised him that, if the water turned blue when soap was added, it was still affected by the pollution incident. However, following our enquiries we have received no confirmation that this was official advice disseminated by SWWA.

"I got shaved, the water turned bright blue the minute the soap touched it."

"…he held this flannel up…he said ‘This was my wife's, it was pink, and look… it's turned blue and she won’t use it’.”

"I thought 'What has happened to my shower cap because it was white and…instead of being white...it was blue’."

“It was coming out -- the only way to describe it, it was like bloo loo - you know - you put those bloo loos in the toilet and it comes out like bloo loo. That’s what came out my tap.”

"My water was still turning blue in the sink and bath when put with soap for a further three weeks after the incident."

3.87 We commissioned WRc-NSF (Water Research Centre-National Sanitation Foundation, now WRc plc) to investigate the appearance of solutions of aluminium sulphate and copper sulphate over a range of concentrations. In these investigations WRc-NSF used finished water obtained from the Lowermoor Water Treatment Works and water-treatment grade aluminium sulphate. Concentrations of aluminium sulphate up to 3,000 mg aluminium/l (19,000 mg aluminium sulphate/l) did not alter the appearance of the solution to the naked eye. However, in the case of copper sulphate solution, which was tested up to a maximum concentration of 1,000 mg copper/l (2,260 mg copper sulphate/l), the results differed depending on the variables used i.e.

different batches of source water or the types of soap, shampoo or shower gel. On one occasion, a deep turquoise-blue colour was obtained on addition of soap to 1000 mg copper/l, as copper sulphate solution, but not at lower concentrations. However, on other occasions, no colour was obtained even at this high concentration.

3.88 In another set of tests carried out by a member of the subgroup, serial dilutions of copper sulphate solution on cotton cloth were exposed to common household cleaning formulations and the colour of the cloth noted (Cross, 2002). The concentration at which colour first became visible varied with the different types of cleaning products used; the lowest concentration at which a blue or green colour was first seen was 250 mg copper/l. A concentration of at least 2,000 mg copper/l was necessary to produce a bright blue colour in the absence of any cleaning product.

3.89 We conclude from these results that it is not possible to recreate the exact circumstances of the incident in laboratory experiments and that the degree of colouration of the water is not a reliable indicator of copper concentration. However, it does appear that a high concentration of copper is necessary to produce a bright blue colour with soap and other detergents.

Other potential contaminants

3.90 In the consultation exercise, one respondent raised the issue of other contaminants which may have been present in the contaminated water at abnormal concentrations. The respondent queried whether these could have been present because the water treatment process at the Lowermoor plant may have been defective following the aluminium discharge, leading to abnormal discharges of chemicals used in the treatment process. The respondent also questioned whether contaminants from the raw water which had been absorbed into deposits in pipes in the water distribution system could have been dissolved out by the acidic water, thus producing higher than usual concentrations in the water at the tap. In this context, humic/peaty substances, metals such as arsenic, cadmium and barium, and organochlorine residues from sheep dip on moors were suggested as possible contaminants.

3.91 We sought advice from both the Drinking Water Inspectorate and South West Water Ltd. The Drinking Water Inspectorate advised that many of these questions could not be answered from a water quality perspective because relevant data from the time, for example, on concentrations of organochlorine residues, do not exist. They also advised that it was unlikely that the addition of aluminium sulphate to the contact tank would have had any effect on the addition of treatment chemicals such as lime or chlorine, which are added at earlier stages (see Figure 2). No fluoride is added as the supply was not fluoridated. As regards contaminants from the raw water, the coagulation, sedimentation and filtration procedures in the treatment process are intended to remove these (see paragraph 3.4), although there may be trace amounts remaining in solution or some small carry over of floc from the works (Drinking Water Inspectorate, personal communication, May 2005).

3.92 South West Water Ltd. replied that the water samples taken at the time were appropriate to what was believed or known to be the source of contamination. Thus, initially, the problem was believed to be a lime pump failure and appropriate sampling was undertaken. Subsequently, more extensive samples were taken appropriate to the known cause i.e. aluminium sulphate. South West Water Ltd. further stated that there

is no evidence that mains deposits in the Lowermoor supply zones contain detectable concentrations of substances such as cadmium or barium. Arsenic has been detected occasionally in the raw water but at concentrations only just above the minimum limit of detection[11]. The data do not show if the arsenic is soluble or insoluble. If insoluble, it will be removed by the treatment process. Analyses of the raw water used in the water supply show that organic and other trace constituents were at concentrations below the level of detection. Organic compounds in the routine testing of the water were not significant (Buckingham, personal communication, October 2005).

3.93 South West Water Ltd. also commented that the records do not support the suggestion that there were abnormal discharges of chemicals used in the treatment process.

3.94 The consultation response asked about the exact nature of 8% Alum and what other materials are present in trace quantity. The aluminium sulphate which may be used for treatment of water intended for human consumption is specified in a British Standard, which sets maximum levels for toxic chemical impurities. The current British Standard is BS EN 878:2004.

3.95 The consultation response also asked whether the major programme of flushing, scrubbing and relining of the mains after the incident would have resulted in further dissolution of any otherwise insoluble toxic substances and whether the cleaning and lining agents used were in any way harmful. We are informed that chemicals used in water treatment and in the distribution system are subject to a prior approval by DWI. At the time of the Lowermoor incident, DWI was advised in this function by the Committee on Chemicals and Materials of Construction for use in Public Water Supply and Swimming Pools. Therefore, these chemicals will have been assessed for safety before use. Also, South West Water Ltd. told us that when the mains were cleaned and/or relined, the debris which was removed from the mains was not allowed into the supply.

3.96 Concern was also expressed in the consultation exercise about the presence of uranium in sludge in the pipes and the possibility that this was dissolved into the water by the acidic solution of aluminium sulphate. Uranium had been detected in a service pipe residue from the Camelford area at a concentration of 20 ± 8 μg/g and in residues from a kettle at 5.5 μg/g (Powell *et al*, 1995). South West Water Ltd informed us that no Lowermoor samples were analysed for uranium or other radionuclides (Buckingham, personal communication, May 2005). We comment further on uranium in Chapters 6 and 7.

Other water pollution incidents involving aluminium sulphate

3.97 We have been informed of a number of other water pollution incidents involving aluminium sulphate. These are listed in Appendix 14. However, none of these was on the scale of the Lowermoor incident.

Key points

[11] Quantitative data were not provided.

1. The Lowermoor pollution incident occurred on the afternoon of Wednesday July 6, 1988 when a tanker driver deposited a delivery of 20 tonnes of a solution of aluminium sulphate, equivalent to 850 kg aluminium, into the chlorine contact tank at the Lowermoor Water Treatment Works instead of into a storage tank. Although complaints about the water in the distribution system began that evening, the mistake and the source of contamination were not discovered until the morning of Friday 8 July.

2. The contaminated water would have reached different points on the network at different times and peak contaminant levels would also have occurred at different times because it takes time for the water to move from the treatment works through the distribution system.

3. The mains water, contaminated with aluminium sulphate, was sufficiently acidic to cause corrosion of metallic plumbing materials. This could have resulted in increased concentrations of copper, zinc and/or lead in the water in the domestic system. Flushing of the mains distribution system to remove the contaminated water resulted in the disturbance of old mains sediments, mainly deposits of iron and manganese oxides, which could also have been present at increased concentrations in the water at the tap.

4. As a consequence of a large scale flushing exercise at different points in the distribution network, it is not possible to determine whether any particular point on the Lowermoor distribution network did or did not receive contaminated water. The extent and severity of the contamination can only be determined by the analysis of samples of water taken at a particular vicinity and time point. Water quality data from South West Water Authority (SWWA) and its successor, South West Water Ltd., provide information up to the end of 1989 on the concentrations of contaminants in the system, and on the time course of contamination at some sites. However, sequential data are not available to enable us to describe the progress of the aluminium sulphate as it travelled through the distribution system.

5. SWWA data show that, initially, high concentrations of aluminium occurred, up to 109 mg aluminium/l on 7 July 1988. Concentrations fell during the next few days and, after 10 July 1988, most samples were below 1 mg aluminium/l. Thirty per cent of samples taken up to the end of 1988 and 6% in 1989 remained above the 1984 WHO Guideline Value for Drinking Water Quality of 0.2 mg aluminium/l. This Guideline Value was set to avoid deposits in the distribution system and discolouration of water, not because of a risk of adverse health effects above this concentration.

6. Measurement of sulphate concentrations by SWWA began on 9 July 1988. No water samples at any time exceeded the 1984 WHO Guideline Value for Drinking Water Quality of 400 mg sulphate/l, which was set on taste considerations. In the first few days after the incident, water samples were frequently acid, with a pH below 6.5, the minimum level in the 1984 WHO Guideline Value for Drinking Water Quality. This Guideline Value was set as a range from 6.5 to 8.5 to avoid excessive corrosion of the pipework at low pH and a taste and soapy feel to the water at high pH.

7. Measurement of copper, zinc and lead concentrations began on 8 July 1988. In the first month after the incident 15% of SWWA samples exceeded the 1984 WHO Guideline Value for Drinking Water Quality for copper of 1 mg/l. This Guideline Value was based on the possibility of staining of laundry and sanitary ware at this concentration, not because of a risk of adverse health effects. The highest concentrations in the first month after the incident were 20 mg copper/l in a hot water sample and 8.8 mg copper/l in a cold water sample. Subsequently, 0.8% of samples exceeded the Guideline Value, although occasional high concentrations were measured, up to a maximum of 390 mg copper/l. In the first month after the incident, only one of 64 SWWA water samples (1.6%) exceeded the 1984 WHO Guideline Value for Drinking Water Quality for zinc of 5 mg/l which was based on taste considerations, not on a risk of adverse health effects above this concentration. This sample was from a hot water tap and contained 7.83 mg zinc/l. Thereafter, less than 0.1% of samples exceeded the Guideline Value.

8. In the month following the incident, 12% of SWWA samples exceeded the 1984 WHO Guideline Value for Drinking Water Quality for lead of 0.05 mg/l. This Guideline Value was set on health grounds, particularly to protect against effects of lead on the neurological and behavioural development of infants and children. The highest concentrations of lead in the first month were 0.46 mg /l in a hot water sample and 0.22 mg/l in a cold water sample. Up to the end of 1990 a further 1.4% of samples exceeded the 1984 WHO Guideline Value for Drinking Water Quality, with concentrations up to 7 mg lead/l.

9. In the month following the incident, 11% of samples exceeded the 1984 WHO Guideline Value for Drinking Water Quality for manganese of 0.1 mg/l. This Guideline Value was based on the possibility of staining of sanitary ware and laundry above this concentration. The highest concentration of manganese in this period was 1.3 mg/l. Only 0.7% of subsequent samples exceeded the Guideline Value, although occasional high concentrations were measured, up to 40.6 mg manganese/l.

10. In the month following the incident, 7% of samples exceeded the 1984 WHO Guideline Value for Drinking Water Quality for iron of 0.3 mg/l. This Guideline Value was based on the possibility of staining of laundry and sanitary ware above this concentration. The highest concentration of iron in this period was 9.5 mg/l. Subsequently, 5% of samples exceeded the Guideline Value for iron, with concentrations up to 245.8 mg/l.

11. A small amount of water quality data are reported from private samples and some of these showed particularly high concentrations of contaminants. A sample taken in Helstone near St Teath on 7 July contained concentrations of 4,500 mg sulphate/l and 9 mg zinc/l. The aluminium concentration was measured on three different occasions at three different laboratories and results of 460, 620 and 720 mg/l were obtained.

12. We commissioned modelling by consultants of the passage of aluminium sulphate in the treatment works and its propagation through the mains network. We were aware that any modelling method has inherent sources of error and

uncertainty as it is an approximation of actual events, not an exact record, but we considered that it could help us to understand the movement of the aluminium sulphate through the treatment works and in the distribution system. The model was run both with and without the assumption that a layer of sludge was present in the contact tank. This work demonstrated that most of the aluminium sulphate would have left the treatment works within 24 hours. Using the assumption that there was no sludge present, it was predicted that the peak concentration of aluminium entering the distribution system would have been 325 mg/l. Using the assumption that sludge was present, it was predicted that it would have been 472 mg/l. The modelled concentrations of aluminium in the mains network for the period 7 to 11 July 1988 showed good consistency with the majority of the WWA sample data and most of the data from other sources, whether or not there was an assumption that sludge was present in the contact tank. The peak concentrations obtained from modelling with the assumption of sludge present were higher than those obtained with the assumption that there was no sludge.

4. The Assessment of Exposure to Contaminants

Introduction

4.1 In order to assess the likely health impacts of the incident, it is essential to know both the quantity of chemical contaminants which individuals consumed and the duration of exposure to those contaminants.

4.2 Contaminated water from the treatment works would only have entered a household supply from the mains when a tap was opened or a lavatory was flushed. Therefore, contaminated water from the mains would not have entered properties which were unoccupied at the time of the pollution incident. If water contaminated with aluminium sulphate was present in domestic storage tanks, or left standing in household pipes, it is probable that this water would have also contained secondary contaminants (e.g. copper or lead) dissolved into the acidic water from the household plumbing. Thus water from the hot tap, or from storage systems, or both, might have contained some secondary contaminants at higher concentrations than water drawn directly from the mains. An indication of the concentrations to which individuals could have been exposed after the pollution incident can be found in the previous chapter.

4.3 Many individuals who spoke with us commented that particular features of the water distribution system may have affected the concentrations of contaminants delivered to their properties and/or the duration of exposure. Reference was made to features such as 'dog legs', 'spurs' and 'dead ends' in the water distribution system. We have been advised that such features would not be a reason for unusually high concentrations and that, in particular, 'dog legs' would tend to increase the dispersion or mixing of the contaminant and thus lower rather than increase the concentration of aluminium sulphate in the water (Crowther Clayton Associates, 2003; Drinking Water Inspectorate, 2003; Brandt, personal communication, 2004). However, 'dead ends' would tend to extend the period of time over which contaminants would be delivered to a household, because a contaminant will be slowly released back into the domestic system from the 'dead end'. In addition, dilution would have occurred as water with lower concentrations of contaminants replaced water in the 'dead end' of the distribution system. The local demand for water would have affected the rate at which contaminated water was replaced by clean water.

Calculated estimates of exposure by the oral route

Water consumption data

4.4 Some individuals gave us information about the amount of water that they drank during the incident (see paragaphs 5.11 to 5.14). However, because of the difficulty of recalling such details accurately after such a long time, we consider that it would be appropriate in an exposure assessment to use information on average and high levels of tap water consumption obtained from a formal population survey. We have used a survey of tap water consumption in England and Wales carried out in 1995 for the Drinking Water Inspectorate (M.E.L. Research, 1996) in our intake estimates for both adults and children.

Adults

4.5 The average intake of tap water among all age groups surveyed in the M.E.L. survey was 1.14 litres a day (l/day) and the average intake of the highest 2.5% of consumers was stated to be "above about 2.4 l/day". These latter consumers were largely in the older age group (46+ years). We use a figure of 2.4 l/day as a high level intake.

Toddlers

4.6 We have considered the exposures of toddlers, rather than older children, because the lower body weight of this group enables us to carry out a risk assessment based on worst-case intake estimates (see Chapter 7). The average intake of tap water in the 0-5 year age group was 0.5 l/day (M.E.L. Research, 1996). We have used this figure as an average intake for toddlers.

Bottle-fed infants

4.7 A figure of 0.9 l/day has been used for the average intake of tap water by bottle-fed infants, which is the fluid requirement of a 6 kg infant at an intake of 0-150 ml/kg for a 0 to 6 month old baby (Clinical Pediatrics and Child Health, 2001).

Possible intakes from food

4.8 We recognise that one route of exposure to aluminium and other contaminants may have been from food. This could have occurred during food preparation when, for example, salad constituents were washed and food items were cooked in contaminated water. There are no data that allow us to quantify this route of food contamination. Similarly, we have no information about whether, and to what extent, contaminated water was used locally in food manufacture and are unable to quantify potential exposure from this source.

4.9 The observation that ice cream made from milk secreted by cows which drank contaminated water contained an increased concentration of aluminium (see Chapter 5, paragraph 5.189) raises the question of the extent to which food manufactured from milk or meat contained increased concentrations of contaminants. We have no data which would allow an estimate to be made but we can conclude that such a process could extend the period of exposure.

Water quality data

4.10 Most water quality data were provided by SWWA but, as described in paragraph 3.66 and Table 13, members of the public also took water samples for analysis on the 6, 7 and 11 July 1988, i.e. in the first few days after the incident. We have used the results from both SWWA and private samples to estimate exposure to contaminants and we present the estimates separately below.

4.11 Some water samples were specified as “cold water” samples and some as “hot water samples”, but most samples were not specified as one or the other. South West Water Ltd. informed us that, unless specified as a hot water sample, the source was likely to be the cold water system and thus we have assumed that all unspecified samples are “cold water” samples. Although water companies advise against the

consumption of water from the hot tap, some individuals told us that they had filled the kettle from the hot tap. Therefore, where we have water quality data which show higher contaminant concentrations in hot water than in cold water samples, we have calculated contaminant exposures using results from cold water samples and hot water samples separately.

4.12 Data on estimated exposures to each contaminant are presented below, firstly, for the time period 7 July to 4 August 1988 and, secondly, for the period 5 August 1988 to 31 December 1989.

Estimated exposures to contaminants from 7 July to 4 August 1988

4.13 The following tables show calculated exposures to each contaminant from 7 July to 4 August 1988. Separate tables are presented for worst-case estimates based on (a) the maximum concentrations of contaminants measured on any day in SWWA water quality data and (b) on the water quality data from the private water samples. All data are for cold water samples (or samples of non-specified origin) except where specified as data for hot water samples. We emphasise that there is no reason to believe that individuals would have experienced these levels of exposure in all locations nor that they would have been exposed to the highest possible concentration of contaminant on each day. The water quality data for each contaminant are described in detail in the previous chapter. However, as described in paragraph 3.24, because most of the water samples analysed by SWWA were 2 minute flush samples, the monitoring data for the metals dissolved out of the domestic pipework (copper, lead and zinc) may not show the highest concentration which occurred after the incident.

(i) Aluminium

4.14 Tables 15 and 16 indicate that estimated exposure to aluminium was highest on the first four to five days following the contamination incident. The highest estimated exposure is calculated from a private sample; this is four to seven times higher than the highest estimated exposure based on SWWA data, depending on which analytical result is used for the private sample (see Table 16). After 11 July 1988, estimated exposure of both adults and children fell markedly although the concentrations of aluminium in water remained above the 1984 WHO Guideline Value. The estimated worst-case exposures calculated from the SWWA data are also shown in Figures 27 and 28.

Table 15: Estimated worst-case exposures to aluminium (calculated using water quality data from SWWA)

Date[a]	Highest aluminium concentration in water (mg/l)	Exposure (mg/day)			
		Adults		Toddlers	Bottle-fed infant
		Average	*High*		
7/7/88	109.0	124.3	261.6	54.5	98.1
8/7/88	34.5	39.3	82.8	17.3	31.1
9/7/88-10/7/88	11.97	13.6	28.7	6.0	10.8
11/7/88	0.69	0.8	1.7	0.3	0.6
14/7/88	2.0	2.3	4.8	1.0	1.8
18/7/88	1.0	1.1	2.4	0.5	0.9
19/7/88 (Hot water sample)	3.0	3.4	7.2	1.5	2.7
20/7/88	0.73	0.8	1.8	0.4	0.7
21/7/88	2.2	2.5	5.3	1.1	2
23/7/88-24/7/88	1.0	1.1	2.4	0.5	0.9
26/7/88	0.72	0.8	1.7	0.4	0.6
27/7/88-28/7/88	0.64	0.8	1.5	0.3	0.6
29/7/88	1.4	1.6	3.4	0.7	1.3
1/8/88	0.37	0.4	0.9	0.2	0.3
2/8/88	0.55	0.6	1.3	0.3	0.5
3/8/88	0.34	0.4	0.8	0.2	0.3
4/8/88	0.29	0.3	0.7	0.1	0.3

a: no data available for missing dates

Table 16: Estimated exposures to aluminium (calculated using water quality data from non-SWWA sources)

Date	Highest aluminium concentration in water (mg/l)	Exposure (mg/day)			
		Adults		Toddlers	Bottle-fed infants
		Average	*High*		
6/7/88	188-251[a]	214-286	451-602	94-126	169-226
7/7/88	460-720[b]	524-821	1104-1728	230-360	414-648
11/7/88 (Hot water sample[c])	3.1	3.5	7.4	1.6	2.8

a: three separate analyses of this sample gave results of 188, 190 and 251 mg aluminium/l
b: three separate analyses of this sample gave results of 460, 620 and 720 mg aluminium/l
c: no data available for cold water samples

Figure 27: Estimated worst-case exposures to aluminium (mg/day) for adults calculated from SWWA water quality data , 7 July 1988 to 4 August 1988

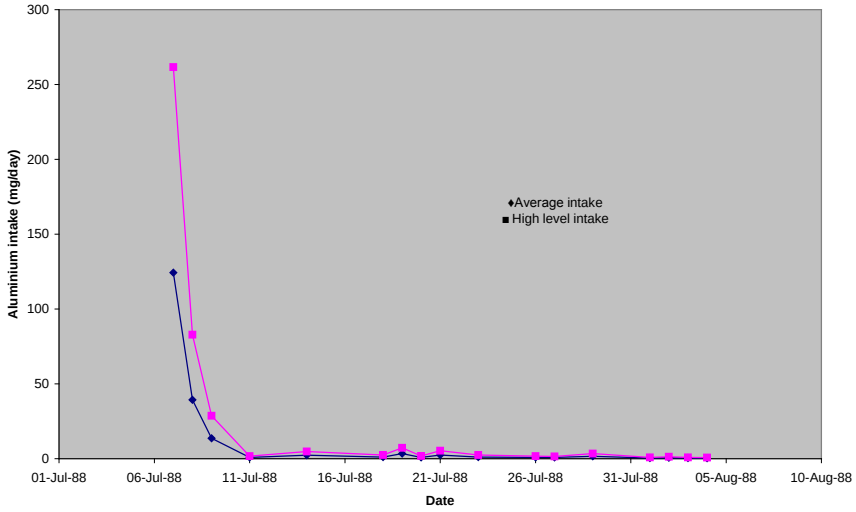
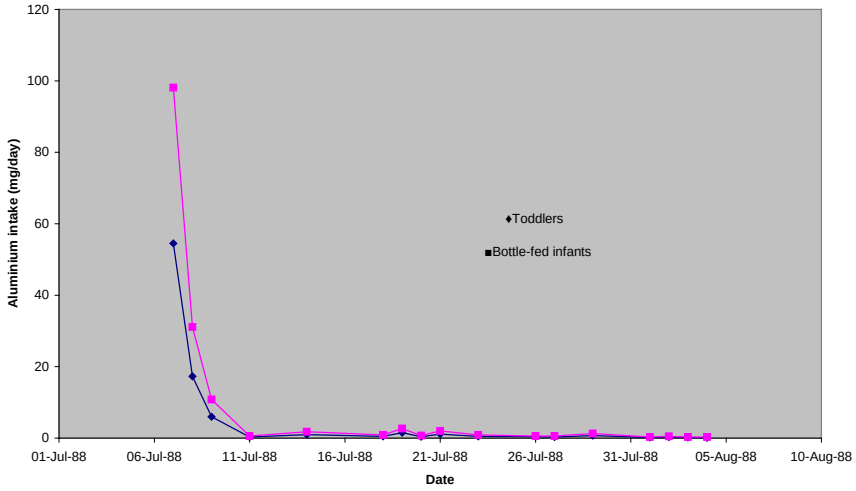


Figure 28: Estimated worst-case exposures to aluminium (mg/day) for toddlers and bottle-fed infants calculated from SWWA water quality data, 7 July 1988 to 4 August 1988



(ii) Sulphate

4.15 It can be calculated that the analysis of sulphate would exceed 400 mg/l only when the concentration of aluminium exceeded 75 mg/l. Three samples exceeded this concentration of aluminium: one taken by SWWA on 7 July which contained 109 mg aluminium/l, and the two private samples taken on 6 and on 7 July 1988. The highest of these contained 4,500 mg sulphate/l. Estimated exposures at this concentration (cold water sample) are calculated to be:

Adult (average): 5,130 mg/day
Adult (high): 10,800 mg/day
Child or infant: 2,250 mg/day
Bottle-fed infant: 4,050 mg/day

(iii) Copper

4.16 The data in Tables 17 and 18 indicate that, as expected, exposures to copper would have been higher from hot water than from cold water. The two private cold water samples were taken earlier than the SWWA samples; together they indicate that high exposures to copper may have occurred on the night of the incident and for the subsequent few days.

Table 17: Estimated worst-case exposures to copper (calculated using water quality data from SWWA)

Date[a]	**Highest copper concentration in water (mg/l)**	**Exposure (mg/day)**			
		Adults		**Toddlers**	**Bottle-fed infants**
		Average	*High*		
8/7/88	1.7	1.9	4.1	0.9	1.5
9/7/88-10/7/88	8.8	10	21.1	4.4	7.9
Hot water sample	20	23	48	10	18
11/7/88	0.05	0.06	0.12	0.03	0.05
Hot water sample	13	14.8	31.2	6.5	11.7
14/7/88-4/8/88	0.8	0.9	1.9	0.4	0.7
Hot water sample	1.1	1.3	2.6	0.6	1.0

a: no data available for 6, 7, 12 or 13 July

Table 18: Estimated exposures to copper (calculated using water quality data from non-SWWA sources)

Date	**Highest copper concentration in water (mg/l)**	**Exposure (mg/day)**			
		Adults		**Toddlers**	**Bottle-fed infants**
		Average	*High*		
6/7/88	6.0	6.8	14.4	3.0	5.4
7/7/88	6.3	7.2	15.1	3.2	5.7
11/7/88[a] (Hot water sample)	22.5	25.7	54	11.3	20.3

a: no data available for cold water samples

(iv) Zinc

4.17 Zinc concentrations were below the 1984 WHO Guideline Value of 5 mg/l at all times in this period, except for concentrations in 3 samples: 7.1 mg/l in a cold water sample on the night of 6 July (private sample), 9.0 mg/l in a cold water sample on 7 July (private sample) and 7.8 mg/l in a hot water sample taken on 19 July (SWWA sample). As monitoring for zinc by SWWA did not begin until 8 July, it is not known whether cold water samples taken by SWWA before this would have shown high concentrations of zinc. The estimated exposures at the three concentrations above are given in Table 19.

Table 19: Estimated exposures to zinc from the 3 samples containing concentrations in excess of the 1984 WHO Guideline Value (calculated using water quality data from SWWA and other sources)

Date	Zinc concentration in water (mg/l)	Exposure (mg/day)			
		Adults		Toddlers	Bottle-fed infants
		Average	*High*		
6/7/88 [a]	7.1	8.1	17.0	3.6	6.4
7/7/88 [a]	9.0	10.3	21.6	4.5	8.1
19/7/88 [b] (Hot water sample)	7.8	8.9	18.7	3.9	7.0

a: private sample
b: SWWA sample

(v) Lead

4.18 Exposure to high concentrations of lead would only have occurred in properties with lead plumbing or where the service pipe from the mains to the house was made of lead. According to South West Water Ltd, "only a small proportion" of dwellings in the supply zone had lead plumbing at the time of the incident (South West Water Ltd, personal communication, 2002). From the data in Tables 20 and 21, high exposures to lead from cold water could have occurred over the four day period of 7 to 10 July 1988. Exposures from hot water samples were higher.

Table 20: Estimated worst-case exposures to lead (calculated using water quality data from SWWA)

Date[a]	Highest lead concentration in water (mg/l)	Exposure (mg/day)			
		Adults		Toddlers	Bottle-fed infants
		Average	*High*		
8/7/88	0.12	0.14	0.29	0.06	0.11
9/7/88-10/7/88	0.22	0.25	0.53	0.11	0.20
Hot water sample	0.46	0.52	1.10	0.23	0.41
11/7/88	<0.05	<0.06	<0.12	<0.03	<0.05
14/7/88-4/8/88	0.009	0.01	0.022	0.005	0.008
Hot water sample	0.02	0.02	0.05	0.01	0.02

a. no data available for 6, 7, 12 or 13 July

Table 21: Estimated exposures to lead (calculated using water quality data from other sources)

Date[a]	Highest lead concentration in water (mg/l)	Exposure (mg/day)			
		Adult		Toddler	Bottle-fed infants
		Average	*High*		
6/7/88	0.025	0.029	0.06	0.013	0.023
7/7/88	4[b]	4.6	9.6	2	3.6

a: the sample taken on 11/7/88 was not analysed for lead
b: a second analysis of this sample by a different laboratory reported a lead concentration of 0.025 mg/l, which is below the 1984 WHO Guideline Value for lead

(vi) Manganese

4.19 Manganese was not analysed in the private water samples. Sixteen of 147 SWWA samples taken during this period exceeded the 1984 WHO Guideline Value of 0.1 mg/l manganese. It is not known whether these are hot or cold water samples. The highest concentration recorded in this period was 1.30 mg manganese/l, which would have led to the following calculated estimates of exposure to manganese:

Adult (average): 1.48 mg
Adult (high): 3.12 mg
Toddler: 0.65 mg
Bottle-fed infant: 1.17 mg

(vii) Iron

4.20 Iron was not analysed in the private water samples. Ten SWWA samples in this period exceeded the 1984 WHO Guideline Value of 0.3 mg iron/l; it is not known whether these are hot or cold water samples. The highest concentration recorded was 9.5 mg iron/l, which would have led to the following calculated estimates of exposure to iron:

Adult (average): 10.8 mg
Adult (high): 22.8 mg
Toddler: 4.8 mg
Bottle-fed infant: 8.6 mg

Estimated exposures to contaminants from 5 August 1988 to 31 December 1989

i) Aluminium

4.21 We were supplied by South West Water Ltd., with 3,645 results from analyses of water samples for aluminium between 5 August 1988 and the end of 1989. In no case was it specified whether the samples were of hot or cold water. From 5 August to the end of 1988, 30% of sample concentrations exceeded the 1984 Guideline Value of 0.2 mg aluminium/l and in 1989 6% of samples exceeded this value. However, most samples contained less than 0.5 mg aluminium/l. The 3 highest concentrations

are given in Table 22, with the exposures which may have resulted from drinking water at these concentrations.

Table 22: Estimated exposures to aluminium from the 3 samples containing the highest concentrations in excess of the 1984 WHO Guideline Value (calculated using water quality data from SWWA)

Date	Highest aluminium concentration in water (mg/l)	Exposure (mg/day)			
		Adult		Toddlers	Bottle-fed infants
		Average	*High*		
29/11/88	7.8	8.9	18.7	3.9	7.0
16/12/88	58.7	66.9	140.9	29.4	52.8
31/1/89	11.0	12.5	26.4	5.5	9.9

ii) Sulphate

4.22 We were supplied by South West Water Ltd., with 2,361 results from analyses of water samples for sulphate for this period. No sample contained more than the 1984 WHO Guideline Value for sulphate of 400 mg/l. Therefore, no exposures have been calculated.

iii) Copper

4.23 We received 3,801 results of analysis of water samples for copper. Thirty-one of these (0.8%) exceeded the 1984 WHO Guideline Value for copper of 1 mg/l, in comparison to 9% of samples taken in 1988 before the incident occurred (see Chapter 3, Table 3). Estimated exposures from the 3 highest concentrations are given in Table 23 but it should be noted that such high values occurred only sporadically, did not show any pattern and we do not know if these are linked in any way to the incident. It is not known if these were hot or cold water samples.

Table 23: Estimated exposures to copper from the 3 samples containing the highest concentrations in excess of the 1984 WHO Guideline Value (calculated using water quality data from SWWA)

Date	Highest copper concentration in water (mg/l)	Exposure (mg/day)			
		Adult		Toddler	Bottle-fed infant
		Average	*High*		
18/8/88	390	445	936	195	351
9/10/89	222	253	533	111	200
3/11/89	155.1	177	372	78	140

iv) Zinc

4.24 Of the 3,177 results we received for zinc concentrations in water samples, 3 exceeded the 1984 WHO Guideline Value of 5 mg/l (0.1%), compared to no samples which exceeded this value in 1988 before the incident occurred (see Chapter 3, Table

3). The estimated exposures resulting from these samples are given in Table 24 but it should be noted that such high values occurred only sporadically, did not show any pattern and we do not know if these are linked in any way to the incident. It is not known if these were hot or cold water samples.

Table 24: Estimated exposures to zinc from the 3 samples containing water in excess of the 1984 WHO Guideline Value (calculated using water quality data from SWWA)

Date	Highest zinc concentration in water (mg/l)	Exposure (mg/day)			
		Adult		Toddler	Bottle-fed infant
		Average	*High*		
29/11/88	83.4	95.1	200.2	41.7	75.1
16/12/88	9.3	10.6	22.3	4.7	8.4
9/10/89	5.3	6.0	12.7	2.7	4.8

v) Lead

4.25 We were supplied by South West Water Ltd., with 3,840 results from analyses of water samples for lead between 5 August 1988 and the end of 1989. In no case was it specified whether the samples were of hot or cold water. Fifty-four results (1.4%) exceeded the 1984 WHO Guideline Value for lead of 0.05 mg/l. This can be compared with 1 of 7 samples (14%) taken in 1988 before the incident occurred (see Chapter 3, Table 3). The results ranged from 0.053 to 7.01 mg lead/l; two other results were particularly high at 5.9 and 6.7 mg lead/l. Estimated exposures from the 3 highest concentrations are given in Table 25 but it should be noted that such high values occurred only sporadically, did not show any pattern and we do not know if these are linked in any way to the incident.

Table 25: Estimated exposures to lead from the 3 samples containing the highest concentrations in excess of the 1984 WHO Guideline Value (calculated using water quality data from SWWA)

Date	Highest lead concentration in water (mg/l)	Exposure (mg/day)			
		Adult		Toddler	Bottle-fed infant
		Average	*High*		
16/12/88	6.7	7.6	16.1	3.4	6.0
6/10/89	5.9	6.7	14.2	3.0	5.3
28/4/89	7.0	8.0	16.8	3.5	6.3

vi) Manganese

4.26 We received 2,693 results of analysis of water samples for manganese. Twenty of these (0.7%) exceeded the 1984 WHO Guideline Value for manganese of 0.1 mg/l, compared to no samples which exceeded this value in 1988 before the incident occurred (see Chapter 3, Table 3). The estimated exposures resulting from the 3 highest concentrations are given in Table 26. It is not known if these were hot or cold water samples.

Table 26: Estimated exposures to manganese from the 3 samples containing the highest concentrations in excess of the 1984 WHO Guideline Value (calculated using water quality data from SWWA)

Date	Highest manganese concentration in water (mg/l)	Exposure (mg/day)			
		Adult		Toddler	Bottle-fed infant
		Average	*High*		
29/11/88	4.8	5.5	11.5	2.4	4.3
16/12/88	40.6	46.3	97.4	20.3	36.5
31/7/89	0.8	0.9	1.9	0.4	0.7

vii) Iron

4.27 We received 3,824 results for iron. Of these, 192 exceeded the 1984 Guideline Value for iron of 0.3 mg/l (5.0 %). This can be compared with 1% of samples taken in 1988 before the incident occurred (see Chapter 3, Table 3). The estimated exposures resulting from the 3 highest concentrations are given in Table 27. It is not known if these were hot or cold water samples.

Table 27: Estimated exposures to iron from the 3 samples containing the highest concentrations in excess of the 1984 WHO Guideline Value (calculated using water quality data from SWWA)

Date	Highest iron concentration in water (mg/l)	Exposure (mg/day)			
		Adult		Toddler	Bottle-fed infant
		Average	*High*		
29/11/88	25.6	29.2	61.4	12.8	23.0
16/12/88	245.8	280.2	589.9	122.9	221.2
28/4/89	18.9	21.5	45.4	9.5	17.0

***In utero* exposures**

4.28 If contaminated water was consumed by pregnant women, it is possible that her unborn child was exposed to contaminants at higher concentrations than usual. Unfortunately, we have no way of quantitating this exposure and thus are unable to provide estimates of *in utero* exposure to individual contaminants.

Modelling of exposure estimates

Modelling by Black & Veatch Ltd

4.29 In Chapter 3 (paragraphs 3.68 to 3.85), we described the modelling which we commissioned from Black & Veatch Consulting Ltd (B&V) of the passage of aluminium sulphate through the treatment works and in the trunk mains system. If the model was run with the assumption that no layer of sludge was present on the base of the contact tank, it estimated that the peak concentration of aluminium which left the works was 325 mg/l. If it was run with the assumption that the bottom of the tank was covered in a layer of sludge, the peak concentration of aluminium was estimated to be 472 mg/l. The maximum contaminant concentration at specific sites

from 7 to 11 July 1988 was also modelled (see Chapter 3, Table 14). The exposures at these modelled concentrations are shown in Tables 28 and 29.

Table 28: Estimated worst-case exposures to aluminium if it is assumed that there was no sludge in the contact tank (calculated using results of modelling by Black & Veatch Ltd, 2004)

Date[a]	Maximum modelled aluminium concentration in water (mg/l)	Estimated exposures to aluminium (mg/day)			
		Adults		Toddlers	Bottle-fed infant
		Average	*High*		
6/7/88	325	371	780	163	293
7/7/88	324	369	778	162	292
8/7/88	129	147	310	65	116
9/7/88	9	10	22	5	8
10/7/88	5	6	12	3	5
11/7/88	2	2	5	1	2

Table 29: Estimated worst-case exposures to aluminium if it is assumed that there was a layer of sludge on the base of the contact tank (calculated using results of modelling by Black & Veatch Ltd, 2006)

Date	Maximum modelled aluminium concentration in water (mg/l)	Estimated exposures to aluminium (mg/day)			
		Adults		Toddlers	Bottle-fed infant
		Average	*High*		
6/7/88	472	538	1133	236	425
7/7/88	466	531	1118	233	419
8/7/88	187	213	449	94	168
9/7/88	5	6	12	3	5
10/7/88	2	2	5	1	2
11/7/88	2	2	5	1	2

Modelling of exposures by Crowther Clayton Associates, Ltd.

4.30 We were also informed that an analysis had been carried out in 1991 for South West Water Ltd as part of its preparation for a legal action. The objective was to prepare an assessment of the probable concentrations of contaminants consumed by specific individuals during the period of the incident. South West Water Ltd., provided us with the report of this analysis (Crowther Clayton Associates, 1991), and it is attached at Appendix 15. The identities of the individuals were removed from the copy of the report for reasons of confidentiality.

4.31 The report included data on modelled intakes of aluminium, sulphate, copper, zinc and lead for 10 individuals from three areas. The pH of the water supply in these areas was also modelled. The areas are:

Area A. St Minver/Port Isaac/New Polzeath, which was served from the St Endellion service reservoir.

Area B. Delabole/Tintagel/Boscastle, which was served from the Delabole and Rockhead service reservoirs.
Area C. Camelford, which was served directly from the Lowermoor site.

4.32 The model was in the form of a mathematical equation consisting of two terms which describe the dispersion of the aluminium sulphate when it entered the water supply (Crowther Clayton Associates, 2003). The equation was then fitted to the monitoring data from SWWA, making the assumptions that the measurements made within a particular area were representative of the whole of that area, and that all localities within each area were separated by only 2 to 4 hours of "flowing time". Maximum and minimum curves were fitted to the output data and from these it was possible to estimate the mean, minimum and maximum concentration values on different days.

4.33 Monitoring data were taken from the sampling and analysis programme carried out by SWWA after the incident in the relevant areas. The sampling data were considered to be representative of the concentrations of contaminants received by households in Areas A, B and C (see paragraph 4.31). Concentrations measured in water from hot water sources were not used. Two reasons were given for this: "Firstly, it is widely accepted that the only tap from which water should be drunk is the tap in the kitchen which is fed directly from the mains; all other taps, in most houses in England, are supplied from a tank in the roof, and this can be subject to contamination from such things as rodents and birds. It …should not be used for drinking purposes…Secondly, the solubility of copper, zinc and lead in hot water is different from solubilities in cold water, and thus the data are qualitatively of a different class, and to include them would introduce a distortion into the analysis" (Crowther Clayton Associates, 1991).

4.34 Where provided by the 10 individuals, tap water consumption estimates were based on this information. Where no estimates of tap water consumption were available i.e. the individual stated that they drank "normal amounts", the report used a default value of 2 litres water/day.

4.35 The output data from the model show that mean aluminium intakes were highest during the first 2-3 days after the incident (7-9 July 1988), with a highest mean value of 221.4 mg/day. Intakes then fell markedly. On 31 July 1988, they ranged from 0.5-1.3 mg aluminium/day and by mid August 1988 from 0.4 to 0.8 mg aluminium/day. The highest and lowest modelled intakes for the 10 individuals are presented in Figures 29 and 30. It should be noted that these results only apply within the limitations of the model for the 10 individuals in the specific areas in which they lived.

4.36 For sulphate, the report states that none of the samples taken by SWWA showed concentrations in excess of the EC Maximum Allowable Concentration (MAC)[12] of 250 mg/l. However, there were no SWWA water quality data for sulphate for the period 6-8 July 1988 and, as a consequence, these levels were estimated from the aluminium concentrations. On this basis, the authors conclude

[12] Maximum Admissible Concentrations (MACs) are set in EC Directives for Water Quality and are usually based on WHO Guideline Values. The authors of the modelling report used MACs rather than WHO Guideline Values as comparison values for the results.

that, for 6 individuals, "it is not possible to say that (these individuals) ingested concentrations in excess of the acceptable limit". For the other 4 individuals during this early period, the authors estimate that intakes may have been from 0.684 to 1.2 g sulphate/day on 7 July, the only day on which the MAC could have been exceeded.

Figure 29: Maximum modelled intake of aluminium for 10 individuals (from Crowther Clayton Associates, 1999)

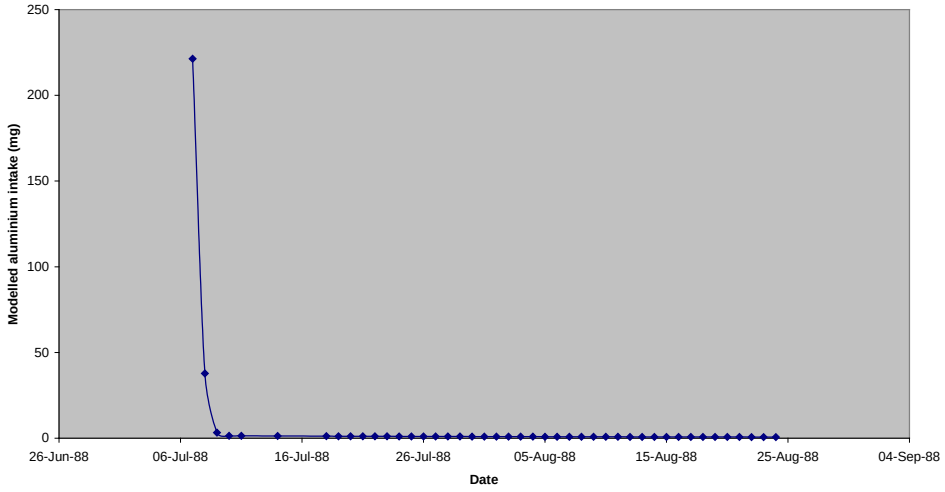
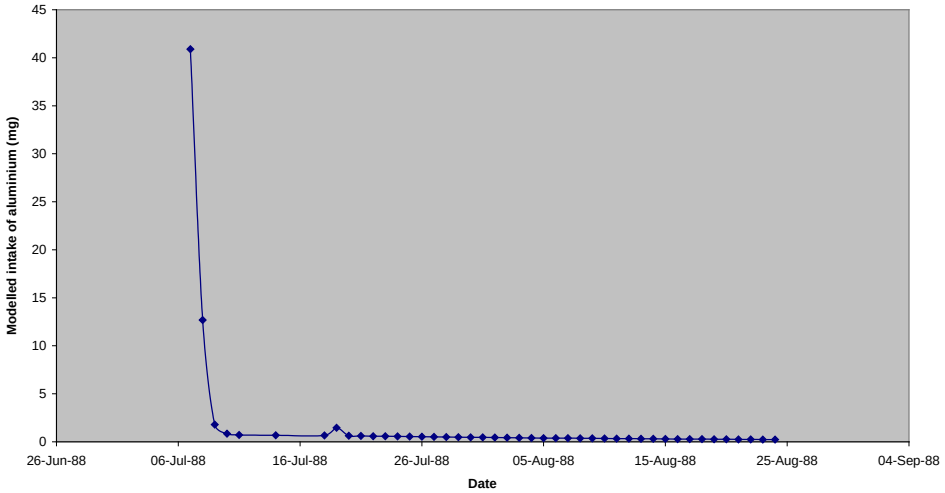


Figure 30: Minimum modelled intake of aluminium for 10 individuals (from Crowther Clayton Associates, 1999)



4.37 The report states that, in all 3 areas, "all samples for copper and zinc showed levels for these two metals at levels very substantially below the EC MAC"[13] although we noted that, in the results for Area A, one sample taken on 9 July 1988 contained a concentration of 8.8 mg copper/l. The authors concluded that "The daily intake of copper and zinc was thus always well below the levels acceptable."

[13] These MAC for copper at the time was 3 mg/l and that for zinc was 5 mg/l.

4.38 For individuals in the St Endellion area, the authors also concluded that "The daily intake of lead was also almost certainly well below the levels considered acceptable, the only uncertainty being those 13 occasions when the concentration was recorded as <80 µg/l (<0.08 mg/l). If the concentration had been 80 µg/l on those three days then (intakes) on those 3 days would have been less than 136 µg *(one individual)*, less than 160 µg *(three individuals)* and less than 227 ug *(one individual*)." In Area B (Delabole and Rockhead), there were 4 days on which the lead concentration exceeded the EC MAC (0.05 mg/l) and several days when the concentrations were recorded as <0.08 mg/l. The author estimated that mean intakes on these days were up to 0.174 mg for the 4 individuals concerned and maximum levels up to 0.440 mg. In the Camelford area, there were 3 days on which the lead concentration was recorded as <0.80 mg/l. The authors estimated that this would have led to a possible intake on those 3 days (if the level was 0.08 mg/l) of up to 0.16 mg/day..

Dermal exposures

4.39 We considered whether individuals bathing or showering in contaminated water might have absorbed contaminants through the skin. A review of the scientific literature showed that absorption of metal ions from aqueous solutions of metal sulphate salts through intact skin is negligible (Fullerton *et al*, 1986; Tanojo H *et al*, 2001).

4.40 We were informed that it was very hot in July 1988 and that many people may have been suffering from sunburn at the time of the incident. We therefore considered the impact of this on likely dermal exposure to contaminants in the water. We sought advice from Dr David Gould, Clinical Director of the Cornwall Dermatology Research Group, Treliske Hospital on two points: firstly, whether sunburn might, by damaging pain receptors in the skin, make people less sensitive to the discomfort of bathing or showering in the acidic water and, secondly, whether sunburnt skin would absorb metal ions and other contaminants more readily than normal skin.

4.41 Dr Gould advised us that he expected that sunburned individuals exposed to acidic water, as in the Lowermoor incident, would experience more pain and discomfort rather than less. This would tend to reduce the potential for dermal exposure. On the second point, Dr Gould advised that any insult to the skin which damaged barrier function will lead to increased absorption of anything placed on the skin surface and that severe sunburn could damage this barrier function. Therefore, in principle, if severely sunburned individuals had been able to tolerate the discomfort of showering or bathing in the acidic water, some dermal absorption of metal ions may have occurred. However, such absorption was likely to have been unimportant compared to that resulting from oral exposure.

Blood concentrations of aluminium

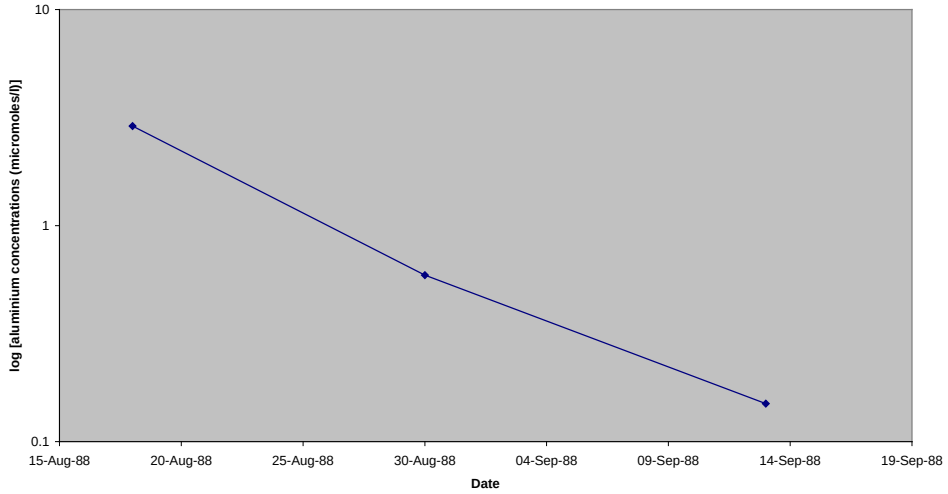
4.42 In Chapter 5 we discuss the studies which report the analyses of samples of blood and other tissues after the incident. One of the respondents to the consultation on our draft report provided data on aluminium concentrations in serum samples taken from a named individual on 3 dates following the incident. The individual lived in Tintagel at the time. The results are given in Table 30:

Table 30: Serum aluminium concentrations in an individual from Tintagel

Date	Aluminium concentration (µmoles/l)
18/8/88	2.89
30/8/88	0.59
13/9/88	0.15

4.43 As shown in Figure 32, a logarithmic plot of these concentrations against time is linear, with a half-life of 6 to 7 days. The plot was extrapolated back to the time of the incident and indicates an initial serum aluminium concentration of 167 µmoles/l, although it is necessary to be cautious about this figure when extrapolating from only 3 points. This figure is similar to the serum concentration of aluminium found in individuals with dialysis dementia (see Chapter 6, paragraph 6.39). The individual informed us verbally on 4 April 2002, that a diagnosis of "…massive kidney damage…" had been made. We are informed that the individual is not receiving dialysis treatment. No information was available on the individual's intake of aluminium from other sources.

Figure 31 Serum aluminium concentrations (micromoles/l) in an individual from Tintagel, 18 August 1988 to 13 September 1988



4.44 The second report of the Lowermoor Incident Health Advisory Group (LIHAG) compared the aluminium concentrations of specimens collected up to one year after the incident from individuals who were in the Lowermoor area at the time. The laboratories concerned were Southampton, Birmingham, Leeds and Kings (Lowermoor Incident Health Advisory Group, 1991). Reported concentrations in the samples sent to the Surrey laboratory were higher than those sent to the other laboratories. LIHAG concluded that contamination was the most likely explanation for this result. When we contacted the analyst for his comments, he replied "…when we found increased concentrations in samples sent to us we would request repeat samples and provided the instructions and specimen containers to ensure that contamination would be minimised. Most of the repeat samples gave results that were consistent with the first samples, although there were some where this was not the case…" (Taylor, personal communication, November 2005).

Key Points

1. In order to assess the likely health impacts of the incident, it is essential to know both the quantity of chemical contaminants which the individuals consumed and the duration of exposure to those contaminants.

2. Contaminated water from the treatment works only entered a household supply from the mains when a tap was opened or a lavatory was flushed. Factors which are likely to have affected the amount of contaminant in the water include whether water used for drinking was stored in tanks or left standing in household pipes for some time before use, and whether water from the hot tap was used for drinking. Both may have increased the concentrations of contaminants which dissolved into the water from the domestic plumbing materials. Also, properties near a 'dead-end' in the distribution system may have received contaminated water over a more extended period of time than other properties. However, features of the distribution system such as 'spurs' or 'dog legs' would not have led to increased or more extended exposures.

3. Using the results of analyses for water quality from the time of the incident until the end of 1989, we have estimated both average and high level oral exposures to contaminants for adults and average exposures for toddlers and for bottle-fed infants. To do this, we have used data on water consumption by adults and young children from a formal survey of tap water consumption carried out in 1995, and established intakes of fluids for bottle-fed babies. We have not included possible intakes of contaminants from cooking nor from food manufacture as we cannot quantify this. We are unable to provide estimates of *in utero* exposure to individual contaminants because we have no way of quantitating this exposure.

4. We have multiplied the water intakes by the maximum concentration of each contaminant measured on each day to obtain worst-case estimates of either "high level" or average exposures for adults, and average exposures for toddlers and bottle-fed infants. However, we emphasise that there is no reason to believe that an individual would have received water with the highest concentration of contaminant on each day. We have used the results of analyses of hot water samples where these exceed the values for cold water samples, to give the worst case estimate.

5. The results indicate that, for **aluminium**, the exposures would have been highest on the first four days following the contamination incident. The estimated worst-case exposures based on a water quality data from SWWA are 261.6 mg/day for adults, 54.5 mg/day for toddlers and 98.1 mg/day for bottle-fed infants. The estimated worst-case exposures based on a private water sample are between 1,104 and 1,728 mg/day for adults, between 230 and 360 mg/day for toddlers, and between 414 and 648 mg/day for bottle-fed infants. Estimated exposures then fell markedly within the next 4 weeks, although 30% of samples up to the end of 1988, and 6% of samples in 1989 exceeded the 1984 WHO Guideline Value of 0.2 mg/l. However, most samples contained less than 0.5 mg aluminium/litre. The highest concentration recorded in this period could have

given rise to high level exposures of 140.9 mg aluminium/day for adults; 29.4 mg/day for toddlers and 52.8 mg/day by bottle-fed infants.

6. Only two water samples contained concentrations of **sulphate** in excess of the 1984 WHO Guideline Value of 400 mg/l. These were private water samples taken on 6 and 7 July 1988. The highest concentration of 4,500 mg sulphate/l could have given rise to estimated exposures of 10,800 mg/day for adults, 2,250 mg/day for toddlers and 4,050 mg/day for bottle-fed infants.

7. The results for **copper** indicate that exposures could have been high for the first few days after the incident. Estimated worst-case exposures in this first month, using water quality data from SWWA, are calculated as 48 mg copper/day for adults, 10 mg/day for toddlers and 18 mg/day for bottle-fed infants, based on the concentration of copper found in a hot water sample. After the first month, 0.8% of samples taken up to the end of 1989 exceeded the 1984 WHO Guideline Value for copper of 1 mg/l. The highest of these would have given rise to an exposure of 936 mg copper/day for adults, 195 mg/day for toddlers and 351 mg/day for bottle-fed infants.

8. In the first month after the incident, only 3 samples contained a concentration of **zinc** in excess of the 1984 WHO Guideline Value of 5 mg/l. Estimated exposures from the highest of these could have been 21.6 mg zinc/day for adults, 4.5 mg/day for toddlers and 8.1 mg/day for bottle-fed infants. Thereafter, only 0.1% of results exceeded the Guideline Value. The highest of these could have given rise to an exposure of 200.2 mg zinc/day for adults, 41.7 mg/day for toddlers and 75.1 mg/day for bottle-fed infants.

9. Exposure to high concentrations of **lead** would only have occurred in properties with lead plumbing or where the service pipe from the mains to the house was made of lead. South West Water Ltd., state that only a small proportion of dwellings in the supply zone have lead plumbing but monitoring was carried out in some of these properties. The results indicate that high exposures to lead could have occurred between 7 and 10 July 1988. Based on water quality data from SWWA, the estimated worst-case exposures to lead are 1.1 mg/day for adults, 0.23 mg/day for toddlers and 0.41 mg/day for bottle-fed infants. From 5 August 1988 to end 1989, 1.4% results exceeded the 1984 WHO Guideline Value of 0.05 mg lead/l. The highest concentration measured in this period would have led to estimated exposures of 16.8 mg lead/day for adults, 3.5 mg lead/day for toddlers and 6.3 mg/day for bottle-fed infants.

10. 1.3% of results for **manganese** from the time of the pollution incident to the end of 1989 exceeded the 1984 WHO Guideline Value of 0.1 mg manganese/l. The highest concentration could have led to estimated exposures of 97.4 mg manganese/day for adults, 20.3 mg/day for toddlers and 36.5 mg/day for bottle-fed infants.

11. 4.5% of results for **iron** exceeded the 1984 WHO Guideline Value of 0.3 iron mg/l. The highest concentration could have led to estimated exposures of 589.9 mg iron/day for adults, 122.9 mg/day for toddlers and 221.2 mg/day for bottle-fed infants.

12. Based on the results of modelling by Black & Veatch Ltd, if the model was run with the assumption that there was no sludge present in the contact tank at the treatment works, estimated worst-case exposures to aluminium would not have exceeded 780 mg/day for adults, 163 mg/day for toddlers and 293 mg/day for bottle-fed infants. If it was run with the assumption that there was a layer of sludge on the base of the contact tank, estimated worst-case exposures to aluminium would not have exceeded 1133 mg/day for adults, 236 mg/day for toddlers and 425 mg/day for bottle-fed infants. We are unable to provide a quantitative estimate of *in utero* exposure.

13. An analysis commissioned by South West Water Ltd in 1991 modelled exposures to aluminium, sulphate, copper, zinc and lead for 10 individuals from 3 areas of North Cornwall. The model used SWWA monitoring data from the relevant areas but excluded the results from hot water samples. Tap water consumption estimates were either supplied by the individuals or a default value of 2 litres water/day was used. The model covers the period up to 7 weeks after the incident.

14. The model shows that mean estimated aluminium exposures were highest during the first few days after the incident (7 to 9 July 1988), with a highest mean intake of 221.4 mg/day, and then fell markedly to 0.4-0.8 mg/day by mid-August. For sulphate, using concentrations for 6-8 July estimated from the aluminium concentrations, it was concluded that intakes for 4 individuals may have been from 0.7 to 1.2 g sulphate on 7 July, the only day on which the EC Maximum Allowable Concentration (MAC) of 250 mg/l could have been exceeded. The other 6 individuals were not considered to have exceeded acceptable exposure limits for sulphate.

15. The report concluded that all results of analyses for copper and zinc showed concentrations substantially below the relevant EC MAC and that the daily intake of copper and zinc was always well below the acceptable levels. Similarly, it concluded that the daily intake of lead was also almost certainly below acceptable levels. However, there were several days on which the concentration was recorded as less than 0.08 mg/l (the level of detection) and 4 days on which the concentration was given and exceeded the EC MAC of 0.05 mg lead/l. The highest exposure was estimated as 0.44 mg/day.

16. We considered the possibility of dermal exposure to contaminants from tap water and concluded that it was unlikely to have been relevant because the absorption of metal sulphate ions through the skin from aqueous solutions is negligible. However, because July 1988 was very hot and many people may have been suffering from sunburn, we sought expert advice on whether this might have led to increased absorption. We were advised that, in principle, if severely sunburned individuals could tolerate the discomfort of showering or bathing in the acidic water, some dermal absorption of metal ions may have occurred. However, such absorption was likely to have been unimportant compared to exposure from drinking or cooking with contaminated water.

17. Results were provided for the aluminium concentrations in three serum samples taken after the incident from an individual in Tintagel. These show that

concentrations decreased from 2.89 µmoles aluminium/l (78.03 µg/l) on 18 August 1988 to 0.15 (4.05 µg/l) on 13 September 1988.

5 Evidence from individuals and population studies from the North Cornwall area

Introduction

Personal evidence

5.1 Evidence from individuals who were residents of, or visitors to, the Camelford area at the time of the incident has been valuable to us. This method of obtaining information has previously proved useful (COT, 1999). We were given information relating to the appearance and taste of the water and estimates of how much water was drunk, together with details of symptoms and medical problems suffered at the time of and since the incident. Some individuals gave us access to biomedical test results or to questionnaires[14] completed after the incident.

5.2 Medical practitioners and psychologists who examined individuals who were concerned that the contamination might have affected their health have also given evidence to us and have provided access to reports of their observations. This information has also been valuable.

5.3 It is the nature of an event such as this that both the individuals involved and the medical practitioners who examined them are aware of the possibility that the individuals were exposed to contaminated water. Information recall bias is the term used to describe the possibility that this might cause people who know that they were exposed to a particular substance to remember details about the occurrence in a different way from those people who do not know whether or not they were exposed. In some cases this can lead to an overestimation of the link between the occurrence and subsequent events. This is an unconscious and unintentional process if and when it occurs. We are also aware that the individuals who gave evidence represent a very small proportion of the total population which was exposed and that they were not randomly selected from the exposed population but were "self-selected". The fact that our collection of evidence took place 13 or more years after the incident occurred should also be borne in mind, although some individuals kept contemporaneous diaries or notes of their experiences and symptoms.

5.4 Nevertheless, although the data provided to us by and about individuals has been valuable, it is also limited. Without sufficient information on the quality of water supplied to different properties, and sufficient detail of personal consumption of contaminated water by both affected and unaffected individuals, it is not possible to use the information to assess whether an individual has suffered long-term or delayed adverse effects because of exposure to chemicals resulting from the Lowermoor pollution incident.

Population studies

5.5 So far as the population is concerned, more information is available. In particular, there are a number of epidemiological studies which compare the rate of

[14] Two types of questionnaire were provided. Most had been completed as part of a study carried out shortly after the incident by Dr Richard Newman, a local GP, and Dr Neil Ward of Surrey University. Others were completed at the request of solicitors.

health outcomes among individuals living in the Lowermoor distribution area with the rate among individuals living in, by comparison, unexposed areas. Thus, an individual's place of residence is used as a proxy measure of exposure. However, in these studies, few details are given of how accurately the populations were defined with regard to their source of water supply. The area is rural and we have been informed that there are many long service pipes, some of which may cross from an area where most properties are served by one water supply network into an area largely supplied by a different network. This may mean that some properties in the "treated" area in the study did not actually receive water from the Lowermoor network but from another network, and *vice versa*, i.e. the studies could have suffered from exposure misclassification. In the studies reviewed, it is not known whether any misclassification could have occurred, nor how this could impact on the results. Moreover, the fact that a property was supplied with contaminated water does not necessarily mean that all or any individuals in that property consumed the water.

Data from personal testimonies made by members of the public

Introduction and method of working

5.6 We received personal testimony from individuals responding to our requests for additional information regarding effects of the incident through various media. Testimony was given in two forms: during personal interviews with individuals from the North Cornwall area and as written correspondence submitted by email or letter (see Chapter 2). In total, 114 individuals provided evidence, including one individual who provided personal evidence during the consultation exercise and 9 who were children at the time of the incident.

5.7 Personal evidence was collected during interviews held in Camelford on five separate occasions between April 2002 and October 2003. Fifty-four individuals provided personal evidence during the course of approximately 35 hours of semi-structured, individual interviews. Most interviews were conducted in the North Cornwall District Council Offices, Camelford by the Chairman and three members of the subgroup: Dr Thomas and the two local representatives with secretariat support from Ms Pollitt. Seventeen individuals spoke to the full committee at one of our scheduled committee meetings or during our visit to Camelford on 4 April 2002. Consent was sought from each individual for tape recording of the interview and individuals were assured that their contributions would be treated in confidence. Transcripts were provided to individuals following the interviews on request. The information was anonymised and stored in a database at the Department of Health, from which the data below have been derived. Personal evidence was also received from sixty individuals in written form. This information was also anonymised and stored in the database.

5.8 Evidence from individuals included first or second hand accounts of:

- Place of residence
- Information on water supply and plumbing
- Water quality prior to the incident
- Water quality during and after the incident
- Subjects' estimate of daily oral intake of water during and after the incident
- Any effects when bathing/showering using the water
- Registration with local GP/primary care services

- Acute and/or chronic health problems during or after the incident
- Effects observed by others living in the same house/dwelling
- Attendance at clinics set up following the incident
- Biological samples provided for testing, and results of tests (e.g. blood, hair, nails, bone)
- Neuropsychological tests
- Other information collected at or near the time of the incident (e.g. questionnaires, see paragraph 5.1, footnote 15)
- Any other relevant matters that participants wished to raise

General observations

5.9 Many of the individuals with whom we spoke commented on the lack of reliable, official information at the time of the incident. Some individuals reported that they received inconsistent and/or contradictory advice, for example, the initial advice that the water was safe to drink was later modified. We were told that this period of confusion and lack of communication about the incident and potential consequences for health led to feelings of uncertainty and later, scepticism and suspicion in the local community. Such feelings persist in the community today. Some individuals regretted that the matter was again being investigated so long after the incident. Others welcomed a re-examination of the incident and its consequences, and a few expressed doubt that any helpful conclusions would be reached.

5.10 Socio-economic effects were also reported; we were told of difficulties with sale of property, and a reduction in tourism. There were tensions within the local community relating to different perceptions of symptom causation and importance. Opinions within the local community sometimes became polarised; we heard from some individuals who doubted the motives of those reporting adverse effects, some suspected that such effects were incidental and unconnected with the incident and others felt that any adverse effects were underreported for financial or commercial reasons.

Water quality, usage and consumption

5.11 Personal evidence revealed that variation in the type, age and condition of domestic plumbing and in individual water usage resulted in people in the same area receiving water which was very different in appearance and taste at a similar time after the incident. We heard that factors such as the presence and composition of storage tanks, the age of the property and the presence of lead pipes in the domestic supply system affected water quality once it had arrived in the property. In an area where many properties are occupied intermittently, contaminated water may have remained in the domestic system for some time after supply. The timing of the first problems with water quality reported to us varied, with the earliest between 5.30 and 6.00pm on 6 July 1988. This may reflect the fact that the contaminated water would have reached different geographical points in the distribution system at different times, depending on distance from the treatment works and demand.

5.12 Many individuals commented that the water was foul tasting and initially undrinkable and that it curdled milk or had a strange appearance or mouth feel or sensation on the skin (“frothy”, “sticky”, “thick”). However, others stated that it was drinkable when mixed with fruit juices or in black coffee (see box), although it had

been asserted that individuals did not and, indeed, could not have drunk significant quantities of the water. Similarly, the water was used for cooking and bathing even after poor quality had been noted.

" The milk was put into the mugs, with the teabags, and when the boiling water was poured into the mugs, the liquid erupted and came over the top like one sees in horror films. Thinking the milk was off, as it was mid-summer and there was an acidic smell to it, I put a mug to my lips and the liquid removed some skin from my lower lip."

"..the following morning we were up early, put the kettle on, made some tea and it was foul tasting and it was still coloured. So, immediately I rang the water board who told us to just boil it. It was perfectly safe to drink…….we kept boiling it and yes we did (drink it), although it had the most foul, foul taste."

" I noticed it didn't taste the same. It's all frothy. I suffer with (a medical condition)…. and I have to drink a lot of water…I just carried on (drinking the water)…..It didn't taste very nice, but we have so many water things down here. I mean, every couple of weeks you turn the tap on, it comes out looking brown and frothy…"

" I didn't detect it because I drink coffee and the coffee disguised the taste."

"All I knew in the period immediately following the incident was that I seemed to have a mouth that was badly burnt…..In the seven days that I'd been home ill, I had not been able to eat because of the state of my mouth, so I'd just been drinking water….I hadn't got a taste because the whole of my mouth had been skinned."

"…my wife said we cannot drink this water it smells awful, I washed or attempted to wash my hands in the old basin we only had cold water at this period, turning on the cold tap there was just a hiss, then a foul stench followed by what could be only described as a filthy dark green sludge…"

5.13 At least 13 years had elapsed between the water pollution incident and when we collected evidence and, not surprisingly, few of the individuals providing personal evidence could give a detailed estimate of the quantity of contaminated water which they consumed. A few individuals stated that they drank and used the contaminated water throughout the incident as normal. Some stated that they switched to bowser water once bowsers were made available or to bottled water some time after the start of the incident. A few indicated that they did not drink any of the contaminated water after an initial tasting and only returned to tap water after some weeks had elapsed. Some individuals supplied estimates of the amount of water consumed per day during the incident. Others were asked what their normal intake of beverages would have been, so that an estimate of possible exposure could be made had normal drinking patterns continued during the incident. Of those who estimated water intake, most said that they drank around 6 to 8 cups or mugs of beverage (approximately 1.1 to 2.4 litres) per day.

5.14 It was reported that some young children did consume the water at the time of the incident. It was also reported that a baby had been bottle fed throughout the incident using tap water to dilute baby milk powder.

Reported health effects - Adults

5.15 Many of the individuals we spoke to or who wrote to us were concerned and distressed about the possible health consequences of the incident in relation both to themselves and to the community as a whole. Individuals reported a variety of health problems (see box). These were both acute (occurring within hours or days of the incident) and chronic (lasting for many weeks or years, and arising either soon or much later after the incident).

"We're going to find this very difficult, because we've got short-term memory loss, which has also been caused since the water and it's happened -- you know, over the years one forgets how many days after the incident that anything happened. I just know that it was in the first few days that we had sort of mouth ulcers and rashes. My husband was actually paralysed."

"For myself I've suffered ever since the incident from muscle and joint pains…and it's gradually getting worse. My memory and concentration are not very good at all. Depression - more a few years ago than sort of recently. Silly things like bleeding gums and that as well."

"I suppose that's the thing that's bothering us most, is memory. I mean, all right, all the aches and pains over the years we've accepted and we've learnt to live with."

"Health-wise, I mean, at the time, as I say, we suffered initially but my main concern is since then onwards I've had -- I've had a heart attack, I've lost my hair, I suffer with severe gout, tiredness."

"I noticed I'd get aggressive. Not aggressive with people, but I'd shut myself off. I have to go and shut myself off in a room. I can't communicate…… I've lost all my feelings. I've lost all my emotional feelings which I used to have."

"…..the main thing is the memory problem. But occasional loss of balance, but all those sort of things one puts down to circulation or something as you get older, you know."

"…we all thought we had a tummy bug and we all had diarrhoea …we had mouth ulcers as well and, because other people were having diarrhoea and mouth ulcers…My problems continue and still to date I still have digestive problems and diarrhoea etc."

"My husband became very ill. He lost an awful lot of weight. We have a photograph taken with our children. They'd come down for his birthday, and he looks an old, old wizened man. Not the same man at all…"

"…my life changed because I wasn't capable of doing all this stuff. So, life sort of came to a standstill housework-wise, and … I was at work and I couldn't function, I couldn't -- my bones hurt, my muscles wouldn't support me, my gums were constantly bleeding, I had mouth ulcers, rashes, and if there was any vibration or knock, or -- I couldn't judge, I couldn't judge spaces, I couldn't judge to put things down, or to go past things, and very quickly I couldn't drive."

"So, I wasn't able to coordinate to drive or to go through a space properly, and I broke masses of things by putting them down on tables. I wasn't able to mentally function properly because the short-term memory was quite affected. I would start saying something and then it would just go, and I'd drift off. I would go upstairs and I'd forget what I was going up there for…"

"Within a few weeks, I would say, yeah. I mean, my health and, apart from my joints, I was diagnosed having to have a hysterectomy in 1990. And whether at base it had anything to do with the water, I really don't know, with the symptoms I was experiencing and that sort of thing as well. But, I would say it was the knee joints more so, with me, than anything else, and the skin."

5.16 Some symptoms were reported by many individuals and some of the symptoms were often reported together. There was variation in the degree to which individuals attributed these reported adverse effects to the incident; some were certain that the incident had caused significant and long lasting damage to their health, others were sceptical. Table 31 shows the common acute and chronic health effects that individuals reported to us and which were believed to be caused by exposure to contaminated water. Only data derived from oral evidence are included, because information provided in writing was not collected in a systematic way. However, individuals who wrote reported similar symptoms to those who spoke with us.

Table 31: Commonly-reported conditions attributed to the incident by 54 individuals

Acute[a]	No.	Chronic[b]	No.
Mouth ulceration	19	Impaired memory	45
Skin irritation	19	Joint pains and/or swelling	40
Diarrhoea	19	Tiredness/lethargy	22
Abdominal pain	7	Coordination problems	14
Nausea	5	Concentration difficulties	12
Vomiting	4	Effects on nails	11
		Depression	8
		Word-finding difficulty	7

a: Occurring within hours or days of the incident

b: Lasting for many weeks or years, and arising either soon or much later after the incident

Note: the numbers are included to indicate the information given to us by the 54 individuals. However, since this group may not be representative of the population as a whole, no conclusions should be drawn from these numbers about the frequency of symptoms in the population as a whole.

5.17 Other health effects were also reported to us, but far less frequently. Table 32 shows some of the less frequently reported conditions.

Table 32: Less commonly reported conditions attributed to the incident

Complaint	Other information
Gynaecological problems	Includes miscarriages, ovarian cysts, fibroids, hysterectomy, and endometriosis.
Diabetes	One Type I, one Type II, 2 unspecified.
Kidney problems	Includes pain, urinary incontinence, kidney stone, enlarged kidney, abscess on kidney.
Cardiovascular problems	Includes heart attack, arrhythmia.
Major gastrointestinal problems	Includes duodenal ulcers, gall stones, colitis.
Hearing difficulties	Includes ear infections, serious hearing problems (child).
Cancer	One case of breast cancer, one of brain cancer and two unspecified cases.
Thyroid disease	Includes goitre, thyroiditis, underactive or overactive thyroid, prominent thyroid gland.
Mouth ulceration	-

Reported health effects - children

5.18 We heard from 9 individuals who were aged 16 or under at the time of the incident. The most common adverse health effects which they reported to us and which they considered might be due to the contaminated water were: joint pains and swelling, memory problems, skin effects, lethargy and personality change.

5.19 In other cases, people who spoke to us to provide personal evidence about their own health also told us about adverse health effects which they had observed in their children, which they considered to be associated with the contaminated water. In all, 8 individuals provided information about 15 children in this way. Joint pains and swelling and lethargy were the most common effects; parents also reported problems with memory, behaviour and concentration. Some parents reported that the children's academic performance had suffered.

Information provided by health professionals

Dr David Miles

5.20 At the time we interviewed him, Dr David Miles was Director of Public Health at West of Cornwall Primary Care Trust. At the time of the incident, he was District Medical Officer at the former Cornwall and Isles of Scilly Health Authority[15].

Oral report

5.21 Dr Miles spoke with us at a formal meeting in Camelford in April 2002. He explained that, at the time of the incident, there was no statutory duty for a water

[15] The Cornwall and Isles of Scilly Health Authority was abolished on 1 April 2002 following the reorganisation of the NHS. Medical responsibility for North Cornwall now falls under the auspices of North & East Cornwall Primary Care Trust.

authority to inform a health authority of a pollution incident, nor did the health authority have any statutory responsibility for the safety of the water supply. This responsibility lay with the local authority, which was required to take such steps as were necessary to determine whether water supplies were wholesome and to notify the water authority if they were not[16]. The role of the health authority at the time was to advise the local authority (in this case, North Cornwall District Council) through the Medical Officer for Environmental Health (MOEH) (DHSS Circular HRC (74)13).

5.22 At the Cornwall and Isles of Scilly Health Authority, the main health professionals involved in handling the consequences to health of the incident were the then Consultants in Public Health Medicine/Medical Officers for Environmental Health. These were Dr Richard Grainger (July to October 1988) and Dr Tony Rowland (October 1988 to March 1991).

5.23 Dr Miles reported Dr Grainger's records of the events from 7 July 1988 to 23 August, as detailed in his notebooks:

- 7 July – a pump failure was reported at the Lowermoor plant with water showing a pH of 4.2-4.8 and possible aluminium levels of 4mg/l. Dialysis patients were advised to use bicarbonate to raise the pH of the dialysis water.

- 12 July – notified of possible aluminium levels of 40mg/l for a short period, and of slightly elevated levels of copper and zinc in the water.

- 19 July – contacted by Gerry Neale MP about reports of sulphuric acid in the supply. Advised Mr Neale that there was no health hazard at the levels of sulphate reported.

- 19 July – SWWA advise that supply is back to normal.

- 20 July – copper concentrations of 8 mg/l reported. North Cornwall District Council received few complaints from members of the public.

- 22 July – correspondence received from Mr Doug Cross (dated 21/07/88) that matters were not as reported by SWWA.

- 8 August – no reason to think there was a continuing problem, as there were no contacts now from GPs or the general public.

5.24 A formal record of the Health Authority's involvement at the time was given in the 1988 Annual Report of its Department of Public Health Medicine, which is attached at Appendix 16.

5.25 Dr Miles informed us that his own involvement with the incident began on 6 August 1988 when the then MP Mr Gerry Neale rang to ask whether it was correct that there had been several Camelford residents admitted to Truro Hospital with kidney failure. The renal physician at Truro assured Dr Miles there was no such problem. However, during the phone call, Dr Miles was informed, for the first time,

[16] The legal basis is laid out in the Water Act 1973 and Section 140 of the Public Health Act 1936.

that 20 tonnes of aluminium sulphate had been emptied into the water supply on 6 July 1988. This information was confirmed by Dr Lawrence of SWWA on 8 August in a phone conversation with Dr Grainger. Therefore, there was a gap of one month before the Health Authority was aware of the full nature of the incident. Dr Miles noted that there had been earlier reports in the local press that the incident was worse than originally reported but the Health Authority had relied on information from SWWA that there was no problem with the supply. He also noted that there had been no calls from general practitioners (GPs) to the Health Authority about the incident. The Health Authority would usually expect to be notified of reports of illness in the area by GPs.

5.26 Once the full extent of the pollution was evident, the Health Authority sought urgent expert advice from the Division of Toxicology and Environmental Pollution of the Department of Health on the possible health risks of the levels of pollution which had been reported. A reply was received on 24 August 1988 and circulated by the Health Authority to local doctors and residents during the last week in August (see Appendix 17 for a copy of the letter). At the same time, the Health Authority instigated a retrospective survey of the occurrence of illness in the population (Rowland *et al*, 1990: see paragraphs 5.55 - 5.56). Subsequently, a clinic was set up at Truro, led by a consultant physician, Dr Coutts (see paragraphs 5.41 - 5.46). At the request of the Health Authority, the Department of Child Health at Bristol University initiated an assessment of birth outcomes in women who were pregnant at the time of the incident (Golding *et al*, 1991: see paragraphs 5.57 - 5.58).

5.27 Dr Miles commented that an episode of 'hand foot and mouth disease' was also reported at the time of the incident in the Camelford area. There were no other unusual patterns of disease.

5.28 Following publication of the second LIHAG report in 1991, the Health Authority initiated the relevant recommendations made in that report regarding monitoring of routine health statistics[17], which continues (see Chapter 2, paragraph 2.6 and paragraphs 5.61 - 5.710 below).

Written information

(a) Patch testing

5.29 The 1991 LIHAG report also recommended that those people who consider themselves to be sensitised to aluminium should be tested for immunological dysfunction, including with a patch test with appropriate controls. Dr Miles reported to us that the Health Authority obtained a protocol for patch testing from Professor ST Holgate, Professor of Clinical Immunopharmacology at Southampton University, which was circulated to all GPs in the area, asking them to advise Dr Miles of any tests carried out. However, enquiries of local GPs in December 1991 indicate that there was no demand from patients for patch testing and so no tests were carried out (Miles, personal communication, October 2003).

(b) Dermatological effects

[17] These are health statistics which are routinely collected by regional or national agencies. They include deaths (mortality), cancer incidence (newly diagnosed cases of cancer) and admission or discharges of patients to and from hospital.

5.30 A number of local individuals have reported onycholysis (damage to and shedding of nails) following exposure to the contaminated water. This was also noted in a letter to a Wadebridge GP from a consultant rheumatologist who examined one of the patients (Hutton, personal communication, 1990). Dr Miles submitted a report dated October 1990 written by Dr JL Burton (subsequently Professor JL Burton), Consultant Dermatologist at Bristol Royal Infirmary, who visited Camelford in September 1990 at the request of Dr Rowland and Dr RJ Newman, a local GP who considered that some of his patients had onycholysis of the great toes due to the contamination incident (Miles, personal communication, 2003). Dr Burton examined 12 patients who had reported dermatological problems, which they ascribed to the incident. His conclusions were as follows:

> "As a result of my examination I conclude that there was unlikely to be a public health problem affecting the skin of the population in the Camelford area. No consistent dermatological abnormality was seen apart from onycholysis, and this was idiopathic in only 3 patients. Since the patients had been selected because they complained of nail loss, the finding of onycholysis is, of course, expected. Psoriasis affects 2% of the normal population, and it sometimes presents with onycholysis before any other skin defect becomes apparent. I would expect to find several cases of mild idiopathic onycholysis and several cases of nail changes due to psoriasis, eczema or trauma in any single GP practice. The prevalence of onycholysis in the general population is not known, but it is not a rare condition. In order to determine whether the prevalence of onycholysis in the Camelford area was related to the water poisoning incident it would be necessary to do a large population survey of the area, with a control survey in a similar socio-economic area where the water had not been poisoned. Even if such a survey did show an increased prevalence of onycholysis in the region, it would not of course prove that the aluminium poisoning incident played a causative role. I am not aware of any evidence that aluminium plays any role in causing either psoriasis or onycholysis. The only skin problem which possibly relates to aluminium, which I have found in the literature, is a report of workers in an aluminium foundry who developed telangiectatic vessels in the skin. None of the Camelford patients I examined showed this change. The skin changes in the foundry workers were thought to be due to exposure to toxic fumes rather than oral ingestion of aluminium salts.
>
> "On the basis of my findings, I would not feel that further metabolic investigation of the hair, skin or nails of these patients is required."

5.31 Dr Miles also sent us copies of correspondence with local GPs and dermatologists dating from summer 2000, which indicated that they had seen no patients with toenail problems attributed to the water incident (Miles, personal communication, 2003).

General Practitioners : Dr Chris Jarvis, Dr James Lunny, Dr Anthony Nash and Dr Richard Newman

Discussion with local GPs

5.32 We invited a number of local GPs to our meeting in Camelford in April 2002 to discuss their impressions of the health consequences of the incident. The following attended:

Dr Chris Jarvis, Bottreux Surgery, Boscastle
Dr James Lunny, The Surgery, Hillson Close, Port Isaac
Dr Anthony Nash, The Medical Centre, Camelford.

5.33 Dr Jarvis reported that the Tintagel/Boscastle practice had around 4,600 registered patients. It was common to see individuals with gastrointestinal upsets in the summer because there was a high number of seasonal holidaymakers. However, there were no more gastrointestinal presentations than usual around the time of the pollution incident. A significant increase in presentations coincided with increased media claims of possible health effects. He also commented that there was an outbreak of 'hand, foot and mouth' disease prior to the incident.

5.34 Dr Lunny reported that there were 7,200 patients registered at the Port Isaac practice at the time of the incident. Half of these had received water from the Lowermoor reservoir and half from the De Lank reservoir. The practice saw no difference in the health of the two populations in the immediate aftermath of the incident. At the Delabole surgery, two subjects had particular complaints (throat irritation; skin rash), but the anticipated increase in patient attendance did not occur. Of some 600 consultations in the period 6 to 31 July 1988, only two mentioned the water as a factor. After August 1988, more individuals presented with symptoms, which they attributed to the water incident but, by January 1989, only a small number had presented with attributed symptoms. A tally was kept of every patient who mentioned the water as a factor and these were referred to specific clinics. Of the 3,500 patients from the exposed area, 50 were referred to clinics and 29 of these attended the clinics. Dr Lunny reported that a meeting of all but one of the GPs in the area, on 27 February 1989, was of the view that there had been no increase in workload nor in any other measure of morbidity as a direct result of the incident.

5.35 Dr Nash reported that his practice had about 5,000 registered patients in 1988. There were some cases of mucous membrane ulceration and mild skin rashes. Following a questionnaire survey of symptoms of aluminium toxicity carried out by local people, some patients reported with health complaints and were referred to the Truro clinic set up by the Health Authority. The practice subsequently had to deal with letters from solicitors in respect of patients who made claims against SWWA. Thereafter, there was little medical activity relating to the incident. There was no indication among the practice's patients of cognitive impairment as a result of the incident.

5.36 None of the GPs who spoke to us considered that there was anything untoward about prevalence of depression in their practices, nor was there any indication of an increase in mouth ulcers, nor in effects in children, at the time of the incident. We were provided with data on consultation rates in a practice with surgeries in Camelford and Delabole, which had been previously presented to the LIHAG committee. These indicate that there were no differences in consultation rates in the month before and the month after the incident.

Correspondence with Dr R Newman

5.37 At the time of the incident, Dr Newman was the senior GP in the Camelford practice with surgeries in Camelford, Delabole, St Teath, Tintagel and St Breward. In 2002, he lived in France but we were able to pose some questions to him through local contacts. In a letter to the contacts he reported:

> " The morning after the pollution occurred I drove through Camelford high street at 4am, at which time all the stop-cocks had been opened and water was pouring down the road. A day or two later it became obvious that there was a health problem, from the complaints of patients in the surgery. This became linked to a water pollution when those washing their hair found it became dyed blue, and there was a large number of dead fish in the River Camel. It was ten days before we became informed as to what had occurred by a report in the local daily paper. Following this there was a meeting called by local council members at which I was asked to ascertain the dangers to health which may require action" (Newman, 2002). .

5.38 The letter went on to say:

> " Bearing in mind that at the time we were not aware of a problem with the water, the initial symptoms were those of diarrhoea, and lethargy, mouth ulcers, and increased arthritic aches and pains, which appeared to be no more than a heavier than average week's work load. When the cause of these became evident, I circulated a paper asking if patients had suffered any of a list of symptoms, a proportion of which were not to be expected as a result of aluminium poisoning. Although this was hardly a scientific way to go about getting information, the results were alarming, and it was noted that many people who had symptoms did not consult their doctors, thus the number affected in more minor ways at the time will never be known….".

5.39 He also wrote:

> " With hind sight, it is my opinion that there will be a substantial number of people permanently affected by drinking tap water at the time. The affects are mainly on memory, joints and skin. Most are a marked increase of processes already present, such as increased arthritic symptoms, increased speed of reduction in recent memory with age, eczematous lesion on already dry skin. In a normal way this could be determined by a detailed health survey, but due to population movement this (is) unlikely to be effective after such a long time. I attempted a pilot survey at the time, comparing Camelford inhabitants with those of St Breward, and there was a marked difference in the complaints of those attending surgery. However all my papers were destroyed so it is unlikely that a copy of this is available."

5.40 Dr Newman also reported that he arranged for "approximately 435" patients to give samples of blood, hair, nails and/or saliva for analyses by Dr Neil Ward of the University of Surrey (see paragaraph 5.167). These were tested for concentrations of metals (Newman, personal communication, 2002).

Dr Ian Coutts

5.41 Dr Coutts is a consultant physician at the Royal Cornwall Hospitals NHS Trust. We spoke to him at our meeting on 19 May 2003. Dr Coutts ran the clinic set up by Cornwall and Isles of Scilly Health Authority for patients who considered that they had continuing health problems caused by the incident. He told us that the purpose of the clinic was to identify symptoms and to arrange for referral to other parts of the health service if necessary. In practice, the sessions tended to consist largely of patient-led consultations, with an emphasis on responding to individuals' concerns.

5.42 The clinic started approximately 1 year after the incident, and ran for 18 months. Two hundred and ninety-seven names were put forward by GPs and 135 individuals accepted an appointment. Most patients were only seen on one occasion but 31 people took up the offer of a second consultation. A presentation of data relating to 109 patients was made at the 1990 Truro conference, when consultations were still continuing (Coutts, 1990).

5.43 Dr Coutts reported that many individuals found the water unpalatable and drank little or no mains water until some days after the incident. However, occasionally people seemed able to tolerate very heavily contaminated water, often as black coffee. Frequently reported symptoms included diarrhoea, mouth ulcers, general malaise, deterioration in memory and joint problems. Joint problems were the most commonly reported symptoms, and tended to be an exacerbation of pre-existing conditions such as injuries and arthritis. These, and memory problems, were usually reported to have started about two months after the incident. Approximately one third of those attending the clinics presented with diarrhoea. This was usually mild and short-lived, but persisted in some cases. Seventeen of the 41 people who reported blistering or ulceration of the mouth and lips also reported malaise, of a type characteristic of a post-viral syndrome.

5.44 Dr Coutts referred to the reported outbreak of 'hand, foot and mouth disease'. He reported that information collected by the Royal College of General Practitioners from 53 monitoring practices did not suggest that there was an outbreak in England at the time of the incident. None of the patients seen at the clinic had reported blisters on their hands and feet, although there had been a couple of reports in the area at the time. Apart from the apparent association of mouth blisters with malaise, there was no real overlap of groups, and no noticeable differences between the groups reporting the different symptoms. It is possible that older people were slightly over-represented, and younger ones under-represented, in those attending the clinic. Dr Coutts considered that this may be because older people are more likely to have pre-existing conditions and are more concerned about their health. Thirty-two patients were referred for psychometric testing at the Clinical Psychology Department, St Lawrence's Hospital, Bodmin (see paragraphs 5.94 to 5.98).

5.45 There were no new health problems among the 31 patients who accepted the offer of a second consultation. Some were still concerned about memory problems: a few considered that they had improved and some that they were slightly worse.

5.46 In Dr Coutt's opinion, the incident had caused real health problems for the individuals seen at the clinic and that it was unhelpful to try to distinguish whether these were caused by psychological or toxicological mechanisms.

Mrs Jenny McArdle

5.47 We spoke with Mrs McArdle, a trained nurse, in Camelford on 6 May 2003. She informed us that, initially, she had visited individuals who had health concerns after the incident at the request of a local campaigner. After a short time, she had decided that there was a need for this to be done on a more official basis and had approached the Cornwall and Isles of Scilly Health Authority to this end. This led to the establishment of a part-time NHS post from November 1990 to July 1992, which she occupied. The post as a community nurse counsellor was funded by South West Water Ltd but came under the auspices of the Cornwall and Isles of Scilly Health Authority.

5.48 Mrs McArdle reported seeing more than 100 individuals during her work although her main work was with 30 individuals. Some were referred by GPs but most were self-referred. Her role was mainly to provide counselling and support but she also referred people on to other agencies for investigation and treatment.

5.49 Mrs McArdle recalled that the main symptoms reported were muscular and joint problems, fatigue, memory problems, and anxiety about the possible health consequences of the incident. There was also considerable frustration in that individuals considered that their concerns were not being heard, and their health problems not believed, by the authorities.

5.50 An interim report written by Mrs McArdle in January 1992, obtained from the Health Authority archives, provided a summary of health problems in 31 people. Broadly, these comprised fatigue (39%), memory problems (35%), arthritis (23%), thyroid problems (23%), depression (23%), kidney problems (6%) and muscle/joint problems (6%). Mrs McArdle reported that she prepared a final report in summer 1992 but that it was in no way significantly different from the interim report (McArdle, personal communication, March 2005). The Health Authority informed us that it did not receive the final report, which was held by Mrs McArdle's line manager at Bodmin (Miles, personal communication, March 2005).

Studies of the North Cornwall Population

Epidemiological studies

Introduction

5.51 Following the pollution incident there have been several studies investigating the occurrence of adverse outcomes in the population who were potentially exposed to the contaminated water. Most of these studies have been reported or are in press in published scientific journals or are available in reports provided to government departments. Additional information on some studies was presented verbally to the committee or sent as separate evidence. The studies which have been carried out are listed below; Appendix 18 summarises and gives a critique of each individual study.

- Water contamination in North Cornwall: A retrospective cohort study into the acute and short-term effects of the aluminium sulphate incident in July 1988 (Rowland *et al*, 1990).
- Aluminium sulphate in water in North Cornwall and outcome of pregnancy (Golding *et al*, 1991).

- Excess aluminium sulphate in drinking water in North Cornwall and growth of children (Hawkins *et al*, undated).
- A review of hospital discharge rates in a population around Camelford in North Cornwall up to the fifth anniversary of an episode of aluminium sulphate absorption (Owen and Miles, 1995).
- Retrospective study of mortality after a water pollution incident at Lowermoor in North Cornwall (Owen *et al*, 2002).
- A study of cancer incidence and mortality in two cohorts in North Cornwall affected by the Lowermoor pollution incident. (Owen *et al*, undated).
- The distribution of leukaemia in association with domestic water quality in Southwest England (Foster AM *et al*, 1997).
- Childhood health events in relation to the Lowermoor water incident and the Camelford leukaemia cluster. (Alexander F, 2002).

5.52 Different study designs have been used to investigate the population. Three (Golding *et al*, 1991; Rowland *et al*, 1990; Alexander, 2002) compared the frequency of occurrence of certain health outcomes in those potentially exposed to the contaminated water with the frequency in a comparison population. Other studies have used a cohort study design to follow up the exposed population and to investigate rates of hospital discharges, mortality and cancer incidence at various times after the incident compared to the rates in one or more comparison populations (Owen and Miles, 1995; Owen *et al*, 2002; Owen *et al*, undated). Standardised rates[18] of disease have been calculated in these studies (e.g. standardised hospital discharge ratio, standardised mortality ratio). The comparison populations used in the studies, to calculate the standardised rate, vary but include other areas in Cornwall, the whole of Cornwall and the Isles of Scilly, and the whole of England and Wales. The comparison population used has depended in part on the availability of appropriate data on the rates of the health outcome under study.

General concerns regarding these studies

5.53 Many of the studies have used 'resident' populations defined as exposed or non-exposed depending on the water supply to the area in which they live. Some studies restricted the populations examined to those who were still resident at the time of the study, so that those who had moved since the pollution incident would have been excluded. In addition, none of the studies included non-residents e.g. holiday makers. Most of the studies do not state explicitly how the populations were selected e.g. at what exact date the populations were defined and how likely it was that the population studied was incomplete or inaccurate. The impact of misclassification of exposure status on the results from epidemiological studies depends on whether the error is thought to be (i) non-differential i.e. the likelihood of exposure misclassification is the same for diseased and non-diseased people, or (ii) differential i.e. the likelihood is different between groups. Non-differential misclassification generally tends to undestimate risk whereas differential misclassification may either under- or overestimate risk. As discussed in paragraph 5.5, there is considerable potential for residents to be misclassified as exposed or non-exposed. The long term

[18] The crude rates of disease in two populations may be different simply because of differences in the age distributions of the population or the proportion of males and females. Standardisation adjusts for the differences using the demographics of a standard population (e.g. often the distribution of people of different ages and of each sex in the UK as a whole). It is then possible to ascertain if there is a real difference between the rates of disease in the two populations.

follow-up studies of mortality and cancer incidence were initiated following the recommendations in the second LIHAG report (1991), i.e. two and a half years after the incident occurred, and are based on populations identified in 1991. The National Health Service registration system in place at the time to track movement of residents into and out of the area was incomplete. Also, many people did not respond to enquiries.

5.54 Many of the studies were limited by other factors including the use of proxy measures of exposure, rather than direct measurements taken at an individual's tap. Also, not all studies have adjusted for confounding factors[19], nor the fact that media reports and other sources of information may have influenced the responses from individuals to questionnaires.

Self-reported symptoms

5.55 Shortly after the pollution incident, a postal questionnaire study was carried out using 500 households in the area receiving contaminated water (the exposed area) and the area supplied by Bastreet Water Treatment Works (the control area) (Rowland *et al*, 1990). The households were identified using water rating information. No information is provided in the publication on the detail of the questionnaire.

5.56 Response rates in the exposed and non-exposed areas were 43.4 and 46%, respectively. There were minor demographic differences between the respondents from the two areas. More respondents in the exposed area reported drinking 5 or more cups of water daily than in the control area (70% versus 54.5%). Almost half (49.9%) of respondents in the exposed area reported changing their usual fluid intakes in July 1988 with almost a quarter lowering their consumption on the 6 and 7 July and many changing their drinking habits for 7 days. Sixty-three percent of respondents in the exposed area noticed that the water was abnormal versus 12% in the control group, with taste and colour most often noted. The study asked about a long list of symptoms, all of which showed higher reported prevalence in the exposed group than the unexposed group. Overall, 49% of respondents in the exposed area reported symptoms, compared with 10% in the unexposed area. However, few respondents in either group reported that they were unable to undertake normal activities. The authors note that their study was conducted shortly after considerable media coverage of the incident, and that a letter mentioning most of the symptoms had been sent by the health authority to residents in the area receiving contaminated water in August 1988.

Pregnancy outcomes

5.57 To address concern that consumption of the contaminated water during pregnancy might have harmed the unborn child, a study was set up to investigate pregnancy outcomes following the pollution incident (Golding *et al*, 1991). Birth notifications, hospital records, stillbirth registrations and GP records were used to obtain information on the live births, stillbirths, miscarriages and terminations of pregnancy in the population supplied from the Lowermoor Water Treatment Works in the 6 months before the incident and up to 42 weeks after the incident (the exposed population). Similar information was obtained from the same sources for a control

[19] See Appendix 4 for a discussion of confounding factors.

population supplied by a different treatment works (Bastreet Water Treatment Works) during the same time period (the non-exposed population).

5.58 There was no excess of perinatal deaths, low birthweight, preterm delivery or severe congenital anomalies in the exposed population compared with pre-incident rates nor with rates from the control area. An increased rate of talipes (club foot) was found. There was a difference in the social class distribution (based on occupation of the mothers' partners) between the control and Lowermoor populations, with the former having a higher proportion of partners in the non-manual classes. The results were not adjusted for this but the authors considered that this was unlikely to have biased the results. It should be noted that the exposed population contained only a small number of mothers (39) in the first trimester of pregnancy. Also, only defects apparent at birth or shortly after birth were considered.

The growth of children

5.59 A similar study to that of pregnancy outcomes was set up to examine the growth of children who were potentially exposed to contaminated drinking water following the Lowermoor incident prior to conception, while *in utero* or during early infancy (Hawkins *et al*, undated). Three groups of children were identified in each area: children who were (i) less than six months old at the time of the incident (infant exposure), (ii) *in utero* at the time of the incident (fetal exposure), and (iii) born between 12 and 48 months after the incident ("pre-conception exposure" i.e. their parents were potentially exposed to the contaminated water). Live births were identified from birth notifications and height and weight measurements (clustered around 9,18 and 36 months) were obtained from community health records and linked to the birth data.

5.60 The study found that, on average, there was a tendency for exposed children to be taller, but not heavier, than control children, particularly at 9 and 18 months. However, there was little difference at 36 months, although these results were based on small numbers. The study was limited by the use of residence of mother at the time of the birth as a proxy measure for exposure. In particular, it was not known where the mothers in the fetal and preconception groups lived during the pollution incident. The height and weight information was obtained from community health records. However, there appear to be substantially fewer numbers of children for whom these data were available than would be expected from the numbers identified from the live birth records. This deficit became more substantial as follow-up increased. No adjustment was made to take account of differences in social class distribution between groups, nor to take account of other factors that might potentially influence growth such as method of feeding and nutritional intake.

Hospital discharge rates

5.61 Hospital discharges are counts of the number of times that hospital departments discharge patients who are admitted with a particular disease or for a particular treatment. Thus they can be used as a crude measure of the rate of some illnesses (those requiring hospital treatment) in a population. The second report of the Lowermoor Incident Health Advisory Group (LIHAG) recommended the monitoring of hospital discharge rates for a period of 5 years (Lowermoor Incident Health Advisory Group, 1991). Owen and Miles (1995) investigated hospital discharge rates

in 8 postcode sectors in the Lowermoor supply area (exposed area) with those in 23 other localities in Cornwall (unexposed area), for the period 1987-1993. The standardised discharge ratios were calculated using Cornwall as the standard population.

5.62 The standardised discharge ratio in the exposed area rose steadily from 93.4 in 1987-88 to 111.9 in 1991-92, with a slight fall to 108.2 in 1992-93. None of the other localities experienced this trend. After the incident, for men and women combined, increased discharge rates were reported for respiratory diseases, for diseases of the arteries, and for signs, symptoms and ill-defined conditions in the Lowermoor population. For men only, there were increased discharge rates for diseases of the digestive system and of the genitourinary system, for arthopathies and related disorders, for diseases of the pulmonary circulation and for other forms of heart disease. The authors comment that the differences were not statistically different but they do not specify whether this was between men and women, or between Lowermoor and other areas in Cornwall.

Mortality

5.63 Populations in the area supplied by the Lowermoor Water Treatment Works and a comparison population have also been followed up for mortality and limited results have now been published (Owen *et al*, 2002). Long-term monitoring of mortality rates was recommended by the LIHAG (Lowermoor Incident Health Advisory Group, 1991). The unexposed population in this study was defined as residents who were not supplied by the Lowermoor reservoir, based on maps from SWWA showing the distribution of the water pipes from the reservoir. In 1991, two and a half years after the incident, all adults then resident in the two areas were "flagged "[20] at the Office of National Statistics (ONS) in order to obtain death and cancer incidence information. All children who were alive at the time of the incident and resident in 1991 were also flagged (children who were *in utero* at the time of the incident were not flagged). The results were compared with England and Wales, and with the populations of Cornwall and the Isles of Scilly as a whole.

5.64 Table 33 shows the Standardised Mortality Ratio (SMR) and 95% Confidence Interval (CI) for both the exposed population ("flagged" individuals) and unexposed populations from July 1988 to December 1997, when compared with Cornwall and the Isles of Scilly (SMR=100). It should be noted that SMRs have not been published for specific causes of death, other than circulatory disease.

5.65 Overall, mortality was lower in both the exposed and unexposed populations when compared with Cornwall and the Isle of Scilly. When the main causes of death were considered, the proportions of deaths due to each cause were similar in exposed

[20] All deaths, and all newly diagnosed cases of cancer, are notified to the Office for National Statistics (ONS) so that national rates of mortality and of cancer incidence can be compiled. The information is also recorded on the National Health Service Central Register. With the appropriate approval, including, if necessary, from a research ethics committee, researchers and bodies such as health authorities can be notified when ONS receives cancer incidence or mortality information on an individual in a group under surveillance if they have been "flagged" or marked on the Central Register. This enables the NHS to monitor cancer incidence rates and death rates for the population resident in the Lowermoor supply area at the time of the incident.

and non-exposed areas, with the exception of slightly more deaths due to traffic accidents in the Lowermoor area.

Table 33: Standardised mortality ratio (95% confidence intervals) for all causes of death, July 1988 to December 1997 (from Owen *et al*, 2002)

Exposed (E) SMR (95% CI)	Unexposed (U) SMR (95% CI)	Ratio of SMRs (E/U) (95% CI)
81.6 (77.2-86.2)	75.9 (69.2 -83.1)	1.07 (0.97-1.20)

5.66 The above analysis was carried out on the population as a whole and no analyses were carried out on particular groups e.g. different age groups. Concerns were brought to the committee by members of the public around mortality rates in specific groups but, despite considerable efforts, no further details became available.

Cancer incidence and mortality

5.67 The populations used in the mortality study have also been used to monitor the rate of newly diagnosed cases of cancer (cancer incidence) and mortality from cancer (Owen *et al*, undated). As shown in Table 34, the rate of cancer incidence from July 1988 to December 1998 (calculated as the European age-standardised rate) of all malignant neoplasms per 100,000 population in both the exposed and unexposed areas was less than those for Cornwall and for the South West as a whole.

Table 34: Cancer incidence for all malignant neoplasms, July 1988 to December 1998[a], direct standardisation (from Owen *et al*, undated)

	Lowermoor (exposed) population	Comparison (unexposed) population	Cornwall	South West
Number of new cancer cases	567	250	26,322	330,272
Rate[b] per 100,000 Population	293.5	298.9	360.5	358.8
95% Confidence Interval	266.9 - 320.1	260.1 - 337.7	355.9 - 365.1	357.1 - 360.1

a: excluding non-melanoma skin cancers
b: European age-standardisation rate

5.68 Direct standardisation was used in this study for evaluating cancer incidence, with the European population as the standard. Usually, indirect standardisation would be used and it is unclear why the direct method was used. It was also unclear why the UK population was not used as the standard rather than the European population, as age-time period specific cancer incidence rates are readily available for the UK. (These points are expanded on below and in Appendix 18).

5.69 Following publication of our draft report we were supplied with Standard Incidence Ratios for total cancer incidence and for leukaemia incidence calculated using an indirect method of standardisation. The South West was used as the comparison population, as before. The results are presented in Table 35. These confirm the reduced incidence in both the exposed and unexposed groups compared with Cornwall as a whole.

Table 35: Cancer incidence for all malignant neoplasms, July 1988 to December 1998, indirect standardisation (from Owen, personal communication, March 2005)

	Exposed	Unexposed	Cornwall
Standard Incidence Ratio (95% CI)	84 (78-90)	87 (78-95)	99 (98-100)
Number of cases	850	384	38,684

5.70 Standardised Mortality Ratios for deaths from all cancers were also much lower than for England and Wales in both populations (Table 36). There was no statistically significant difference in the rate between the exposed and unexposed populations.

Table 36: Cancer mortality for all malignant neoplams, July 1988 to December 1998 (from Owen *et al*, undated)

Exposed (E)			Unexposed (U)			Ratio of SMRs (E/U) (95% CI)
Observed	**Expected**	**SMR**	**Observed**	**Expected**	**SMR**	
388	454.17	85	142	190.56	75	1.15 (0.94-1.40)

5.71 The only specific cancer for which results are available is leukaemia (see below), although numbers would be sufficient for specific analyses to be carried out of all cancer subgroups. Specific subgroup analyses could also be carried out for non-malignant diseases. We make recommendations for such work in Chapter 9.

Leukaemias

5.72 In 1995/1996, 3 cases of acute leukaemia (2 acute lymphoblastic, 1 acute myeloid) occurred in children aged between 13-14 who attended the same tutor group in Sir James Smith School in Camelford and who were resident in the area at the time of the pollution incident in 1988. Two studies have been carried out specifically in relation to leukaemia but, it is stressed that, as described in paragraphs 5.5 and 5.53, the degree and length of exposure in the exposed group will not be the same throughout and such nondifferential exposure misclassification tends to underestimate risk.

5.73 A study investigated whether there was any general variation in the incidence of haematological malignancies (including leukaemia) between 46 U.K. water supply areas in the period 1984 to 1988 (Foster *et al*, 1997). The areas were defined using ordnance survey and water supply maps, and the populations were based on electoral ward maps. Data on the incidence of haematological malignancies were obtained from the Leukaemia Research Fund's Data Collection Study.

5.74 The distribution of cases across the water supply areas was examined to determine if there was any significant variation in incidence between areas. Only acute leukaemia (lymphoblastic and myeloid taken together) and myeloproliferative disorder showed a significant variation.

5.75 The incidence of cases was also examined for correlations with various water quality indicators. It should be noted that three water quality indicators (pH, nitrates and aluminium) did not conform to WHO guidelines for drinking water quality during the study period and varied considerably over the period. Significant correlations were observed between standardised incidence ratios of cases in 5 disease categories, and concentrations of aluminium and trihalomethanes. The authors point out that patterns in water quality indicators may shadow other social or environmental factors e.g. radon exposure. No adjustment was carried out for potential confounding factors, neither were the issues of the relevant timing of exposure and latency addressed. The independent advisory committee, the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment, considered this study in 1997 and noted a number of limitations in the design and analysis. It concluded that the results did not indicate that aluminium was a risk factor in AML and myelodysplastic syndromes (Committee on Carcinogenicity, 1997).

5.76 The role of infection in the aetiology of leukaemia has been the focus of much research. Alexander (2002) investigated this as part of a study of childhood health events in relation to the Lowermoor incident and the 1995/1996 leukaemia cluster. She studied cohorts of children who were aged under 10 years at the time of the pollution incident and who were still registered with a local GP when the study was conducted. Children were classified as exposed or non-exposed to the Lowermoor water supply and the study utilised GP records of their health. The exposed cohort had a higher frequency of infectious illnesses, in particular chicken pox and other herpes virus infections, than the unexposed group. However, multivariate analysis, adjusting for age, gender and availability of GP records (which varied considerably), showed that there was more infectious illness overall *before* the incident for the exposed cohort than the unexposed. The author considered that the results were consistent with the hypothesis that incidence of leukaemia could be affected by prior exposure to infectious agents. These results are in line with those of more recent research on childhood leukaemia and infections (Roman *et al*, 2007).

5.77 The study of cancer incidence and mortality described in paragraphs 5.67 to 5.70 also investigated leukaemia incidence and deaths. The age standardised incidence ratio per 100,000 population for leukaemia for the exposed area was slightly lower than that of the non-exposed area, of Cornwall and of the South West as a whole (Table 37, calculated using direct method of standardisation, and Table 38, calculated using indirect method of standardisation). The mortality ratio for leukaemia was, however, slightly raised in both the exposed and unexposed areas (Table 39).

Table 37: Leukaemia incidence, July 1988 to December 1998, direct standardisation (from Owen *et al*, undated)

	Lowermoor (exposed) population	Comparison (unexposed) population	Cornwall	South West
Number of new Leukaemia cases	18	7	766	9433
Rate[a] per 100,000 Population	9.6	10.6	10.8	10.5
95% Confidence Interval	4.4 - 14.8	1.9 - 19.3	10.0 - 11.6	10.3 - 10.7

a: European age-standardisation rate

Table 38: Leukaemia incidence, July 1988 to December 1998, indirect standardisation (from Owen, personal communication, March 2005)

	Exposed	Unexposed	Cornwall
Standard Incidence Ratio (95% CI)	87 (56-130)	101 (52-177)	100 (94-106)
Number of cases	24	12	1,089

Table 39: Leukaemia mortality, July 1988 to December 1998 (from Owen *et al*, undated)

Exposed (E)			Unexposed (U)			Ratio of SMRs (E/U) (95% CI)
Observed	**Expected**	**SMR**	**Observed**	**Expected**	**SMR**	
13	10.87	120	5	4.58	109	1.10 (0.37 - 3.92)

Neuropsychological testing

Introduction

5.78 Following the contamination incident, neuropsychological testing was carried out on some individuals who were living in the affected area. Some of this testing was carried out locally by Mr Antony Wilson, then clinical psychologist at St. Lawrence's Hospital, Bodmin. Other testing was carried out by Professor Tom McMillan, then consultant psychologist at Atkinson Morley's Hospital, London, and by Dr Paul Altmann, consultant nephrologist at The Radcliffe Hospital, Oxford. We do not know the details of all those who underwent testing, because of patient confidentiality, but it is likely that some individuals participated in more than one of these sets of investigations.

5.79 We have reviewed the publications resulting from these studies and have spoken with Professor McMillan, Mr Wilson and Dr Altmann about the tests and the results. We have also reviewed an analysis undertaken by Professor McMillan and others of the results of routinely administered psychological test results given to Cornish schoolchildren before and after the pollution incident.

5.80 We took expert advice on the neuropsychological testing, and on the interpretation of the results, from Professor MD Rugg, formerly of the Institute of Cognitive Neuroscience, University College, London and now at the University of Texas, Dallas, USA.

Studies by Professor McMillan and colleagues

5.81 Professor McMillan carried out a number of psychometric tests on individuals from the North Cornwall area. The individuals were originally referred to him by GPs or by a consultant nephrologist at St George's Hospital, London. Later, a further group of individuals was referred by solicitors acting for the plaintiffs in claims brought against the SWWA Residuary Body. Results were published in 1990 and in 1993. Professor McMillan informed us that there was some overlap between the two groups described in the publications but that they were not identical. This means that the results for some people may appear in both papers. The work is summarised below.

5.82 The first report (McMillan, 1990) describes a serial cognitive assessment in a group of 11 individuals (4 males, 7 females), aged 17-71 years. The battery of tests administered is given in Table 40. All were resident in or around Camelford at the time of the pollution incident, one was a holidaymaker and the remainder resided permanently in North Cornwall. None had any significant psychiatric history prior to the incident.

5.83 No exposure assessment was reported and no control group was included. Professor McMillan considered that it was impossible to obtain a valid control group because of the publicity that there had been about the incident by the time of the first referral. Results were compared with published control data to assess whether or not they were abnormal.

5.84 Overall, IQ was reasonably consistent with that predicted from the NART reading test. Mean age-scaled scores on subtests comprising these IQ scales were unremarkable, apart from a high average score for the block design test (a test of spatial and constructional ability).

Table 40: Battery of tests administered by McMillan *et al* (1990, 1993)

Test	Function assessed
National Adult Reading Test (NART)	an estimation of pre-accident intelligence
Wechsler Adult Intelligence Scale Revised (WAIS-R)	current intelligence
Test of ability to learn verbal material	auditory verbal learning
Rey Figure test	spatial memory
Paced Auditory Serial Addition Test (PASAT)	information processing
'FAS' Verbal Fluency Text	fluency of speech
Beck Depression Inventory and routine clinical interview	severity of depressive symptomatology
Spielberger State-Trait Anxiety Inventory (STAI)	trait anxiety

5.85 The results of the tests for memory showed that there was no impairment of verbal memory nor of complex figure memory (Rey Figure test), but auditory verbal learning was impaired. Verbal fluency was average. Performance in the PASAT test was average when the auditory information was presented at a slower speed but not at a faster speed, indicating some impairment of information processing. Ability in the test of visuomotor coordination was not impaired initially (Trails A test) but when an added element requiring flexibility was added (Trails B test)[21], average performance was impaired.

5.86 The mean score for the Beck Depression Inventory was below that required for diagnosis of mild depression. Anxiety scores approximated to those of a control group of similar age although trait anxiety[22] was a little higher than expected.

5.87 It was concluded that there was evidence of cognitive impairment in the small sample of the population tested. The deficits found were mild to moderate, and unlikely to interfere with the ability to carry out day to day activities. It was not considered that the cognitive impairment was explained by current emotional factors such as low mood or anxiety, since there was no evidence for this. However, in the absence of a control group, and of any corroborating physiological or neurological evidence, it was not possible to say whether the cognitive impairments were due to organic damage.

5.88 The second paper (McMillan *et al*, 1993) reported on a group of 9 individuals (2 males, 7 females), aged 19-53 years, who underwent a repeated cognitive assessment between 8 and 26 months after the pollution incident. Two patients were tested at 8, 14 and 21 months after the incident; seven were examined at 12-17 and 26 months after the incident. All were referred by their GPs. Details of the

[21] The Trails A test requires the subject to join up a series of numbered dots on a piece of paper as quickly as possible. In the Trails B test, half the dots are numbered and half have letters. The task is to join the dots up in numerical/alphabetical order, alternating between the two types of symbol. The difference in the time taken to perform B vs A is taken as a measure of 'central' processing speed, independent of motoric factors.

[22] Trait anxiety is a measure of personality - the extent to which a person has an anxious disposition. It can be contrasted with state anxiety - transient anxiety associated with a specific event.

subjects, and how long after the incident they were investigated, are given in Table 41. No exposure assessment was reported and no control group was included for the reasons discussed above (McMillan *et al*, 1990). The same tests were used as described by McMillan *et al* (1990) (Table 40), with the addition of the Wechsler test of Logical Memory, which tests the ability to learn verbal material.

5.89 Other investigations comprised haematology and biochemistry tests; plasma aluminium, zinc and copper concentrations; blood lead concentration; erythrocyte sedimentation rate (ESR) and rheumatoid factor. Lung function tests were undertaken and 7 subjects underwent magnetic resonance imaging (MRI) of the brain. All patients underwent bone biopsy for histological investigation and measurement of aluminium content (these results are discussed elsewhere, see paragraphs 5.160 - 5.161).

Table 41: Details of subjects examined by McMillan *et al* (1993)

Patient	Age (years)	Gender	Time of neuropsychological assesment (months after the pollution incident)
1	42	F	8, 14, 21
2	49	M	8, 14, 21
3	19	F	12, 26
4	40	M	14, 26
5	42	F	13, 26
6	43	F	14,26
7	45	F	17,26
8	47	F	12,26
9	53	F	16,26

5.89 Neuropsychological tests revealed no impairment of intelligence in these subjects.

5.90 The auditory verbal learning test revealed impairment in 8 out of 9 subjects assessed 12 to 14 months after the incident and in 7 out of 9 subjects at follow-up. The test of complex figure memory revealed impairment in 5 out of 9 subjects at the first assessment and in 5 of the 8 subjects tested at the final assessment. The authors concluded that these results corroborated complaints of persistent impairment of memory in these subjects. The mean score in the PASAT test was lower than that in published control data at both the first and the final assessment. Overall, scores in the verbal fluency were reported as above average.

5.91 Two subjects were assessed as not being depressed at any time. Of the remaining 7, one showed evidence of depression at the first assessment. At follow-up, 4 out of 6 subjects were moderately to severely depressed as assessed by the self-report inventory; the other subject did not complete the inventory. Tests indicated little evidence of anxiety before the incident but, with time, the group exhibited anxiety. However, no significant correlation was found at any assessment between the results of those tests where the group scored poorly and questionnaire ratings of anxiety or of depression. In only one subject was there evidence that a possible psychological problem was present before the incident as judged from GP records or interview.

5.92 The paper stated that other tests revealed "no notable abnormalities".

5.93 The authors concluded that the results of the neuropsychological tests "revealed impairment of memory for new material and abnormalities of information processing in many of the patients. In particular, verbal learning was impaired." The authors also concluded that "In general, the lack of significant correlations between the anxiety and depression ratings and the scores upon which cognitive impairment was based suggests that cognitive impairment was not obviously influenced by anxiety or depression" but that "such an interpretation could not be excluded entirely… since the exact relationship between cognitive impairment and psychological dysfunction has not yet been clearly defined".

Psychometric assessment at the Clinical Psychology Department, St Lawrence's Hospital, Bodmin

5.94 A number of individuals underwent psychometric assessment at St Lawrence's Hospital, Bodmin by Mr A. Wilson. They were referred by GPs, solicitors, Dr Ian Coutts (consultant physician), Mr Peter Smith (homeopath), or they came forward on their own initiative. Formal assessments were undertaken on "about" 130 people between mid 1989 and 1992, most of whom were adults. However, the only publication was based on the results from 32 individuals, published in the Proceedings of the 1990 Truro Conference (Wilson, 1990).

5.95 The test used was the Wechsler Memory Scale – Revised (WMS-R), which examines different aspects of memory. A control group of individuals from Looe in South-East Cornwall (the number of controls was not given in publication) was also tested. These were matched for age, education and occupation but not for water intake or other variables. For all subjects, results of the WMS-R test were compared with the norms for gender and age. Mr Wilson explained to us, when we spoke with him on 6 May 2003, that he had obtained these data from the test manual.

5.96 According to Wilson, 1990, the results of the WMS-R test indicated that 75% of the Lowermoor group had significant memory deficit of some kind (1 standard deviation or more below the norm). The remaining 25% had "no significant memory deficit evident from the test (although their scores were considerably lower than expected according to age and educational background). The results of the Control Group showed no significant deficits below the norm."

5.97 It was also stated in the paper that "all (the Lowermoor individuals) reported memory losses of some kind since drinking the water" and that "the majority of the group recorded an overwhelming loss of confidence and ability to concentrate. Many felt tired, listless, anxious and vulnerable." Personality changes and loss of sense of judgement, direction and coordination were also reported. The paper concludes that "The WMS-R test reveals that the people referred ….as a group have significant memory deficits. The test results equate with the group's self-reports of short-term memory loss and deterioration in attention/concentration and delayed recall".

5.98 In discussion with us on 6 May 2003, Mr Wilson commented that he had been surprised at the results obtained for individuals from the affected area. He was of the opinion that these results were similar to those expected for individuals with a learning disability. Mr Wilson has also informed us that he saw his task at those times

as a need to quantify the cognitive difficulties reported by the clients concerned and to devise, if possible, rehabilitative steps for them.

Critical appraisal of McMillan (1990), McMillan et al (1993) and Wilson (1990)

5.99 Professor Rugg advised us that the tests used in these publications are standardized tests commonly used in neuropsychological assessment. However, in the context of assessing the effects of exposure to the contaminated water, he also advised us that it is difficult to draw conclusions from the results because of problems with the design of the studies. For example, it would be expected that those tested would be selected in a random manner from the population affected by the incident. This was not the case in these studies and thus the sample may not have been representative of the exposed population. In this context, in Professor McMillan's study, there were no controls for the reason he cites in paragraph 5.83. In Mr Wilson's study, the controls were not randomly selected and were not matched to the test subjects for all criteria. Some of the group sizes were very small. In addition, there was no quantitative information on the exposure of the subjects to the contaminated water. This makes it impossible to conclude whether or not the adverse findings are related to water quality. Therefore, in summary, the studies provide important, qualitative, observational data, but do not provide evidence of a causal link between the pollution incident and the adverse effects recorded.

5.100 We were informed by Dr Wainwright, the then Director of Psychology at St Lawrence's Hospital, Bodmin, that most of the results of Mr Wilson's tests were retrievable from St Lawrence's Hospital and we obtained a spreadsheet containing some anonymised, individual test data. We considered commissioning an analysis of these data but concluded that it would not be helpful, since it would be impossible to interpret the results in the absence of an appropriately selected control group and of exposure data.

The study by Altmann et al (1999) and colleagues

5.101 Altmann *et al* (1999) conducted a retrospective study of 55 individuals who claimed to have suffered cerebral damage. The intention was to establish whether these individuals had suffered organic brain damage as opposed to psychological trauma. It is not explicitly stated in the paper but it was implied that the subjects consumed contaminated drinking water. The study was conducted in 1991 but, for legal reasons, publication of the results was delayed until 1999.

5.102 The 55 people tested (25 males, 30 females), aged between 15 and 70 years, all of whom claimed to have suffered cerebral damage as a result of the contamination incident, were considering litigation. Fifteen siblings of the study group acted as controls. Each control was selected because they were nearest in age to one of the test group and did not live in the area receiving contaminated water at the time of the incident.

5.103 The psychological tests carried out in this study are shown in Table 42. Brain function in all participants was also examined by measuring the difference between

flash and pattern visual evoked potentials (VEPs)[23]. The authors considered that this could be used as an objective measure. They judged that this test would be resistant to any subject or observer bias (i.e. it would be impossible for the person carrying out the test or the person doing the test to produce an untrue result, either intentionally or unintentionally).

5.104 Standard clinical laboratory techniques were used to measure routine haematology and blood biochemistry parameters. Serum aluminium concentrations were performed by using a Varian AA1275 atomic absorption spectrophotometer and GTA95 electrothermal atomiser fitted with an autosampler.

Table 42: Tests carried out by Altmann *et al* (1999)

Test	**Characteristic assessed**
National Adult Reading Test (NART)	An estimation of pre-accident intelligence (pre-morbid IQ)
Bexley Maudsley automated psychological screening (BMAPS), (comprises 5 separate tests)	• visual spatial ability • visual perceptual analysis • verbal recognition memory • visual spatial recognition memory • cognitive impairment due to organic brain dysfunction (symbol-digit coding test[24])
Symptom checklist 90[25]	Anxiety

5.105 All 55 subjects complained of short term memory loss and impaired concentration. Visual analogue scales were used to score each subject's general appearance and affect and their own views of their symptoms one month after the incident and at the time of the study. The authors considered that the scores indicated deteriorating memory and concentration. Physical examination yielded no abnormal findings in test subjects.

5.106 The IQ assessment indicated that the test subjects were of above average intelligence before the incident (pre-morbid IQ). In the psychomotor tests (the Bexley Maudsley screening tests), the group performed less well on the symbol digit coding test[25] than the others. Overall, the participants performed below the level expected for their estimated premorbid IQ.

5.107 The results of the visual evoked potentials (VEP) of the test subjects were compared with historical control data obtained from 42 control subjects studied

[23] This technique involves presenting 2 types of visual stimulus: simple light flashes and a checker-board pattern. The brain responds with an electrical discharge (a "cortical potential") to both. A negative cortical potential is usually recorded in response to a flash, after around 120 milliseconds (msecs), and a positive response to a pattern after 100 milliseconds. The difference in time between the two responses is known as the "flash-pattern" difference (David AS and Wessely SC, 1995).

[24] In this test, the subject is given a sheet of paper with a number of different symbols drawn on it. Each symbol is coded with a unique number. The subject is then separately given another sheet with a row of the symbols on it and has to write down, in order, the numbers corresponding to each symbol within a given time period. This test is considered to be a sensitive measure of organic brain dysfunction.

[25] Described in Altmann *et al* (1999) as: "A multidimensional self report symptom inventory designd to measure symptomatic psychological stress (Derogatis, 1977)".

separately (mean age 44 $\pm$ 2 years). The mean flash-pattern difference of the test subjects was statistically significantly greater than for these control subjects. The authors report that there was an association between the flash-pattern difference and the symbol digit coding response times.

5.108 The authors stated that 36 of the 55 test subjects "were available for anxiety testing, which was carried out at a different location and time". Using symptom checklist 90, the authors concluded that the results indicated "relatively low levels of anxiety".

5.109 The results for the siblings showed that "although the sibling pairs were indistinguishable (paired Student's *t* test) in terms of age and pre-morbid IQ, the results of both the symbol-digit coding tests and the flash-pattern differences were significantly worse (by paired Student *t* test) in the Camelford participants than in their unexposed siblings".

5.110 There were no significant abnormal findings in the haematology or biochemistry analyses. Serum aluminium concentrations were less than 10 µg/l. The urinary aluminium concentrations were all within the normal range (less than 25 µg/day) "except for a minor increase in one participant". In several cases, current tap water aluminium concentrations in samples forwarded by participants were described as being "high" (the containers were supplied by the authors).

5.111 The authors concluded that the pattern of abnormalities seen was similar to findings they had previously described in "aluminium loaded but asymptomatic patients undergoing dialysis" (Altmann *et al*, 1989; Altmann, 1991). The authors also concluded that "these studies suggest the participants responded to (their) tests, as a group, in a manner compatible with the presence of organic brain disease and in a way similar to dialysis patients exposed to aluminium".

Critical appraisal of the study by Altmann et al (1999)

5.112 We have been advised by Professor Rugg that the overall pattern and consistency of response are the key features in assessing the implications of the test results in this study. No abnormalities were seen in most of the psychological tests, including those relating to memory, but there was a decrease in performance in the symbol digit coding test. Importantly, Professor Rugg considered that the decreased performance was unlikely to have been due to a psychological factor such as depression, nor to intentional bias. He suggested that the results are likely to indicate subtle neuropsychological effects. He further commented that the specific VEP measurement made in the study is not a method commonly used in neurological assessment, although abnormal patterns in these tests are seen in patients with aluminium neurotoxity. We are further advised by Professor Rugg that they are consistent with the results from the symbol digit coding test and that, overall, they suggest a subtle impairment of neurological function.

5.113 Nevertheless, it is impossible for us to attribute this impairment to the water pollution incident because of fundamental shortcomings in the study design. These are similar to those in the previous studies:

- the non random selection of test subjects,

- the lack of an appropriate control group (the use of siblings as controls was inappropriate as they would not have been blind to the purpose of the study, and their performance may have been influenced by knowledge of the complaints reported by their siblings),
- the lack of exposure data.

5.114 We are aware that the authors recognise that there are shortcomings in the study including the difficulties in assessing a self selected group. Dr Altmann told us, when we met him on 29 May 2002, that the funding and opportunity necessary for the design and completion of an ideal study were not available.

5.115 However, although it is not possible to conclude from this study that the contamination incident led to adverse neuropsychological effects in exposed individuals, we consider that the results indicate the need for further work and have been so advised by Professor Rugg. We have made recommendations for such work in Chapter 9.

Analysis of educational assessment test results in schoolchildren (McMillan et al, 1993)

5.116 We have placed a discussion of this paper in this section of our report because McMillan *et al* (1993) comment that "any widespread and marked psychological effects on children (receiving contaminated water) might have been expected to have had an impact on Richmond Test performance." They further comment that these tests were the only pre- and post-pollution psychological test data available on the "population of Lowermoor" before and after the accident.

5.117 The study made use of Richmond Tests administered to schoolchildren in Cornwall, as part of their routine, continuing educational assessment. The results of the tests carried out in May 1988 (before the contamination incident), and those carried out in May 1989 and May 1990 (after the incident) were analysed.

The Richmond Tests

5.118 Richmond Tests are tests of educational attainment rather than of cognitive ability and comprise a battery of 11 separate tests which are used to assess a child's development. Each test has six levels of difficulty and is administered in four sessions, lasting a total of 5.25 hours. They are suitable for children between 8 and 14 years of age and are usually administered and scored by teachers. Standard age scores (the scores expected for the age group) have an average of 100 and a standard deviation of 15. Richmond Tests are not designed to pick up subtle or transient effects or effects on memory. However, any widespread and marked effects on childrens' cognitive function would be expected to affect performance in these tests (McMillan *et al*, 1993).

Study design

5.119 The subjects were 39 children from four schools in "the Lowermoor area of North Cornwall" (not further defined) who were aged either 8 or 9 years in 1988. They comprise the entire population of schoolchildren in this age group from schools in the affected area who completed Richmond Tests, between 1988 and 1990. Data

from children with special educational needs, attending special schools, were not available to the authors. A sample of 64 schoolchildren, also aged either 8 or 9 years, from nine Cornish schools outside the affected area, formed the control group. Controls were otherwise selected simply on the basis of having taken the Richmond Tests each year between 1988 and 1990 *(sic)*. Scores, standardised by age, were compared between the test group and control group.

Results

5.120 Before the incident, there was no significant difference between average test results for the Lowermoor and control areas. After the incident, there was no change in performance in subjects from the 4 schools in the Lowermoor area, nor any difference in the children's performance compared to control schoolchildren (see Table 43).

Table 43: Average Richmond Test scores and year of administration

Location	Year	Average score (SD)
Lowermoor	1988	104.3 (9.9)
	1989	103.6 (9.0)
	1990	104.5 (9.9)
Control	1988	105.9 (11.2)
	1989	105.8 (12.0)
	1990	106.7 (12.4)

Source: McMillan *et al* (1993)

5.121 The authors noted that not all of the children in the Lowermoor area necessarily drank the polluted water. Nevertheless, if there had been an effect on Richmond Tests performance which had persisted for the 10 months after the incident, the authors would have expected a larger group of test children than of control children would have shown a deterioration in test performance when comparing the 1988 and 1989 scores. There was no indication of this.

5.122 It was concluded that the findings suggest that there was "no gross effect on school achievement in this subgroup of the Lowermoor population."

Critical appraisal of the study by McMillan et al (1993)

5.123 The authors noted a number of limitations to their study. Firstly, the Richmond Tests would not normally have been those chosen in order to detect possible cognitive effects of the water pollution. However, they were the only relevant pre- and post-incident test data available. Secondly, the study used test scores which had been standardised to account for age (scaled scores). Raw test scores could not be used because they are not routinely retained by schools and thus were no longer available when the data was requested for this study in 1991. This means that possible changes in individual test scores caused by exposure to contaminated water could have been masked by the scaling procedure. The data allowed only a relatively rough indication of change over time. Lastly, the authors note that any conclusions drawn from this study apply only to children aged 8 or 9 years, and might not be valid in other age groups who may be more or less susceptible to effects of contaminants.

5.124 We agree with the authors about these limitations. In addition, we note that the number of children for whom test results were available for analysis in this study was very small (39 children from the Lowermoor area, 64 controls) and insufficient to detect a small difference between scores (e.g. 2 to 3 points) in children from the affected and control areas. To detect a difference of 3 points with 80% confidence, approximately 200 children would be needed in each group; and in order to detect a difference of 2 points, approximately 400 children would be needed in each group. Therefore, the study does not rule out the possibility that a small effect may have occurred.

Questionnaire Surveys

5.125 A questionnaire survey was carried out by Mr Doug Cross and Dr Richard Newman soon after the contamination incident to gauge the scale of the immediate health impact. Preliminary results of completed forms for 200 individuals were reported in a paper prepared by the Camelford Scientific Advisory Panel, dated 15 August 1988 (Cross, personal communication, May 2002 and November 2004).

5.126 In the survey, copies of a form were made available at "accessible points in the main villages" in the area and an announcement was made on Radio Cornwall to inform listeners of this. The form listed a number of signs or symptoms and asked responders to tick those which they considered that they and their families had suffered as a direct result of the incident.

5.127 The effects reported in the sample for which results were available comprised: sore mouth, tongue or throat (reported by 68% of sample); feeling generally unwell or very tired (63%); very thirsty (50%); stomach ache, nausea and/or vomiting and diarrhoea (38-48%); sore eyes (35%); mouth ulcers (23%); muscle cramps (23%); increased pain of pre-existing arthritis (22%); onset of new joint pains (21%); skin rash (18%); urinary tract problems (11%) and recurrence of dormant eczema (9%).

5.128 Bridges (1989), in a report prepared for the police in June 1989, refers to a further questionnaire survey. He states: "…we have attempted to characterise the (health) effects by administering a questionnaire to a number of consumers in the affected area. Between 13.3.89 and 14.4.89, questionnaires were sent to 848 individuals selected on the basis of persons who have made a claim either directly or through a solicitor against SWWA, or who contacted their General Practitioner following some illness. Of these, 476 had responded by 17.5.89. The questionnaire was devised to get a profile of effects which were experienced at various times following the incident from a few hours to several weeks."

5.129 The results from the questionnaire were analysed in two categories: acute effects (those experienced within one week of the incident) and longer term effects (Bridges, 1989). The acute effects reported comprised aches in joints (48%), tiredness (42%), generally feeling unwell (41%), lethargy (34%), headaches (27%), lack of stamina (25%), loss of memory (25%), loss of concentration (25%), dizziness (15%), gastrointestinal effects (diarrhoea, sore mouth, dry mouth, nausea, stomach pains, sore throat, and sickness and vomiting (19 to 35%)), and irritant effects (itchy skin, sore and itchy eyes, and rashes (16 to 26%)).

5.130 With regard to longer term effects, Bridges (1989) reports that many of the symptoms which were experienced shortly after the incident continued for more than 14 days. The most commonly reported symptom was aches in joints (42% of respondents). Tiredness and lethargy, feeling unwell, persistent sore mouth and sore throat, and itchy skin were reported to be other notable symptoms.

Homeopathic data

5.131 A report prepared for the North Cornwall Homeopathic Project (NCHP) describes symptoms reported by individuals who considered that they had been affected by the Lowermoor water pollution incident (Smith *et al*, 1992). A copy of the report is attached at Appendix 19. The individuals had either received homeopathic treatment from, or had given information to, the NCHP and the Lowermoor Support Group. The report lists symptoms in 30 men and 40 women as at 8 March 1992. Three hundred and seventy different symptoms are presented in total. The symptoms described are similar to those described to us in interviews with members of the public or in written information (see paragraphs 5.15 to 5.17 and Tables 31 and 32). The most commonly reported symptoms (occurring in over 50% of individuals) included anxiety; depression; difficulties with concentration; an inability to cope; irritability; tiredness; lethargy; exhaustion; confusion; malaise; memory problems; and a dry thirst.

5.132 The report also states "Some 19 men and 42 women, not all in this group, have demonstrated a clear sensitivity to tapwater." This sensitivity has been further described as a reaction occurring within 20 minutes of consuming the water, which is associated with aching, gut pains, headaches and other symptoms (Smith, personal communication, 2004). The individuals were reported to react in this way even when they did not know that they were drinking local tapwater because they had been given it by family or friends. When individuals avoided the tapwater, their health improved.

5.133 This reaction does not seem to be the immune condition defined as sensitisation. In this immune condition, the body makes an antibody to the sensitising agent (the 'antigen'). When the antigen subsequently enters the body, an antigen-antibody reaction occurs which initiates a reproducible immune reaction. The symptoms of this can be gastrointestinal (nausea and vomiting, abdominal pain and diarrhoea). They would be expected to occur on ingestion of the substance to which the individual is sensitised, whether the substance is present in drinking water, food or any other source. Immunological dysfunction of this type can be tested for, and we note that testing was made available through local GPs after the 1991 LIHAG report, but was not taken up.

5.134 In the context of the reaction described in paragraph 5.132, we have discussed the condition termed "chemical sensitivity" (Rea, 1997). As described by Rea, chemical sensitivity "can be triggered by a single, acute environmental exposure or by multiple exposures occurring over time. It can involve any or all of a majority of anatomical systems, manifesting as an isolated symptom restricted to one organ or a multiple of symptoms and signs involving one or more organs."

5.135 A review of the related topic of Multiple Chemical Sensitivity (MCS), now termed Idiopathic Environmental Intolerance (IEI), was carried out by the Institute of Occupational Medicine (Graveling *et al*, 1999) and the issue has been considered by the COT on three occasions (Committee on Toxicity 2000, 2001, 2011). The review

describes a large number of case series of sensitivity to chemicals and notes that the condition is not based on, or supported by, firm mechanistic evidence. A further difficulty is the lack of a robust means of diagnosis. The COT, in its most recent consideration, was unable to identify any toxic mechanism that could satisfactorily account for all of the clinical features and descriptive epidemiology of the condition. In particular, the COT found no convincing evidence for any biological mechanism that would explain why such diverse symptoms are induced in some individuals by such a wide range of chemicals, at levels of exposure well below those that are tolerated by the majority of people (Committee on Toxicity, 2011).

Study of absorption of aluminium in local individuals

5.136 An individual sent us a copy of a protocol and the results from a study of the intestinal absorption of aluminium carried out in 1990 by Dr Andrew Taylor, Department of Clinical Biochemistry, St Luke's Hospital, Guildford. The study population comprised 6 adult volunteers who had consumed contaminated water. Serum aluminium concentrations in these individuals were analysed three times: (1) in basal conditions, (2) following one week's consumption of tap water collected at Guildford, where the aluminium concentrations are described as "less than 0.01 mg aluminium/l", and (3) following a further week's consumption of tap water from the same source but supplemented to contain aluminium at 0.2 mg/l . Mean serum aluminium concentrations are reported as 0.24 + 0.15, 0.12 + 0.03, and 0.24 + 0.12 mg aluminium/l, respectively. We are unable to draw conclusions from this study for a number of reasons including the failure to control for intake of aluminium from food, lack of controls, and high and overlapping confidence intervals.

Case of severe congophilic angiopathy in a resident of Camelford

5.137 During the final stages of our investigation, we were made aware of an enquiry by the West Somerset coroner into the death of a 59-year old individual who lived in Camelford at the time of the Lowermoor incident and who had died in 2004 after a short illness with symptoms of dementia. The cause of death was given as severe cerebral amyloid angiopathy (CAA) (also called congophilic angiopathy or beta amyloid angiopathy), a form of cerebrovascular disease usually associated with Alzheimer's disease.

5.138 We received advice on CAA from Dr A Davies-Jones, consultant neurologist at The Royal Hallamshire Hospital, Sheffield. He advised us that there are two types of CAA - familial and sporadic (Davies-Jones, personal communication, 2006). We were informed that there was no history of neurodegenerative disease in the individual's family (personal communication from family member, December 2005).

5.139 Dr Davies-Jones informed us that the classic presentation of CAA is lobar cerebral haemorrhage, often recurrent and multi-focal, in an elderly individual. The other presentations are recurrent transient cerebral neurological symptoms and deficits or a rapidly progressive dementia. Both may occur in the same individual. Dementia is quite frequent and more rapidly progressive than Alzheimer's disease, and typically is stepwise or stuttering in progression. Over 40% of patients with CAA-related intracranial haemorrhages have some degree of dementia during life and at least a similar number show changes at autopsy (Vinters, 1987).

5.140 CAA is present in up to 92% of the brains of persons with Alzheimer's disease. However, CAA can occur without the other pathological changes of Alzheimer's disease, and Alzheimer's disease can occur without the changes of CAA. CAA is found in normal asymptomatic elderly individuals - 36% in an autopsy series of normal brains (Tomonaga, 1981). Unselected adult autopsy series estimate the frequency of CAA with or without cerebral haemorrhage to be between 23% and 57%. The most important risk factor for sporadic CAA is age. In a series of 128 brains from elderly subjects, Tomonaga (1981) found CAA in 8% of subjects aged 60-69, 20% of those aged 70-79, 37% of those aged 80-89, and 58% of those aged 90 or older. The overall incidence was 36%. Sporadic CAA is almost never seen in persons under 50 years of age (Davies-Jones, personal communication, 2006).

5.141 Exley and Esiri (2006) have reported on the neuropathology of the brain in the present case and on aluminium concentrations in samples taken from affected areas of the brain. There was no evidence of presenilin 1 mutations which are causative for Alzheimer's disease. Apolipoprotein E (APOE) genotype was found to be ε4/4, which is associated with an increased risk of developing Alzheimer's disease (Blennow *et al*, 2006). At a meeting with Professor Esiri at our meeting on 16 October 2012, she informed us that, although Lewy bodies were present in the brain, there were no senile plaques, and the pathology was not characteristic of Alzheimer's disease. She was aware of one other case in the literature of severe CAA not associated with Alzheimer's disease. In this case, a 14 year old boy, the distribution of CAA was very different to that in the current case (Shaw, 1979).

5.142 The concentrations of aluminium found in the samples of the individual's brain and the brains of three other individuals analysed by Exley and Esiri (2006) are given in Table 44. The information provided to us about the individuals concerned is as follows:

Case 1: the Camelford individual (frontal cortex samples),
Case 2: an individual with neuropathology similar to that of the Camelford case, but 22 years older and of unknown origin and aluminium exposure,
Case 3: an individual with classical Alzheimer's disease,
Case 4: an elderly individual with depression without dementia.

5.143 Normal concentrations of aluminium in the brain are given by IPCS (1997), based largely on historical data, as 0.23 to 11.9 µg/g dry weight. Andrasi *et al* (2005) quotes concentrations of 1.4 to 2.5 µg/g dry weight in 3 subjects. Typical cortical concentrations in Alzheimer's disease were found to range from 6.4 to 10.2 µg aluminium/g dry weight in 3 subjects. A recent paper measured the levels of aluminium in over 700 samples of tissue from 60 brains which had been donated to the Medical Research Council (MRC) study on Cognitive Function and Aging (http://www.cfas.ac.uk/). The ages of the donors of the 60 brains ranged from 70 to 103 years. Concentrations of aluminium ranged from the Method Blank Value[26] to 33 µg aluminium/g dry weight with a median value of 1.02 mg/kg dry weight (House et al, 2012).

[26] To estimate contamination of the samples, 170+ method blanks were prepared, interspersed with the tissue digests and analysed. The Method Blank Values (MBV) were then subtracted from the tissue digest values to give aluminium content in the range MBV to 33 µg aluminium/g dry weight

Table 44: Aluminium concentrations in brain samples analysed by Esiri and Exley (2006)

	Case 1	Case 2	Case 3	Case 4
No. samples	5	2	1	1
Concentration of aluminium in each sample (µg/g dry weight)	3.24 4.33 5.71 11.01 23.00	4.76 25.16	2.46	1.47

5.144 During our first discussion with Professor Esiri in January 2007, she suggested a number of useful lines of further research and called our attention to the publication by Pratico *et al* (2002) (reviewed in Appendix 22) which reported that feeding an aluminium-enriched diet for 9 months to transgenic mice predisposed to Alzheimer's disease led to increased amyloid β peptide formation and deposition in the brain. She was not aware of any evidence that the APOE ε4/4 genotype was associated with an increase in aluminium absorption. In a study in France on individuals exposed to different concentrations of aluminium in drinking water, Rondeau *et al* (2006) found that there was no significant interaction between APOE ε4 and aluminium exposure on the risk of Alzheimer's disease (see Appendix 25).

5.145 An editorial which accompanied the publication by Exley and Esiri noted a number of uncertainties, for example, that the environmental source of aluminium in the brain is unclear, and commented that the role of aluminium in the pathogenesis of Alzheimer's disease remains controversial (Perl, 2006).

5.146 In the course of the coroner's enquiry into the death of this individual, he commissioned further work into the metal content and pathology of tissue from 60 postmortem brains donated to the MRC study on Cognitive Function and Aging (see paragraph 5.143). As well as aluminium, iron and copper content were determined in samples of tissue, and the extent and severity of CAA and senile plaque density were scored in sections of the frontal, temporal, parietal and occipital cortex. There were no statistically significant correlations between age of donor and brain burden of aluminium, iron or copper. Age of donor was statistically significantly positively correlated with brian burden of CAA and senile plaques although, when individuals without CAA or without senile plaques were excluded from the analyses, the positive correlations were no longer statistically significant. There was a positive statistically significant correlation between the brain burden of CAA and that of senile plaques. There were no statistically significant correlations between the brain burden of aluminium or iron and that of CAA or senile plaques. There was a negative correlation between brain copper burden and the degree of severity of both senile plaque and congophilic amyloid angiopathies, with the former reaching statistical significance when zero values for CAA and senile plaques were excluded from the analysis (House et al, 2012; Exley et al, 2012).

5.147 We discussed this work with two of the authors, Dr Exley and Professor Esiri, at our meeting on 16 October 2012. They commented that it was necessary to be cautious in concluding that there was no association between aluminium and CAA on the basis of this work given the variability found in the levels of each in the brain.

5.148 The coroner's enquiry concluded in March 2012. He received confirmation during the inquest from two consultant neuropathologists that it is exceptionally rare for an individual as young as the subject of the enquiry to develop CAA. The coroner concluded his verdict as follows:

"As the deceased was exposed to an excessive amount of aluminium in July 1988 and in the absence of any evidence of any other incident or occasion when she might have ingested an excessive amount of aluminium, the aluminium discharged as a result of the problems at Lowermoor Treatment Works at the beginning of July 1988 give rise to the very real possibility that such aluminium may be a factor in her death.

"The cause of her death Cerebral B amyloid angiopathy is a common accompaniment of Alzheimer's diseases but findings of Alzheimer's disease were not present in her brain. The high levels of aluminium which were found in her brain may have increased the peptide B-amyloid there.

"Despite the fact she had a genotype with 2 alleles for ApoE4 (a strong risk factor for Alzheimer's disease and CAA in old age), in the absence of any evidence of a genetic cause of Alzheimer's disease and CAA, the very real possibility exists that her death was contributed by the ingestion of aluminium.

"However as this would be the first such reported case of severe CAA without associated Alzheimer's pathology in the United Kingdom in someone of this age, the suggestion that aluminium was a causative factor must remain only a slight possibility."

A copy of the coroner's summing-up, which includes the verdict, can be found in Appendix 20.

5.149 The case described above is clearly an important observation but we agree that there are many uncertainties which make it impossible to conclude whether it is causally associated with the contamination incident or not. These include lack of information on the causes of congophilic angiopathy and on whether the high concentrations of aluminium in the brain were causal to or consequent upon the development of congophilic angiopathy. We consider that further work is required to follow up this observation and we make recommendations in Chapter 9.

Data on Educational Assessment

Children with special education needs

What are Special Educational Needs?

5.150 Special Educational Needs (SEN) is a very broad term which covers the full range of children's needs, from mild dyslexia and behavioural problems to complex medical conditions. Children with SEN have in common the need for some 'additional or different provision' in school (Audit Commission, 2002).

5.151 SEN assessments between 1994 and 2001 were based on definitions provided in the 1994 Code of Practice issued by the Department for Education (DFE, 1994). That Code

gave practical guidance to Local Educational Authorities (LEAs) and to the governing bodies of all maintained schools concerning their responsibilities to children with SEN. The Code presents a 5 stage strategy:

- **Stage 1**: class or subject teachers identify or register a child's special educational needs and, consulting the school's SEN coordinator, take initial action.

- **Stage 2**: the school's SEN coordinator takes lead responsibility for gathering information and for coordinating the child's special educational provision, working with the child's teachers.

- **Stage 3**: teachers and the SEN coordinator are supported by specialists from outside the school.

- **Stage 4**: the LEA considers the need for a statutory assessment and, if appropriate, makes a multidisciplinary assessment.

- **Stage 5**: the LEA considers the need for a statement of special educational needs and, if appropriate, make a statement and arrange, monitor and review provision.

5.152 The first three stages are based at school. At stages 4 and 5 the LEA shares responsibility and the provision of resources with the school. The Stage 5 "Statement" contains prescribed information identifying the child's special educational needs, the special educational provision required, the placement (location where the special provision is to be provided) together with the non-educational needs and their provision[27]. Schools make an annual return in January of each year to report numbers of children on the register at the various stages of assessment.

5.153 In January 2002, a new Code of Practice came into force which replaced the 5-stage programme described above, although statutory assessments and "Statements" of special needs are still required (Audit Commission, 2002).

Statements (SEN Stage 5)

5.154 According to the Audit Commission (2002), several factors independent of a child's level of need appear to influence the likelihood of a statement being made. These include differing local educational policies, decisions to delegate SEN budgets to schools, and factors relating to individual schools. The proportion of children with statements varies fivefold between local authorities – ranging from 1% to 5% of pupils in England and Wales (Audit Commission, 2002). More children than those who have been formally classified as SEN Stage 5 are likely to have special educational needs. Socioeconomic and health inequalities are closely linked (Acheson, 1998) and this may account for the consistent small increase in the percentage of children with SEN in Cornwall when compared to England as a whole and to Devon. A child with certain needs living in one area may be less likely to be classified as SEN Stage 5 than a child with the same needs living in another area with a higher level of resource provision. The link between special education needs and socio-economic factors has long been noted, although there is only a weak correlation between the prevalence of children classified as SEN Stage 5 in local authority areas and the level of deprivation.

[27] In common usage this is referred to as a child being 'statemented'

Local concerns

5.155 Mr Constable, then a Devon journalist, wrote to us in February 2002 with data on the proportions of SEN children in primary and secondary schools in Cornwall (Constable, personal communication, 2002). The key data related to the numbers of SEN children at Stage 5 in secondary schools in North Cornwall, compared to those for all other secondary schools in Cornwall. The data showed that there was a higher proportion of children with full SEN statements in the 5 secondary schools in North Cornwall, between the years 1997 and 2000, than in schools in the rest of Cornwall. An informal, preliminary statistical analysis, carried out for Mr Constable by Dr Ken Read, Senior Lecturer in Mathematical Statistics at Exeter University, showed that this difference was statistically significant in 1998 ($p<0.001$), 1999 ($p<0.001$) and 2000 ($p<0.01$). Concern was expressed locally that the higher proportion of SEN Stage 5 children could be related to exposure to contaminated water following the pollution incident either in the womb or in early life.

Information from Cornwall Local Education Authority (LEA)

5.156 We sought information from Cornwall LEA, who informed us that there are 55 schools in the North Cornwall district, of which 50 are primary schools (Colvill, personal communication, March 2002). The 5 secondary schools were at Camelford, Launceston, Bude, Wadebridge and Bodmin. The Camelford secondary school, Sir James Smith's School, had intakes of pupils from 5 primary schools which are believed to have received water from the Lowermoor Water Treatment Works, namely Otterham, St Teath, Camelford County Primary, Port Isaac County Primary and Delabole County Primary. Thus, Sir James Smith's School was likely to have had the highest proportion of children in North Cornwall from the area with the contaminated water supply. It was therefore relevant to compare SEN Stage 5 rates at this school with those for other North Cornwall secondary schools. However, it must be noted that children from the area will also have gone to other secondary schools.

5.157 Table 45 presents the data on the percentage of SEN Stage 5 children in Sir James Smith's school, other North Cornwall schools (combined) and all other Cornwall schools (combined) for the years 1997 to 2001, inclusive, and compares them with the percentage for England as a whole (Colvill, personal communication, May 2002). It should be noted that 1997 data refers to children born between the years 1979 and 1985. These were approximately 3 to 11 years old at the time of the incident. The 2001 data would refer to children born in the years 1983 to 1989. Some children born in 1989 would have been *in utero* at the time of the incident, all others being aged 0 to 5 years of age.

Table 45: Percentages of Children with Statements (SEN Stage 5), 1997 - 2001

Year[a]	Sir James Smith's School (SJS), Camelford	N Cornwall Schools (excluding SJS) (n=4)	All Cornwall schools (excluding SJS)	England as whole[b]
1997	4.3%	5.5%	5.0%	2.90%
1998	5.5%	6.5%	5.2%	2.95%
1999	6.6%	6.2%	5.2%	3.00%
2000	5.1%	6.0%	5.1%	3.05%
2001	3.8%	4.7%	4.7%	3.10%

a: 'Year' means the year in which the annual return is made i.e.1997 data relates to the school year 1996-7.
b: Source: Audit Commission (2002).

5.158 The data in Table 45 do not indicate any consistent difference in percentages of children with statements between Sir James Smith's School, Camelford and other schools in Cornwall, although all these percentages were higher than national percentages. With the exclusion of the percentages for Sir James Smith's School, rates of SEN Stage 5 children in North Cornwall schools were higher than those in all Cornwall schools for the years 1997-2000. In 2001, the percentages were the same.

Expert opinion on SEN data

5.159 In 2002, we sought the advice of two expert educational psychologists in interpreting these data: Dr Norah Frederickson from University College, London, and Professor Irvine Gersch from The University of East London. We were advised that the determination of children with SEN is influenced by many different factors including the referral rates within schools, local socio-economic factors, the quality of teaching and provision, migration effects, the criteria used for determining the degree of special need required for an LEA to agree an assessment and Statement, availability of Education Psychologists, parental pressure, SEN Tribunal directions locally and their impact upon LEA decision making, collaboration with health and Social Service Departments and schools' policy on inclusion and SEN and a schools's capacity to meet the needs of children with SEN. Therefore, no conclusions can be drawn from the SEN figures in relation to long term impact of the incident on health. It was also pointed out that it was difficult to interpret the data in terms of the pollution incident as they do not distinguish between children who may have drunk the contaminated water (or whose mothers may have drunk it when pregnant) and those children who did not drink it (Frederickson, personal communication, 2002; Gersch, personal communication, 2002).

Tissue analyses

5.160 A small number of samples of blood and other tissues were taken for analysis immediately after the pollution incident but the majority of samples were collected much later. The published data are summarised below.

Taylor (1990)

5.161 Taylor (1990) reported that 31 serum samples from 23 individuals, defined as "residents of North Cornwall and individuals who were on holiday in the area at that time" were collected during the year following the pollution incident. The first samples were taken in August 1988 and further samples were taken between January

to June 1989. In no case was patient-specific information provided. A concentration of 10 μg/l was taken as the upper reference concentration for serum aluminium and 21 samples were found to contain more than this. The results were scattered and there was no trend with time.

Eastwood *et al* (1990)

5.162 Eastwood *et al* (1990) took bone biopsy samples from two individuals (1 male aged 49, 1 female aged 41 years) between 6 and 7 months after the incident. Both individuals are reported to have had acute symptoms following the incident (including mouth and nasal ulceration) and were unwell at the time the biopsies were taken. Concentrations of aluminium, copper and zinc in plasma and of lead in blood were within the normal range. Both bone biopsies contained infrequent, discrete lines of positive staining for aluminium between 15 and 40 μm beneath the bone surface. Staining was carried out with solochrome azurine at pH 5, a sensitive technique for detecting aluminium deposits. Using an electronmicroscopic technique, aluminium was detected in one biopsy in a single trabeculum. However, the concentration of aluminium in the bone samples was within the normal range. Stains for iron and copper and the use of an electronmicroscopic technique to detect iron, copper, beryllium, titanium and lead were negative in both subjects.

5.163 The authors state that they have previously examined several thousand specimens stained with solochrome azurine and had only previously found positive staining in patients undergoing regular dialysis and in those with renal failure not on dialysis who were ingesting aluminium-containing phosphate binders.

McMillan *et al* (1993)

5.164 McMillan *et al* (1993) took further bone biopsies from the two individuals described in paragraphs 5.158 to 5.159 19 months after the incident. Biopsies were also taken from a further 8 individuals (2 males, 6 females, aged between 19 and 79 years) at 12 and 17 months after the incident. All individuals had lived "in the Camelford area" for up to 17 years. Bone aluminium concentrations were also measured, using the methodology described above.

5.165 In the two patients in whom aluminium had been found earlier, there was no residual staining and all quantitative and qualitative measures were normal (no detail supplied). The paper also reports that "In 7 patients dynamic bone measurements were normal. In 4 of the 7, cancellous bone volume was normal; in 3 there was borderline osteopenia (2 to 3 S.D. below means of a control group matched for age and sex) of uncertain significance. One bone sample was lost. The aluminium content of the bones of the 8 patients assayed was normal (1.12-6.26 μg/g dry weight)."

Powell *et al* (1995)

Study No. 1

5.166 Powell *et al* (1995) took blood and hair samples 31 months after the incident from 14 residents from the Lowermoor supply area (5 males, 9 females, mean age 48 years). The subjects were recruited through their GPs and had continued to report adverse health effects. The samples were analysed for trace metals. Whole blood lead and plasma zinc, copper, iron and magnesium concentrations were normal.

However, one individual had sufficiently long hair to date back to mid-1988 and metal analysis within that hair using a nuclear technique (thus avoiding surface contamination) detected lead (maximum concentration 6±3 μg/g), but no other metals, in 3.5 cm of the distal end of the hair i.e. the section of hair corresponding to the time of the incident. However, no lead was detected more proximally (detection limit 1 μg/g).

Study No. 2

5.167 Thirty-five months after the incident, further long hair samples were taken from another 5 individuals (all female, aged 20-45 years) from the Camelford area. One individual reported that she had consumed only contaminated water at the time, two reported that they had drunk some contaminated water, and two reported that they had mainly consumed bottled water. In hair samples corresponding to the time of the incident, high lead (maximum concentration 13±5 μg/g) were found in the distal 3 cm of hair from the individual who reported drinking only contaminated water. Increased lead concentrations (3-5±3 μg/g) were found in the two individuals who reported drinking some contaminated water. No lead (<1 μg/g) was found in the hair samples of the two individuals who reported drinking mainly bottled water.

Study No. 3

5.168 Forty-two months after the incident, a third study was carried out involving 9 individuals (7 males, 2 females, aged 25-60 years) from the Lowermoor area who continued to complain of symptoms. They were given calcium (ethylenedinitrilo)tetraacetic acid (Ca-EDTA) to mobilise tissue lead into the urine. Five of these individuals were from the original group of 14 and an additional four were recruited through local GPs. Results showed the expected increases of lead excretion in response to EDTA administration and no evidence of abnormal body lead burdens.

5.169 The authors concluded that the results indicate that the presence of lead in sections of hair indicate that an acute exposure to lead occurred in these individuals but that such brief exposure is of no known clinical significance (Powell *et al*, 1995).

Howard (1993)

5.170 This study was undertaken by Dr Ward of Surrey University and was presented in an MSc thesis in statistics by Ms P Howard (Howard, 1993). Additional data were provided to the subgroup by Dr Ward at a meeting on 30 September 2002.

5.171 Six months after the pollution incident, 435 “local residents of North Cornwall” participated in a study arranged through a local GP in which scalp hair, fingernail, toenail, urine, saliva and blood samples were analysed for 7 elements (aluminium, calcium, copper, iron, lead, magnesium and zinc). The results for 231 individuals (91 males, 139 females, 1 unrecorded gender) were reported in the MSc Thesis (Howard, 1993). Individuals were classified into 5 groups: 3 groups with individuals from the affected area classified according to type of symptom (n = 30, 120 and 14, respectively); one group from the affected area with no symptoms (n = 39); and one group with individuals from outside the area with acute and chronic symptoms (no further details supplied) (n = 28) (Ward, personal communication, 2002).

5.172 The analyses demonstrated raised aluminium concentrations in hair samples, but lowered aluminium concentrations in fingernail and toenail samples among those within symptomatic groups compared to the group without symptoms. The aluminium to zinc ratio was higher in the groups with symptoms than that in the group without symptoms in blood, scalp hair (both $p<0.0001$), urine and toenails (both $p<0.05$).

5.173 Further sampling took place in 2002 from 27 individuals from within the population of 435 individuals referred to above. Of these, 12 continued to report that they were affected by the contamination incident, describing joint pains, depression, concentration difficulties and problems with speech. The remaining 15 were no longer reporting adverse effects. Serum concentrations of all metals were now similar in symptomatic and non-symptomatic individuals. In scalp hair samples the mean aluminium and copper concentrations were slightly higher in the symptomatic group. One individual continued to have the highest aluminium concentration in blood, washed scalp hair and nails, and the lowest iron and zinc concentrations of all the samples analysed. This individual was reported to have numerous health problems, including major concentration and memory difficulties, mouth ulcers, speech problems, and stomach and bowel irritation (Ward, personal communication, 2002).

5.174 In discussion with the subgroup in 2002, Dr Ward expressed the view that consumption of high copper and aluminium concentrations in the contaminated water after the pollution incident led to increased body burdens of these metals and lowered concentrations of zinc and, in some cases, iron.

Ward (1989)

5.175 Ward (1989) took samples of washed scalp hair, finger nails, urine, saliva, whole blood and serum samples from three groups of holiday makers: (i) 21 children, (ii) 18 adults and (iii) 9 'senior adults[28]', all of whom are reported to have been exposed to contaminated water for more than 5 days following the Lowermoor incident. It is not clear when the samples were taken but all individuals are reported as having health problems which persisted for more than 6 months. The samples were analysed for aluminium, calcium, copper, iron and zinc, and the results were compared with reference values taken from the scientific literature.

5.176 Hair and nail samples from all 3 groups showed elevated copper and aluminium concentrations, whereas concentrations of iron and zinc in these tissues were below the reference values. In the two adult groups, some individuals had raised calcium concentrations in hair and nail. The results for urine, saliva, whole blood and blood serum analyses did not show such a clear pattern. All groups contained some individuals with increased aluminium, copper and calcium concentrations, and lowered iron and zinc excretion in the urine.

Critical appraisal of studies on tissue analysis (paragraphs 5.161 to 5.176)

5.177 All these studies are difficult to interpret because of deficiencies in the conduct of the study and/or in the manner in which the study was reported. There were no concurrent controls in most of the studies. There are controls in the studies by Ward of residents (Howard, 1993; Ward, personal communication, 2002) but it is not clear if these were

[28] 'Senior adult' is defined in the paper as aged more than 60 years of age

matched to the subjects receiving contaminated water. In no study was there sufficient demographic information about the subjects tested or how they were selected.

5.178 We note that the results of hair analyses by Powell *et al* (1995) indicate that some individuals may have suffered an acute exposure to high concentrations of lead. It is not clear from the scientific literature whether metal concentrations in hair are a good quantitative indicator of exposure to metals, although they are used as a screen for metal deficiency in certain contexts e.g. in the developing world (Takyi, 2000). Wilhelm *et al* (1989) and Wilhelm and Idel (1996) favoured the use of hair analysis as a screening method for measurement of exposure but Wilhelm *et al* (2002) reported that hair lead concentrations did not correlate with blood lead concentrations in children. Pineau *et al* (1993) noted that although plasma aluminium concentrations of haemodialyzed patients with chronic renal failure were significantly higher than in healthy volunteers and positively correlated with time on dialysis, hair aluminium levels were widely distributed with no significant distinction between patients and controls. They concluded that hair aluminium analysis is of no value as an indicator of body aluminium accumulation, as did Wilhelm and Idel (1996).

5.179 The finding by Eastwood *et al* (1990) of aluminium in bone biopsies from two exposed individuals between 6 to 7 months after the incident is interesting but difficult to interpret. We note that no stainable aluminium was detected in further biopsies taken 12-13 months later nor in bone from 8 other exposed individuals (McMillan *et al*, 1993).

5.180 The mode of presentation of the data in the study on residents by Ward (Howard, 1993; Ward, personal communication, 2002), i.e. the fact that the results were written up in a form suitable for a thesis for a degree in statistics rather than as a scientific paper, together with the general deficiencies in study design outlined above, makes it very difficult to interpret the results.

Samples provided as personal evidence

5.181 During our enquiry, a few individuals provided the results of analyses of samples of blood or body tissues such as nails which had been taken after the incident. In most cases, results were provided on the concentrations of metals in the samples, especially of aluminium. A set of results provided in response to the consultation exercise provided serial data on aluminium concentrations in serum samples taken at three timepoints (see paragraphs 4.42 to 4.44). More information of this type would have been useful to us but, unfortunately, due to its paucity, its usefulness was limited.

5.182 In the consultation exercise, a respondent suggested that analysis of individuals who were exposed to the contaminated water could be carried out now to determine their aluminium body burden. He informed us that a new, non-invasive method had been developed which avoided the need for bone biopsy. We obtained further information on this method - *in vivo* neutron activation analysis (IVNAA) - from the scientific literature (Pejović-Milić *et al*, 2005; Davis *et al*, 2008; Aslam *et al*, 2009). It appears that the method is undergoing investigation but has only been used in preliminary studies in humans.

5.183 In individuals who have been occupationally exposed to aluminium, the initial half-life of aluminium (i.e. the time it takes the amount in the body to reduce by half)

has been shown to be approximately 8 hours, and in workers exposed for less than 2 years to be about 9 days (Sjogren *et al*, 1985, 1988). The data discussed in paragraphs 4.42 to 4.44 indicate a half-life in this individual of 6 to 7 days. It is now (October 2012) more than 24 years after the water contamination incident occurred. If individuals' body burdens of aluminium had been increased by exposure during the incident, they will have decreased considerably by now. Therefore, we do not recommend a study of aluminium body burdens.

Effects on livestock and domestic animals

Types of Effects Reported

5.184 A number of health and welfare problems were described in domestic and farm animals. Whilst the health and welfare outcomes in animals cannot necessarily be extrapolated to humans, the data may provide indicators of potential human health effects. In Chapter 3, we discussed the fact that the flushing of the contaminated water from the main distribution system into rivers and other waterways soon afterwards led to the death of a large number of fish.

5.185 Cross (1990b) reported deaths in a number of different local animal populations after the pollution incident: 40 ducklings on a farm in Helstone; 13,000 laying hens at a unit in Camelford; 10 of 40 weaned lambs at Otterham Down Farm, near Camelford; and 6 of 27 rabbits in a breeding flock in Trevethy, near Tintagel. Ulceration of the gastrointestinal tract was the most common *post mortem* finding in fowl. It was also reported that breeding performance was impaired in the rabbits at Trevethy and among pigs at Treburgett (Cross, 1990b). *Post mortem* examination of the male rabbits showed severe gut ulceration, but no evidence of infectious disease. There was a high rate of spontaneous abortions and of low birth weight calves among those cows which were pregnant at the time of exposure in a dairy unit in St. Endellion.

5.186 Effects were also reported in domestic pets (Cross, 1990b). Several cases of severe illness in cats and dogs and deaths of guinea pigs, budgerigars and small parrots in Camelford and nearby hamlets were reported soon after drinking tap water on the morning after the incident or within a day of exposure to tap water. We spoke to individuals whose animals became ill or died subsequent to the incident (see box). Bridges (1989) listed 82 claimed effects of the incident on animals which included refusal to drink, diarrhoea, vomiting, and deaths of fish and rabbits.

" …my daughter bathed (the puppies)…I heard this screaming and howling from the puppies…I rushed them up to the vet…Two had already died. ….three were so ill that they obviously had to have intense treatment. …I think at the time that they said that they had been severely poisoned….."

"Six (cows) were really ill; we had to put penicillin into them for six weeks. The rest the coat went like wire, we couldn't -- they were really ill for six months…… We had about 200 other cattle, which were perfectly okay, because they had access to springs in the river."

Concentrations of Contaminants in Animal Tissues

5.187 Ward (1991) analysed samples from 14 organs and tissues, taken 6 months after the incident, from 4 sows from the piggery at Treburgett. The tissues were analysed for aluminium, copper, iron, lead and zinc. The sows were reported to have been affected by the incident, but no specific symptoms were recorded in the paper. Tissues from four non-exposed sows from the same farm were used as controls. The results are summarised in Table 46.

5.188 Aluminium and copper concentrations were markedly higher in several tissues from exposed sows compared to controls, although not in muscle, brain or nail. The origin of the high copper levels is unclear as it is reported that the pipework to the piggery was made from polyethylene (Cross, 2004). Elevated lead concentrations were recorded in the liver and decreased iron and zinc concentrations were recorded in many tissues, particularly liver and kidney.

Table 46: A summary of changes in metal concentrations in pig tissues from exposed animals compared to tissues from non-exposed animals

Tissue	Ratio of mean metal concentrations[a] (Exposed/Control)				
	Aluminium	**Copper**	**Iron**	**Zinc**	**Lead**
Hair	3.6	4.3	0.8	0.8	1.1
Kidney	7.3	2.3	0.6	0.7	1.5
Liver	3.6	1.6	0.4	0.8	1.9
Rib Bone	3.2	1.0	0.9	1.0	0.9
Muscle	1.0	1.5	1.0	0.9	1.1

Source: Ward, 1991.
a: The standard deviation of the mean was frequently high.

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The concentration of aluminium in ice cream

5.189 A batch of ice cream from a dairy herd at St. Endellion, which was made with milk taken from cows 4 days after the incident, contained 36 mg aluminium/kg (Cross,1990b). In comparison, a batch made one week before exposure, and stored at -20°C in food-grade polythene drums, contained 1.8 mg aluminium/kg. Eight weeks after exposure, the aluminium concentration in ice cream samples made with milk from the herd was 3.8 mg/kg (Cross, 1990b).

Fish

5.190 Of the estimated 60,000 dead fish collected from the River Camel, 7 were collected privately and sent for analysis for aluminium concentration in gill tissues. Gills from the dead fish contained 4,332 mg/kg of aluminium (Welsh Water Authority, personal communication, 1998). According to Bielby (1988), the aluminium content was 76 times higher than that in gills from control fish preserved in formalin.

Discussions with Mr Cooper

5.191 On 28 October 2003 in Camelford we spoke to Mr Cooper, then a representative of the National Farmers Union (NFU). At the time of the incident, he covered the North Cornwall area.

5.192 Mr Cooper told us that, in 1988, shortly after the incident occurred, he was contacted by a representative of North Cornwall District Council who informed him that there was a water contamination incident in the Lowermoor area. Subsequently, several farmers contacted him about problems with their livestock. These included the deaths of all the chickens in a battery unit and problems at two or three dairy farms because the cows would not drink the water. The NFU sent a veterinary surgeon to examine the animals and, subsequently, 3 farmers received compensation from SWWA. Mr Cooper commented that the number of farms confirmed as being affected was small compared to the 500-600 farms located in the area as a whole. He considered that it was possible that problems might have occurred at other farms, but that farmers and veterinary surgeons may not have associated them with water contamination. In addition, animals with access to water from bore holes or from uncontaminated streams would not have been affected.

Report by Dr W. M. Allen

5.193 In August 1988, Dr Allen, then a veterinary surgeon based in Newbury, Berkshire, was commissioned by SWWA to review the possible short and long term effects of the contamination incident upon the health and welfare of livestock. Dr Allen reviewed SWWA monitoring data on concentrations of contaminants in the water together with relevant contemporary scientific literature. No clinical or pathological investigations of animals were conducted.

5.194 Allen (1988) concluded that the objectionable taste of the water during the early hours after the incident may have resulted in the refusal of some animals to drink water from the mains and that this may have caused severe thirst, a possible short-term problem of welfare. He also concluded that, on the basis of the reported observations and a review of the scientific literature, the water contamination was unlikely to have resulted in any serious short or long term effects on the health of any domestic animal or bird. The reader should note that this report was completed before details of the effects on livestock and animals emerged.

The Veterinary Investigation Centre

5.195 We noted that the second LIHAG report refers to observations of the local Veterinary Investigation Centre (VIC), which revealed no noticeable increase in health problems of farm animals in the Lowermoor area following the incident (LIHAG, 1991). We sought a formal report of these observations from the VIC's successor, the Veterinary Laboratory Agency, but none was located.

Appraisal of the effects on livestock and domestic animals

5.196 The information in this section comprises a series of observations of ill-health in animals which drank or were exposed to water contaminated in the Lowermoor pollution incident. In some cases the effects were sufficiently serious to cause death. *Post mortem* examination of fowl and rabbits demonstrated severe effects in the gastrointestinal tract. With the limited information available, we cannot conclude categorically from these observations that the contaminated water caused the adverse effects in every case. However, animals with alternative sources of water did not appear to suffer the same effects. We find it difficult to assess the results of the study by Ward (1991) on metal concentrations in tissues from sows reportedly suffering from adverse health effects.

Increased concentrations of several metals, particularly aluminium, were found in the tisues sampled. Aluminium is usually poorly absorbed from the mammalian gastrointestinal tract but it is possible that absorption may have increased if the gut was damaged by the contaminated water or for other reasons. However, provided kidney function was not impaired, it would have been expected that the aluminium would be excreted rapidly, and accumulation would not occur. Similarly, damage to the gastrointestinal tract of cows and increased absorption of aluminium may have accounted for the observation of an increased concentration of aluminium in ice cream made from milk from cows exposed to the contaminated water. However, it is impossible to reach firm conclusions on the information available.

Key points

1. We took evidence from individuals resident in the Lowermoor area at the time of the incident and from a smaller number of individuals who were on holiday in the area at the time. One hundred and fourteen individuals, including 9 who were children at the time of the incident, provided evidence in total. Of these, 54 individuals gave evidence in interviews. The information included general observations about the incident, information on water quality and consumption, and information on health effects in children and adults.

2. The most common general observation was on the lack of information and advice at the time of the incident. In relation to water quality, we learned that the variation in the type, age and condition of domestic plumbing and in individual water usage resulted in people in the same area receving water which was very different in appearance and taste at a similar time after the incident. Some individuals told us that the water was initially undrinkable but others stated that they had drunk it, despite the unpleasant taste. Most had used it for cooking and bathing, despite the evident poor quality.

3. Individuals reported a variety of health problems. Mouth ulceration, skin irritation and gastrointestinal symptoms such as diarrhoea and abdominal pain were among the most frequently reported effects and occurred within hours or days of the incident. Other effects occurred either soon after the incident or much later, and lasted for many weeks or, in some cases, years. In both adults and children, the most frequently reported of these persistent symptoms were impaired memory; joint pains and/or swelling; tiredness and/or lethargy. Adults also experienced coordination and concentration difficulties, and effects on nails. In children, effects on skin were also reported and parents reported problems with memory, behaviour and concentration.

4. We spoke to a number of health professionals who were involved at the time of the incident or in its aftermath. All gave us valuable information about the events immediately after the incident, including data about clinics held at the time, together with subsequent clinical and epidemiological investigations. The GPs who spoke to us indicated that there had been no immediate increase in the number of consultations after the incident, although there was an increase in the number of consultations with people who attributed their health symptoms to the incident after reports of possible health effects appeared in the media. One GP who worked in the area at the time, who wrote to us, reported that individuals did suffer symptoms such as those described above but many did not consult their doctors. We also heard from a consultant physician who ran a specialist clinic for patients reporting continuing health problems

due to the incident and a community nurse counsellor who visited individuals in their homes. Both reported that the most common problems included gastrointestinal symptoms, malaise, deterioration in memory and joint problems.

5. A questionnaire survey carried out shortly after the pollution incident indicated that 49% of respondents in the Lowermoor supply area reported symptoms, compared with 10% in the area supplied by the Bastreet Water Treatment Works.

6. A number of epidemiological studies were carried out to investigate whether the rates of certain adverse health effects had increased in people exposed to the contaminated water. There are problems with the design of those studies. One is that usually an individual's place of residence was used as an indicator of exposure i.e. those living in the Lowermoor water supply area at the time were considered to have been exposed to the contaminants, whereas a comparison (control) population living in an adjacent area was considered not to have been exposed (i.e. it was considered to be unexposed). It is not certain that every property classified as being in the Lowermoor supply area was supplied by the Lowermoor Water Treatment Works, nor that all properties in the 'unexposed' areas were not. Moreover, the fact that a property was supplied with contaminated water does not necessarily mean that all or any individuals in the property consumed the water. Exposure misclassification such as this would have affected the reliability of the results of a study. It should be noted that none of the studies included holiday makers present in the area at the time of the pollution incident.

7. A study of pregnancy outcomes, up to 42 weeks after the incident, in the population supplied by the Lowermoor Water Treatment Works showed no excess of perinatal deaths, low birthweight, preterm delivery or severe congenital anomalies in the Lowermoor population compared to a control population supplied by the Bastreet Water Treatment Works. There was an increased incidence of club foot in the Lowermoor population.

8. A further study compared the growth of children in the Lowermoor supply area with those in the Bastreet supply area. Potential exposure in the Lowermoor group was via: the parent(s) drinking contaminated water before the child's conception, exposure in the womb, and exposure in early infancy. Children in the Lowermoor supply area were statistically significantly taller at 9 and 18 months of age, but not at 36 months of age, than those in the Bastreet supply area.

9. There was a higher rate of hospital discharges (a crude measure of the rate of serious illness in a population) in the 8 postcode sectors in the Lowermoor supply area in 1991-1992 and in 1992-1993 compared with the rate in 1987-1988. This trend was not seen in 23 other postcode sectors not supplied by the Lowermoor Water Treatment Works. Hospital discharge data require careful analysis and the limited reporting of the study makes these findings difficult to interpret.

10. Further studies report similar rates of health outcomes after the pollution incident among the population in the Lowermoor supply area and the population in an adjacent area supplied by a different water treatment works:

- The mortality rate up to December 1997 was lower in both areas than that for Cornwall and the Isles of Scilly as a whole.

- Rates of new cases of cancer (cancer incidence) up to December 1998 in both areas were lower than those for Cornwall as a whole or those for the whole South West.
- Rates of deaths from cancer up to December 1997 in both areas were lower than those for England and Wales as a whole.

11. Between 1995 to 1996, 3 cases of acute leukaemia occurred in children who attended the same tutor group in Sir James Smith's School in Camelford and who were resident in the area at the time of the pollution incident in 1988. Infection is thought to be associated with leukaemia and so a specific study was commissioned to look at child health events, especially infections, in relation to the pollution incident and the leukaemia cluster. The study showed that there was more infectious illness overall in children living in the Lowermoor supply area compared to those living in other parts of Cornwall, but that this higher rate occurred before the pollution incident. The authors of the study concluded that the findings were consistent with the hypothesis that leukaemia is associated with infection.

12. The cancer incidence and mortality study referred to in bullet point 10 above examined the overall leukaemia rate for the Lowermoor supply area from the time of the pollution incident to December 1998. The incidence of leukaemia was slightly lower than the rate in an adjacent comparison area, and than the rates in Cornwall as a whole and in the South West as a whole. However, the mortality rate for leukaemia was slightly raised in the Lowermoor supply area compared to the comparison area.

13. Another study investigated whether there was any general correlation between the incidence of cancers, or precancerous conditions, of the blood and bone marrow (including leukaemia) and various water quality indicators. The populations investigated lived in 46 different water supply areas in the UK and the period covered by the study was 1984 to 1988. It found that there were correlations between aluminium concentrations, and certain other contaminants which arise from chlorination and rates of illness in 5 of the disease categories examined. However, there are problems with the design and reporting of this study which make it difficult to interpret the results.

14. Three studies have been reported in which investigators administered neuropsychological tests to adults from the Lowermoor supply area after the pollution incident. The aim of these studies was to investigate whether the incident had caused any effect on brain function and, if so, whether this was due to physical brain damage or was secondary to psychological illness e.g. anxiety or depression. There are problems with the design of all the studies: a lack of suitable controls, non-random selection of subjects, a lack of information on exposure to the contaminated water, and small group sizes. Therefore, although the studies reported impairment of brain functions, and it was concluded that it was not explained by psychological factors, it is not possible to conclude that the contamination incident led to adverse neuropsychological effects in exposed individuals.

15. Another study investigated whether educational achievement by schoolchildren was affected by the pollution incident, by comparing the results of standard tests of educational achievement (Richmond tests) before and after the incident. No difference was found, nor was there any worsening of performance in schools in the Lowermoor supply area compared to a group of schools outside the area. There are a number of

limitations in the study, including the small number of children for whom test results were available, and the study does not rule out the possibility that a small effect may have occurred.

16. A case of severe neurodegenerative disease, diagnosed as congophilic amyloid angiopathy, has been recorded in an individual who lived in Camelford at the time of the contamination incident. The details have been published in the scientific literature. The individual was aged 59 years, which is an unusually young age to develop such a disease. A relatively high aluminium concentration was recorded in the individual's brain. A coroner's enquiry concluded that "the very real possibility exists that (the individual's) death was contributed by the ingestion of aluminium. However, as this would be the first such reported case of severe congophilic amyloid angiopathy without associated Alzheimer's pathology in the United Kingdom in someone of this age, the suggestion that aluminium was a causative factor must remain only a slight possibility."

17. Numbers of children with Special Educational Needs (SEN) Stage 5 ('Statemented') were investigated to address concerns raised by a local journalist that, between the years 1997 and 2000, there was a higher proportion of children with SEN Stage 5 in North Cornwall schools than in schools in the rest of Cornwall and that this was related to the contamination incident. It was found that the percentage of children with SEN Stage 5 in Sir James Smith's School, Camelford (the secondary school likely to have the highest proportion of children in North Cornwall from the area with the contaminated supply) did not differ consistently between 1997 and 2001 from that in other schools in Cornwall. In all cases, the percentages of children with SEN Stage 5 were higher than national percentages. According to two expert educational psychologists who were consulted, it was not possible to interpret SEN statistics in terms of possible health effects in children, because of the many factors which affect the allocation of SEN stages.

18. A report prepared in 1992 for the North Cornwall Homeopathic Project describes symptoms reported by 70 individuals who considered that they had been affected by the pollution incident. The symptoms are similar to those reported to us in personal evidence. The most common were: anxiety, depression, difficulties with concentration, an inability to cope, irritability, tiredness, lethargy, confusion, malaise, memory problems, and "a dry thirst".

19. There are studies of concentrations of metals in tissues from individuals from the area receiving contaminated water. The tissues analysed include blood, hair, bone, nails, urine and saliva. Increased concentrations of several metals were found, compared to reported normal values, including lead, aluminium, copper and mercury. Unfortunately, several factors make it difficult to interpret these results: limited reporting of the studies; absence of matched, concurrent controls; absence of information on the subjects; and on how they were selected.

20. There are reports of effects on livestock and domestic animals following the pollution incident. These include deaths in a number of local animal populations, including fish, laying hens, ducklings, lambs, and rabbits. There were also reports of impaired breeding performance among rabbits, pigs and cattle. Where *post mortem* examinations were carried out, it is reported that the animals suffered damage to the gastrointestinal tract. Increased concentrations of aluminium, lead and copper, and

decreased concentrations of zinc and iron, were reported in the tissues of four sows from an affected piggery. The contaminated water caused severe adverse effects in some animals with no access to alternative sources of water. However, on the limited data available, it is not possible to be certain that it was the cause of every reported case of ill health from the limited information available. Effects seen in livestock and environmental species can be the earliest sign of the consequences of a contamination incident. Effects on animals indicate other possible routes of contamination in humans eg lactation or via food, and often raise concern about other routes of examination e.g. human milk.

6. Toxicological and epidemiological data on contaminants from the scientific literature

Introduction

6.1 Different types of information can be used when assessing the potential of a chemical to cause adverse health effects:

1. Epidemiological studies of people exposed in the workplace or to known amounts of the chemical in food, or the environment. These are particularly useful.
2. Data from studies in human volunteers are sometimes available, although these commonly provide information about the absorption and excretion of chemicals, rather than about the exposures at which they are toxic.
3. Often, studies of effects in laboratory animals are used together with information from human studies. Animal studies entail exposures to high doses of the test chemical, to maximise the chance of observing an adverse effect.
4. *In-vitro* studies in microbes, cell cultures or tissue preparations can provide information about possible mechanisms of toxicity.
5. With some chemicals, experience of use in medicine or knowledge of other exposures (e.g. normal exposures via the diet) supplement the available toxicological and epidemiological information.

6.2 Several aspects of the quality of a study have to be taken into account in order for someone assessing the study to have confidence in the reported findings. In epidemiological studies, it is important to avoid bias and to make appropriate adjustment for confounding factors. Bias might be caused, for example, by incorrect assessment of exposure to the contaminant of interest. Confounding occurs when another variable is associated with both the exposure of interest and the disease of concern. In the case of animal studies, key considerations include the range of doses used (the dose-range), the survival of the animals, and the types of effects and of tissues examined. We have taken such factors into account when evaluating the available studies on the contaminants which were present at elevated concentrations in drinking water following the Lowermoor pollution incident.

6.3 Many of the chemicals of relevance in the Lowermoor incident are common contaminants and have been of interest to regulators and specialist international groups for many years. As a result, the toxicological and epidemiological databases on these chemicals include numerous reviews and evaluations by technical experts, such as those which underpin the Guidelines for Drinking Water Quality proposed by the World Health Organization. We have drawn on such reviews by authoritative bodies of national and international standing, although we also commissioned original reviews of the scientific literature on aluminium, the key contaminant of interest.

6.4 We were interested, ultimately, in making a risk assessment of the contaminants by comparing individuals' estimated exposure to each of them with the recommended maximum safe intake of the contaminant. For many of the contaminants, we were able to make use of maximum safe intakes recently recommended by other expert committees. There is a conventional procedure which

is used by toxicologists to set a recommended maximum safe intake (often termed a 'tolerable daily intake' or 'tolerable weekly intake'). Typically, the intake level at which no adverse effects are observed in animal or human studies (i.e. the No Observed Adverse Effect Level or NOAEL) is divided by an appropriate uncertainty factor (Committee on Toxicity, 2007). Uncertainty factors are empirical values used in the absence of more detailed data. They are used to account for differences between animals and humans in susceptibility to a compound (inter-species variation), and for differences in susceptibility between humans (inter-individual variation) .

6.5 The numerical value of the uncertainty factor used varies in size depending on the nature of the data and the various uncertainties that have to be taken into account. The factors vary in size according to the type of data being considered, and could range from a value of 1 if adequate data were available for potentially vulnerable human subjects up to 100 or more when the safe intake has to be based on a study in animals, because adequate human data were not available. The differences in sensitivity may result from differences in, for example, the absorption, metabolism, or biological effect of the substances under consideration. Uncertainty factors can also be applied to account for uncertainties due to:

- database deficiencies, such as the absence of a NOAEL requiring extrapolation from the Lowest Observed Adverse Effect Level (LOAEL; the lowest level at which adverse effects have been observed in toxicological studies),
- a study involving few subjects,
- the severity of a particular adverse effect.

Uncertainty factors have a long history of use by national and international regulatory bodies in order to establish safe levels of intake of compounds. They have been shown in custom and practice to be a reasonable approach in toxicological risk assessment (Committee on Toxicity, 2007).

6.6 It was not our intention, nor was it necessary, for us to review every aspect of the science of the contaminants. We were concerned with their potential effects on human health when present in drinking water. The ways in which people could have been exposed to the contaminants in the water were either by consuming it (oral exposure) or through the skin when bathing/washing in it (dermal exposure). Thus, scientific studies in laboratory animals or humans using exposure by these routes were relevant to determining an NOAEL. However, studies in which the contaminants were administered by other routes e.g. intravenously (by injection into the veins) or intraperitoneally (by injection into the abdomen) were unlikely to be relevant because chemicals administered to animals or humans by these routes do not need to cross the gut wall or the skin before they are absorbed into the body, and so a far higher proportion of the chemical reaches the blood and tissues. Therefore, not all scientific papers on the contaminants of interest were relevant to our assessment.

Aluminium

Introduction

6.7 For our review of aluminium, we used the following sources:

- a comprehensive and fully-referenced review of the scientific literature available up to 1997 carried out by the International Programme on Chemical Safety[29] (IPCS, 1997).
- a fully-referenced review of the scientific literature on the toxicology and epidemiology of aluminium which was published between 1994 and April 2002, prepared by the Department of Health Toxicology Unit at Imperial College, London (Appendix 21).
- a fully-referenced update of the literature on the toxicology and epidemiology of aluminium which was published between January 2002 and October 2003, prepared by the Department of Health Toxicology Unit. This is included as Appendix 22 to this report.
- a fully-referenced update of the literature on the toxicology and epidemiology of aluminium which was published between November 2003 and April 2005, prepared by the Department of Health Toxicology Unit. This is included as Appendix 23.
- fully-referenced updates of the literature on the toxicology and epidemiology of aluminium which were published between May 2005 and December 2006, prepared by the secretariat. These are included as Appendices 24 and 25.
- a fully-referenced update of the literature on the toxicology and epidemiology of aluminium which was published between January 2007 and September 2011, prepared by the Health Protection Agency Toxicology Unit at Imperial College. This is included as Appendix 26.
- a fully-referenced update of the literature on the toxicology and epidemiology of aluminium which was published between October 2011 and September 2012, prepared by the Health Protection Agency Toxicology Unit at Imperial College. This is included as Appendix 27.

6.8 In carrying out their reviews of aluminium, the Health Protection Agency Toxicology Unit at Imperial[30] and the secretariat followed the usual procedure for conducting a scientific review. Specific databases (MEDLINE (PUBMED), TOXNET, WEB OF SCIENCE SCI) of published scientific papers were searched using keywords to ensure that relevant publications were selected (for example, searching [aluminium or aluminum] in combination(s) with several other words, for example, toxico*,toxici* brain, neuro*, renal, liver, bioavailability, or [aluminium or aluminum] with limits such as "mesh major topic", "subset toxicology"). All papers selected were then reviewed and those considered not to be relevant to our investigation were rejected. Hundreds of papers were reviewed in this way and those considered relevant were summarised and included in the reviews published as Appendices 21 to 27 for discussion by the Subgroup.

6.9 Where appropriate in the text below, we have presented dose levels of aluminium (in animal toxicity studies) as both the dose of aluminium salt administered and the equivalent dose of aluminium ion. However, occasionally, it is not clear from the original paper whether the dose of aluminium salt provided is of the hydrated or unhydrated salt. Where there is doubt, we have taken a view on whether it is most likely to be the hydrated or unhydrated salt, based on the extent of the information provided in the paper.

[29] IPCS reviews (termed Environmental Health Criteria) are published under the joint sponsorship of the United Nations Environment Programme, the International Labor Organization and the World Health Organization.

[30] Previously known as the Department of Health Toxicology Unit.

6.10 There were two major problems encountered during the conduct of our assessment of aluminium. Firstly, there were few toxicity data on aluminium sulphate, the salt involved in the incident. Therefore, it was necessary to extrapolate from studies using other salts. Secondly, the exposure to aluminium was unusual in that it was high and of short duration. There are no toxicity data which examine the long-term effects of such an exposure and it was necessary to extrapolate from studies in which high doses of aluminium were administered for much longer periods of time.

6.11 Many of the toxicological studies on aluminium are limited by a lack of information in the report of the study on the aluminium content of the animals' diet. According to the U.S. Agency for Toxic Substances and Disease Registry (ATSDR): "Commercial grain-based feeds for laboratory animals contain high levels of aluminium that typically far exceed the aluminium content of the human diet……Base diets containing 250-350 ppm Al were used in some rat and mouse studies, but this cannot be assumed to be a normal or representative concentration range because analyses for aluminium were not performed routinely, substantial brand-to-brand and lot-to-lot variations are apparent, and formal surveys of aluminium content of laboratory feed are not available. For example, concentrations ranging from 60 to 280 ppm Al for Panlab rodent standard diet and 150-8,300 ppm for Purina Rodent 5001 Laboratory Chow have been reported" (ATSDR, 1999). A level of 250-300 ppm in the diet would provide an adult rat with an intake of approximately 25-30 mg aluminium/kg bw/day. In the animal studies cited below, the amount of aluminium in the basal diet and, therefore, the total dose received by the animals, are unknown unless stated otherwise.

General information

6.12 Aluminium (Al) is a silvery-white, ductile and malleable metal which is usually found in aluminium compounds in the trivalent form (Al^{3+}). It occurs ubiquitously in the environment in the form of silicates, oxides and hydroxides, combined with other elements such as sodium and fluorine and as complexes with organic matter. Aluminium is highly resistant to corrosion, is light and strong and is thus often alloyed with other metals. Aluminosilicates are a major component of soils and occur in high concentrations in dusts derived from mining, agriculture and coal combustion. In urban areas, airborne aluminium levels in street dust range from 0.004 to 0.012 mg/kg.

6.13 Surface freshwater and soil water concentrations vary considerably depending on physico-chemical and geological factors. Dissolved aluminium concentrations in water of neutral pH range from 0.001 to 0.05 mg/l, rising to 0.5-1 mg/l in acid water. The current WHO recommended Guideline Value for aluminium in drinking water is 0.2 mg/l. This level was set to avoid depositions in the distribution system and discolouration of the water and not on health grounds (WHO, 1998).

6.14 Concentrations of aluminium in the human diet are relatively low although the use of some aluminium based additives, such as aluminium phosphate emulsifier in processed cheese, and baking powders containing acidic sodium aluminium phosphate, may increase concentrations. For example, a slice of cake or bread may contain 5-15 mg of the element (Priest, 2004). The mean intake from food and

beverages[31] by adults, estimated from the 1988 Total Diet Study for the UK population[32], was 3.9 mg/day, which is equivalent to 0.07 mg/kg/day[33] based on a mean body weight of 60 kg[34]. For children aged 2 to 6 years, it was 1.9 mg/day (range 1.0 - 3.7) which is equivalent to an intake of 0.10 mg/kg bw/day (range 0.05 – 0.20) based on a mean body weight of 18.7 kg[35]. Intakes of aluminium by infants from infant formulae[36] were estimated as 0.03 to 0.05 mg/day for those consuming cows' milk-based formulae and 0.27 to 0.53 for those consuming soya-based formulae (Ministry of Agiculture, Fisheries and Food, 1993). Mean aluminium intakes estimated from the most recent Total Diet Study in 2006 were 0.07 mg/kg bw/day for adults, 0.12 mg/kg bw/day for young people and 0.19 mg/kg bw/day for toddlers, based on mean body weights of 60, 41.5[37] and 14.5[38] kg, respectively (Rose *et al*, 2010). The age groups used were not consistent between 1988 and 2006. High level intakes in the 2006 study were estimated to be 0.14 mg/kg bw/day for adults, 0.25 mg/kg bw/day for young people and 0.35 mg/kg bw/day for toddlers.

6.15 Some antacids containing aluminium glycinate and/or hydroxide may contain high levels of aluminium (20-200 mg) and are used to relieve symptoms of ulcer and non-ulcer dyspepsia and reflux oesophagitis. Consumption of aluminium from these sources can be up to approximately 800 mg aluminium/day (British National Formulary, 2012).

The chemistry, absorption and bioavailability of aluminium

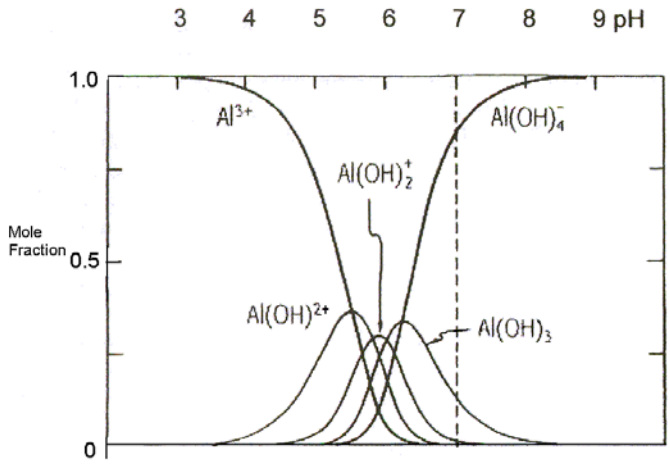
The measurement and chemistry of aluminium

6.16 Aluminium concentration can be measured with a sensitivity of 1.9-4.0 μg/litre in biological fluids and 0.0005-0.5 μg/g dry weight of tissue depending on the method of sample processing. Error in measurements may occur from contamination by aluminium derived from air, containers or reagents.

6.17 The speciation of aluminium in water depends on the pH. At low pH (<5), soluble aluminium complexes exist mainly as the hexahydrate of aluminium. As pH increases, a mixture of species exist as a result of successive deprotonations (see Figure 32).

[31] "Beverages" does not include tap water or drinks containing tap water.
[32] Where the data are available, two sets of data on intakes from foodstuffs are provided for the metals discussed in this report. The first set is based on the Total Diet Study carried out closest in time to the date of the water contamination incident from which data are available. The second is from the most recent survey in 2006.
[33] Range not given.
[34] This figure is routinely used as the mean adult body weight in toxicological assessments.
[35] The mean body weight for children aged 2 to 6 years, based on data from the Health Survey for England 2010 (http://www.ic.nhs.uk/pubs/hse10report).
[36] Based on the assumption that infants up to 4 months of age, weighing 3-6 kg, consume 0.15 litres of infant formula per kg body weight per day.
[37] The mean body weight for a young person derived by the Food Standards Agency from food consumption surveys.
[38] The mean body weight for a toddler derived by the Food Standards Agency from food consumption surveys.

Figure 32: The speciation of aluminium in water at different pH, after Martin (1991) and Priest (2004)



6.18 The total amount of free Al^{3+} species existing in solution depends on the ligands present (such as citrate and phosphate) and on their stability constants with Al^{3+} (see below).

Factors that influence absorption of aluminium

6.19 Ingested aluminium may be solubilised in the acidic environment of the stomach but the majority is precipitated in the duodenum as a result of the dependency of the form of aluminium (and thus its solubility) on pH (Reiber *et al*, 1995). Although, based on physicochemical characteristics (Priest, 2004), the ionised hexahydrate of aluminium (see above) is unlikely to be absorbed, a variety of neutral, complexed species, such as aluminium citrate, may remain in solution further down the intestine and may be absorbed. Thus absorption of aluminium appears to occur mainly after passing through the stomach. Complexing may, in part, explain why dietary citrate can enhance aluminium uptake. Coburn *et al* (1991) found a 2 to 5 fold enhancement of absorption of ^{26}aluminium in rats by citrate[39]. Aluminium as the citrate can be absorbed up to 50 fold more efficiently than aluminium as the hydroxide and enhancement of absorption of the latter by citrate co-administration can be up to 14-fold depending on the concentration of citrate (Jouhanneau *et al*, 1997; Priest *et al*, 1995a). In addition to making aluminium more soluble, citrate may enhance absorption by increasing the permeability of tight junctions between mucosal cells (Taylor *et al*, 1998). Other soluble complexes may be formed in the gut with ascorbate, oxalate and malate. These organic anions, like citrate, increase tissue concentrations (and presumably uptake) of aluminium in rats (Testolin *et al*, 1996). Certain polyphenolic acids present in brewed beverages such as tea also increased tissue aluminium concentrations in rats (Deng *et al*, 2000). Ascorbic acid (vitamin C) at a dose of 2,000 mg significantly increased urinary aluminium excretion in human volunteers taking 310 mg aluminium as the hydroxide three times a day (Domingo *et al*, 1991).

[39] ^{26}aluminium (^{26}Al) is a radioactive isotope of aluminium which can be used as a tool in experiments to study the absorption, distribution and excretion of aluminium in the body.

6.20 In contrast to the production of soluble complexes, co-ingestion of high concentrations of phosphate or silicic acid lowered the bioavailability of ingested aluminium because of the formation of insoluble precipitates (Powell and Thompson, 1993). Silicate (referred to as silicon in the paper) co-administration lowered aluminium bioavailability (Belles *et al*, 1998). Studies in rats suggest that the kinetics of uptake from the gut are not linear with respect to dose and that absorption may increase above a threshold concentration of approximately 10 mg/l (Glynn *et al*, 1999). It has been postulated that more than one mechanism of absorption occurs depending on the dose (Skalsky and Carchman, 1983; Greger and Sutherland, 1997). Aluminium may share uptake mechanisms with calcium (Van der Voet and De Wolff, 1998) but there is uncertainty regarding a potential sharing of uptake mechanisms with iron (Ittel *et al*, 1996; Cannata and Diaz-Lopez, 1991; Cannata *et al*, 1991) (see discussion of metal-metal interactions below).

Quantification of aluminium absorption after oral ingestion

6.21 Ingested aluminium is poorly absorbed from food, because of the pH dependency and the formation of insoluble complexes described above. It is excreted in faeces mainly as aluminium phosphate (Spencer and Lender, 1979; WHO, 1989).

6.22 Human subjects fed aluminium lactate with fruit juice and food (in doses of 5 or 125 mg aluminium/day for 20 days) excreted >96 % and >74% of the respective doses in faeces (Greger and Baier, 1983). Skalsky and Carchman (1983) referred to five excretion balance studies in human subjects when they concluded that, if assessed by the difference between dose administered and that excreted in faeces, it was difficult to detect absorption other than at a high dose (in excess of 225 mg/day). A proportion of apparently absorbed material may, however, reflect aluminium retained in the epidermal cells of the intestinal wall (Feinroth *et al*, 1982; Van de Voet and De Wolff, 1984). Ganrot (1986) concluded that 0.1-0.5 % of dietary aluminium is absorbed and this is rapidly and extensively excreted in urine based on measurements of urinary excretion of aluminium (rather than the indirect measurement of loss from the intestine). He concluded this after assessing the urinary excretion of aluminium (known to be the major route) rather than the indirect, and less reliable, measurement of loss from the intestine. Schonholzer *et al* (1997) estimated that the percentage absorption in rats was 0.1% for aluminium hydroxide and aluminium maltolate, 0.7 % for aluminium citrate and 5.1% for aluminium citrate administered with sodium citrate. Powell *et al* (1994) found that when a 93 μM (3.2 μg/ml) aluminium sulphate solution was perfused through rat small bowel, one third of the aluminium was taken up but more than 90% of this was then recovered from the intestinal mucus/mucosa. Similarly, Arnich *et al* (2004) found that perfused aluminium solution (48 and 64 mM), even as a citrate complex, crossed the brush border with difficulty (0.4% of the perfused amount) and about 60% of this was retained in the intestine. An unpublished study reviewed by the European Food Safety Authority (EFSA) in 2011 determined the bioavailability of a number of aluminium compounds in rats using ^{26}aluminium-labelling. The compounds were administered as a solution in water or a suspension in carboxymethylcellulose. The mean fractional absorption of the soluble citrate, chloride and nitrate salts ranged from 0.045 to 0.079% of the dose and that of the soluble sulphate salt was 0.21%. In the case of the aluminium compounds adminstered as a suspension, the percentage of the dose absorbed ranged from 0.018 to 0.12% (Priest N, 2010; European Food Safety Agency, 2011). In a series of

unpublished bioavailability studies recently reviewed by the Joint Expert Committee on Food Additives (JECFA) of the WHO and the Food and Agriculture Organisation (FAO), absorption of aluminium was generally in the region of 0.01 – 0.2% following ingestion of various aluminium compounds by rats (aluminium sulphate, aluminium ammonium sulphate and aluminium lactate) and the more water-soluble aluminium compounds were generally more bioavailable (WHO, 2012). In addition, Stauber *et al* (1999), in a study of 29 healthy volunteers, concluded that only 0.3-0.4% of aluminium in water was absorbed. Likewise, Priest *et al* (1995b, 1998) gave young male adult subjects ^{26}aluminium in drinking water and found a fractional absorption of 0.22% for aluminium by comparing urinary concentrations with subjects given an intravenous injection. In humans, ingestion of 280 mg of aluminium given as aluminium sulphate diluted with orange squash, to mimic the conditions that might have occurred during the Lowermoor incident, led to less than 1% absorption of the dose (0.45 ± 0.12 % of the dose was excreted in urine within 20 hours; n = 3 subjects) (Taylor *et al*, 1998).

Variability in aluminium absorption

6.23 Aluminium absorption varies between individuals and may increase with age (Taylor *et al*, 1992). Following ingestion of aluminium citrate, the mean peak blood concentration was higher in elderly subjects (aged between 77 and 87 years) than in young adults. The mean blood aluminium concentration in the elderly subjects was 0.1 mg/l (range 0.03 to 0.23 mg/l) (Taylor *et al*, 1992). This may reflect changes in absorption or excretion with age. It appears that some individuals may absorb a higher proportion of aluminium than others for reasons that are not clear. Taylor (1992) reported that one healthy volunteer absorbed up to 10 times more aluminium than than 9 other young adults studied when it was given in the presence of citrate. Premature infants have been found to accumulate aluminium in their tissues from intravenous fluids used for parenteral feeding (Sedman *et al*, 1985). However, when infants consumed soy-based infant formulae which contained aluminium at concentrations several times higher than those found in human milk, plasma aluminium concentrations were found to be similar to those found in breast-fed infants (Litov *et al*, 1989).

6.24 Food constituents may influence aluminium uptake. Glynn *et al* (1999) found that the bioavailability of aluminium from drinking water in rats was dependent on the amount and nature of aluminium-binding components in the gastrointestinal tract. However, Yokel *et al* (2001) found that the presence of food in the stomach simply delayed absorption of low doses of aluminium (4 mg/l given in drinking water) rather than affecting its bioavailability. Fasting increased the absorption of ^{26}aluminium from drinking water in rats 10-15 fold when compared to non-fasted rats (Drueke *et al*, 1997).

Absorption via inhalation or through the skin

6.25 Although the normal daily intake of aluminium from inhalation is relatively low (estimated at approximately 0.02 μg/day: Priest, 2004), there is potential for uptake of soluble forms of aluminium in aerosols. In humans, the absorption of aluminium oxides in the lungs was estimated to be 1.9% using ^{26}aluminium, but mechanical clearance is likely to occur (Priest, 2004). Absorption of aluminium across the skin has been demonstrated (Anane *et al*, 1995; Flarend *et al*, 2001). In

mice, absorption of aluminium chloride (0.4 μg applied to 4 cm^2 shaved skin daily for 130 days) led to elevation of serum aluminium concentrations by approximately 2–fold (Anane *et al,* 1995). Similarly, the cutaneous application of 0.4 μg/day aluminium chloride to pregnant mice led to a 63% increased aluminium concentration in maternal serum and a 21% increase in amniotic fluid (Anane *et al*, 1997). Increased concentrations were also reported in maternal and fetal organ samples. Skin absorption may therefore contribute to bioavailability although the uptake mechanism is saturable. According to a study by Flarend *et al* (2001), only 0.012% of aluminium was absorbed, over a period of 7 weeks, across the skin of two adult human subjects when applied as aluminium chlorohydrate to the axilla which was then covered by an occlusive dressing.

Summary of bioavailability

6.26 Although, in general, studies indicate that absorption of aluminium is low across the gut following ingestion or across the skin, the chemistry of aluminium and the complex interactions that it may undergo make the precise quantification of absorption and the underlying mechanisms involved difficult to determine. There is thus a considerable potential for variability in the extent of absorption in humans. Recent unpublished animal studies found that absorption of different aluminium compounds after oral administration was generally in the region of 0.01 to 0.2% in rats and aluminium absorption is usually around 0.2–0.4% in healthy young adults. However, it has been shown to be 10 times higher in one case in a young adult (Taylor *et al,* 1992) and may also be enhanced during fasting.

The distribution of aluminium in the body

6.27 Once absorbed, aluminium exists free in blood as aluminium citrate (approximately 10%) with the majority of aluminium (approximately 90%) bound to transferrin (Ohman and Martin, 1994). Taylor *et al* (1998) found the aluminium concentration in the blood of three normal male subjects to be in the range 6.5 to 8.5 μg/l. A small proportion (found to be 10% in one subject) may be bound to albumin (Priest, 2004). According to Zafar *et al* (1997), orally administered ^{26}aluminium preferentially accumulates in rat tissues in the following descending order: bone, spleen, kidney and liver, brain. In rats, the accumulation and half-life of aluminium in tissues are affected by age (Greger and Radzanowski, 1995). Uptake into the brain possibly involves aluminium citrate uptake by the monocarboxylic acid transporter (Walton *et al*, 1995; Yumoto *et al*, 1997) and/or an organic anion transporting protein (Yokel *et al*, 2002). Although transferrin-mediated endocytosis may contribute to uptake into brain cells, this appears to be minor (Barker *et al*, 1997). The monocarboxylic acid transporter may also actively remove aluminium from the brain (Yokel *et al*, 1999) and this is expected to remove aluminium that may have been taken up by specific areas of the brain such as the pineal and the area postrema that lack a blood:brain barrier (Ray, personal communication 2004). Only a small proportion of the aluminium in the blood is taken up by the brain. However, it appears that some aluminium enters brain compartments from which there is slow elimination (Yokel, 2002a). In 21-day old rats higher brain concentrations were achieved, when compared to adult (8 months) or old (16 months) rats, following chronic exposure to aluminium (Domingo *et al*, 1996; Gomez *et al*, 1997). It is important to note that, if uptake into the brain can occur in specific areas that lack a blood:brain barrier, this will be taken into account in the derivation of a "No Observed

Adverse Effect Level" (NOAEL)[40] in animals. These areas in man are well modelled in rats and other species. Therefore, if uptake did occur in such areas, adverse effects would be seen in animal studies of aluminium (Ray, personal communication, 2004).

6.28 Fattoretti *et al* (2003) gave aged male rats (22 months old) 2 g/l Al chloride hexahydrate in drinking water for 6 months (22-27 mg Al/kg bw/day if it is assumed that rats drink 10-12 ml/100g/day). Aluminium concentrations in the brain increased preferentially in the hippocampus, which showed morphological changes, and there were changes in the concentrations of copper, zinc and manganese.

6.29 According to Priest (2004), aluminium is thought to be deposited on all bone surfaces by exchange with calcium or by complexing with organic matrix components. It may also be incorporated into hydroxyapatite as it is formed. Removal of aluminium from the bone may involve uptake by osteoclasts.

6.30 IPCS (1997) quotes typical brain and bone concentrations in normal human subjects which vary widely: 0.2-11.9 mg/kg dry weight and 2.4-10.6 mg/kg dry weight, respectively. As reported in paragraph 5.143, Andrasi *et al* (2005) reported brain aluminium concentrations for 3 normal subjects as 1.4-2.5 mg/kg dry weight. House et al (2012) found that the aluminium content of 60 brains donated to the MRC study on Cognitive Function and Aging Study ranged from the Method Blank Value to 33 mg/kg dry weight with a median value of 1.02 mg/kg dry weight. In the past, a combination of renal failure and exposure to aluminium through dialysis treatment has occurred and this was found to elevate brain aluminium concentrations substantially (up to 85 fold) with much patient-to-patient variability (Alfrey, 1980; Ellis *et al*, 1979; Flendrig *et al*, 1976).

The excretion of aluminium

6.31 Following absorption, aluminium is rapidly excreted by mammals via the urine. In rats, after single intravenous doses of up to 0.1 mg/kg, aluminium was quantitatively recovered from urine (Wilhelm *et al*, 1992). In normal subjects given doses of between 23 and 313 mg aluminium/kg body weight orally as antacids, aluminium concentrations in the urine were elevated 2 to 6 fold (Gorsky *et al*, 1979). When injected into human volunteers as ^{26}aluminium, 83% and 1.8% of the dose was recovered in urine and faeces, respectively, during a 13 day period (Priest *et al*, 1991, 1996) although inter-individual variability has been described by Talbot *et al*, (1995). In a single human volunteer who received ^{26}aluminium (3.8 ng with 63 ng ^{27}aluminium) in citrate solution by intravenous injection, whole body retention was 15% at 13 days after administration and 4% at 1178 days, corresponding to a biological half-life of 7 years (Priest et al, 1995a). Subsequently, excretion data suggested that the current retention half-life for this volunteer is in the region of 50 years (Priest, 2004). It appears from these studies, and that of Sjogren *et al* (1985), that the initial half-life of aluminium is approximately 8 hours but that this increases with the passage of time as aluminium is gradually released from tissues such as the bone where it has accumulated. Importantly, single doses of aluminium can produce high urine concentrations despite modest increases in blood aluminium concentrations (Gitelman, 1995; Nagy and Jobst, 1994), demonstrating the efficiency of urinary excretion. Impaired renal function can elevate aluminium concentrations in the body

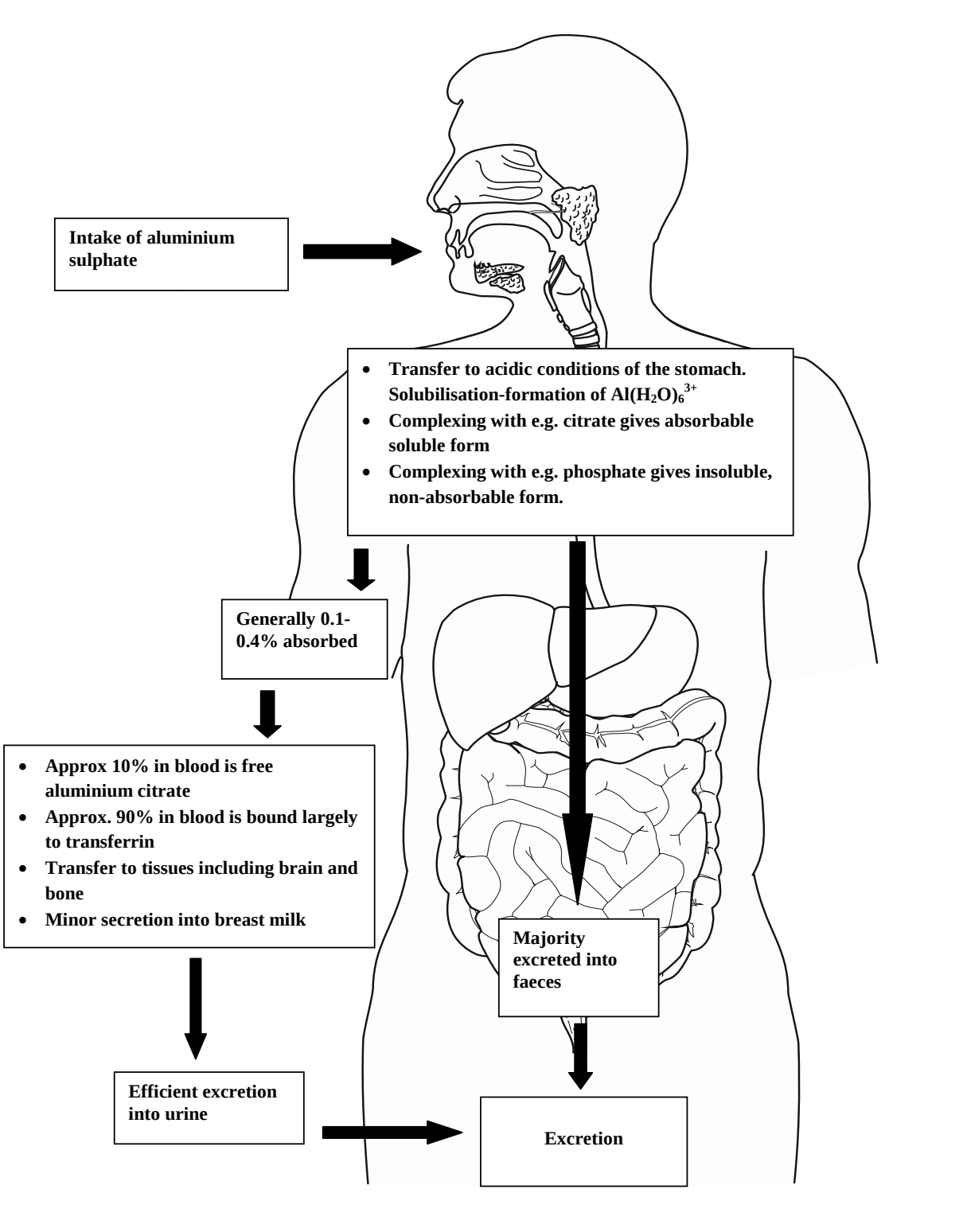
[40] See glossary for a detailed discussion of NOAELs and Lowest Observed Adverse Effect Levels (LOAELs)

and this may be the basis of increased aluminium accumulation with age (Liu *et al*, 1996). Until children are 1-2 years old, clearance by glomerular filtration is less than that in adults and thus aluminium excretion is relatively inefficient (FDA, 2003).

6.32 Administration of an intravenous bolus of ^{26}aluminium to rats resulted in a peak brain level of 0.0005% of the administered dose, which had a half-life of approximately 150 days, irrespective of whether it was administered as aluminium transferrin or aluminium citrate (Yokel *et al*, 2001). Evidence of the bioavailability of aluminium from milk to suckling rats was provided by Yumoto *et al* (2003). This reported that 0.2-0.4% of ^{26}aluminium chloride injected subcutaneously appeared in the milk of lactating rats. Importantly, the persistance of aluminium in rat brain was indicated following intake of aluminium chloride via suckling. Up to 20% of the level of ^{26}aluminium in the brain at Day 20 post partum remained after 730 days (Yumoto *et al*, 2003). Although not studied experimentally, we note that there is a report of aluminium being eliminated via the milk of cows (see paragraph 5.185). Aluminium is reported to be secreted in human milk: Baxter *et al* (1991) reported a mean aluminium concentration of 0.027 mg/l (range 0.003 – 0.79 mg/L) in milk from 8 women from a breastfeeding group in the United Kingdom.

6.33 In Figure 33 we show a simplified description of the fate of aluminium in man when ingested as aluminium sulphate.

Figure 33: A summary of the general fate of ingested aluminium sulphate in the body



Toxicity of aluminium – acute and short term effects

6.34 Aluminium has not been shown to be acutely toxic in humans by the oral route (IPCS, 1997) and doses of up to 800 mg/day are sometimes taken in medicinal antacid/antiulcer products (see paragraph 6.15). Fourteen studies have investigated the relationship between high aluminium exposure from antacids and cognitive decline and no significant positive association was found (Appendix 21). Additionally, in a double blind randomised controlled study, Molloy et al (2007) demonstrated an absence of short term cognitive effects following aluminium ingestion, contained in a single dose of antacid, in normal volunteers or in individuals with dementia.

Experimental animals

6.35 High doses of aluminium are required to produce acute oral toxicity in animals. The reported oral LD_{50} values of aluminium compounds, including aluminium sulphate, are between 162 and 980 mg/kg body weight (bw)[41] (IPCS, 1997). It is useful to compare the relative acute toxicities of the various salts since this may reflect differences in absorption. In the rat, toxicity was seen in the following descending order of potency: aluminium bromide, aluminium nitrate, aluminium chloride, aluminium sulphate.

6.36 Hicks *et al* (1987) found no treatment-related effects in rats fed up to 302 mg aluminium/kg bw/day (as the hydroxide) for 28 days. At 261 mg aluminium/kg bw/day (but not at 52 mg/kg bw/day), given to rats as aluminium nitrate in drinking water for 100 days, body weight gain was lower than that in untreated rats because of a decrease in food consumption (Domingo *et al*, 1987a). No other effects were seen in this study and there was no dose-dependent accumulation of aluminium in tissues.

6.37 In contrast, Roy *et al* (1991a) found that male rats given aluminium sulphate in deionized drinking water for up to 21 days showed some adverse effects at lower doses than noted in the studies cited in paragraph 6.36. Dose-related histopathological changes were seen in the liver and kidney at intakes of 17 mg aluminium/kg bw/day (the lowest dose administered) with neuronal degeneration of the cerebral cortex at a dose of 28.6 mg aluminium/kg bw/day. Degeneration of calcified bone and hyperplasia and ulceration of the stomach were seen at 172 mg/kg bw/day. There are some limitations of the study that hinder interpretation of the findings. In particular, there are potential tissue fixation artefacts and uncertainty regarding irreversibility of effects.

6.38 Somova *et al* (1996, 1997) treated male Wistar rats with aluminium chloride in the drinking water for a longer period (6 months) at doses of 5 and 20 mg/kg bw/day. The authors are ambiguous as to whether the doses cited are those of aluminium or of the salt; we have assumed that they refer to the metal. There were reductions in body weight and in haematological parameters at both dose levels, but these were not dose-related. At 20 mg aluminium/kg bw/day, spongiform changes and neurofibrillary degeneration in the hippocampus of the brain and atrophy and

[41] See glossary

fibrosis in the kidney were observed. It is difficult to interpret these results because of the lack of dose-relationship in the body weight and haematological results.

6.39 Two studies have been reported in dogs in which aluminium was administered as sodium aluminium phosphate (SALP) in the diet over a period of 6 months. In one study, using SALP acidic, no toxicological effects were observed at any dose, giving a NOAEL of approximately 85 mg aluminium/kg bw/day, the highest dose administered[42] (Katz *et al*, 1984). In the other study, which used SALP basic, effects were seen in the liver and testis in high dose males, giving a NOAEL of 27 mg aluminium/kg bw/day in males and 80 mg aluminium/kg bw/day in females, respectively (Pettersen *et al*, 1990). The concentrations of aluminium in the diet was measured in this study so this is the total intake of aluminium by the dogs. At the end of this study, no increase was seen in the trabecular bone concentrations of aluminium in any dose group and an increase in brain aluminium concentration was seen only in the high dose female group (80 mg aluminium/kg bw/day). It should be noted that phosphate reduces the bioavailability of aluminium (see paragraph 6.20).

The neurotoxicity of aluminium

Studies in humans

6.40 In observational studies, cases of an encephalopathy (dialysis dementia) have been reported as a result of the use of exposure to dialysis fluids containing aluminium in patients with renal impairment. These effects are associated with elevated concentrations of aluminium in the brain (Alfrey *et al*, 1972; Flendrig *et al*, 1976; McDermott *et al*, 1978; Reusche *et al*, 2001). Reported symptoms included nausea, vomiting, abdominal pain, weight loss and general malaise. At plasma concentrations of aluminium greater than 500 μg/l, neurotoxic symptoms and signs such as agitation, confusion, muscle twitching and seizures of sudden onset occur and can lead to coma and death. In a limited study, Bowdler *et al* (1979) found that impaired visuo-motor coordination, poor long-term memory and increased sensitivity to flicker were found in subjects (aged 56-90 years) with an aluminium concentration of 504 μg/l compared to 387 μg/l serum. However, it should be noted that serum aluminium concentrations in this study appeared to be between 2 and 3 orders of magnitude higher than those typically reported.

6.41 Dialysis dementia is reversible on lowering of aluminium concentrations in the plasma and brain, for example, by use of the chelating agent desferrioximine (Ackrill and Day, 1985).

6. 42 It has been suggested that aluminium ingestion may be a risk factor for the development of both Alzheimer's disease and impaired cognitive function in the elderly. Alzheimer's disease is a neurodegenerative disorder that currently affects nearly 2% of the population in industrialized countries (Mattson, 2004). Brain regions involved in learning and memory processes are reduced in size in patients with Alzheimer's disease as a result of degeneration of synapses and death of neurons. Because there can be other causes of memory loss, definitive diagnosis of Alzheimer's disease requires postmortem examination of the brain, which must

[42] The figure of 70 mg/kg bw/day in Appendix 21 of this report was taken from IPCS (1997) and is incorrect.

contain sufficient numbers of “plaques” and “neurofibrillary tangles” to qualify as affected by Alzheimer’s disease (Mattson, 2004). Plaques are extracellular deposits of fibrils and amorphous aggregates of amyloid β-peptide (β-amyloid). Neurofibrillary tangles are intracellular fibrillar aggregates of the microtubule-associated protein tau that exhibit hyperphosphorylation and oxidative modifications.

6.43 A large number of studies have investigated an association between aluminium, Alzheimer’s disease and impaired cognitive function. Most epidemiological studies have been ecological, prevalence surveys or case-control designs[43] and aluminium concentration measurements in the public water supply (either concurrent or historical) have generally been used as an estimate of exposure. Confirmation of disease outcome varied and included information from death certificates, ‘clinical’ diagnosis, the use of cognitive function testing and histopathological tests. The results from these studies have been conflicting. A positive association between the disease and aluminium exposure was indicated by some studies (Martyn *et al*, 1989; Neri and Hewitt, 1990; Flaten *et al*, 1991; McLachlan *et al*, 1996; Rogers and Simon, 1999; review by Jansson, 2001; Rondeau *et al*, 2000 and 2009); in contrast, others (Forster *et al*, 1995; Martyn *et al*, 1997; Wettstein *et al*, 1991) have found no significant association between the risk of Alzheimer’s disease and aluminium levels in drinking water. In addition to potential inaccuracies and misclassification of exposure and disease, inadequate adjustment has been made for confounding factors such as age, sex, education and socio-economic status. The risk estimates from these studies are generally low and, for the reasons given above, likely to be imprecise.

6.44 There have also been conflicting data on the association of brain aluminium concentrations with Alzheimer’s disease. Bjertness *et al* (1996) avoided a number of common methodological deficiencies such as inadequate neuropathological assessment, failure to age-match controls, small sample size and geographical heterogeneity associated with some previous studies. They found no correlation between aluminium concentrations in various tissues, including frontal and temporal cortex, and histological features of Alzheimer’s disease in their study group. These results contrast with those of Andrasi *et al* (1995) who found consistently higher aluminium concentrations in ten areas of brain in patients who had suffered from Alzheimer's disease compared to controls. It is possible that aluminium is localised in the brain in only a subpopulation of Alzheimer's disease patients and may not be involved in pathogenesis (Kasa *et al*, 1995; Savory *et al*, 1996). It is also relevant that both increased absorption of aluminium and increased serum concentrations have been reported in patients with Alzheimer's disease (reviewed in Jansson, 2001). However, Gao et al (2008) did not find a significant association between plasma aluminium concentrations and cognitive function in a rural, elderly Chinese population. There remain conflicting views on whether aluminium is an aetiological factor in Alzheimer’s disease or not (see, for example, Munoz and Feldman, 2000: Tomljenovic, 2011).

6.45 Other neurological diseases such as amyotrophic lateral sclerosis, Parkinson's disease and the forms of these diseases found in individuals from Guam have been associated with accumulation of aluminium in the brain (Gajdusek and Salazar, 1982;

[43] See Appendix 4 for a discussion of different types of epidemiological studies.

Perl *et al*, 1982). However, according to JECFA (2007), the role of aluminium, if any, in the initiation and development of the disease is not elucidated in these studies since the effect of the other factors potentially associated with the disease or their interactions are not yet fully understood.

Studies in experimental animals

6.46 There is considerable evidence that aluminium is neurotoxic in experimental animals at high doses, although there is substantial variation between species. In susceptible species, notably the rabbit, toxicity following parenteral administration is characterised by progressive neurological impairment. The encephalopathy is associated with neurofilament damage in large and medium sized neurons, predominantly in the spinal cord, brainstem and some areas of the hippocampus. As discussed above, spongiform changes and neurofibrillary degeneration in the hippocampus of the rat brain were reported at 20 mg aluminium/kg bw/day following 6 months treatment in drinking water (Somova *et al*, 1997). A similar dose of 25 mg aluminium/kg bw/day by gavage on alternate days for 1 year in monkeys (only 3 animals per group) was shown by Sarin *et al* (1997) to produce various biochemical changes in brain that are discussed below. Roy *et al* (1991a) observed neuronal degeneration of the cerebral cortex in rats at a dose of 28.6 mg aluminium/kg bw/day following treatment in the drinking water for a much shorter period of time (21 days). The limitations of this study are noted in paragraph 6.37.

6.47 Importantly, behavioural anomalies have been observed in the absence of overt encephalopathy or neurohistopathology in experimental animals exposed to soluble aluminium salts, administered in the diet or drinking water, at doses of 200 mg aluminium/kg bw/day or more (WHO, 1997). Bowdler *et al* (1979) found that the lowest dose capable of producing increased sensitivity to flicker using an electroretinogram in rats following repeated oral gavage of aluminium (given daily for 21 days as the chloride) was 45 mg aluminium/kg bw/day. An apparent NOAEL was 22.5 mg/kg bw/day. Other neurobehavioural tests showed no effects at this dose or at 67.5 mg/kg bw/day. The study is of limited quality and the results are difficult to interpret. Impairment of performance in studies designed to test passive and conditioned avoidance responses have been reported in rats at doses above 200 mg aluminium/kg bw/day (Thorne *et al*, 1986; Wu *et al*, 1998; Connor *et al*, 1988; Gonda and Lehotsky, 1996). In a clearly described study, Mameli *et al* (2006) investigated the effect of aluminium, given as aluminium chloride in drinking water for 90 days, on the vestibular-ocular reflex (VOR) of male rats. A NOAEL of 21.5 mg aluminium/kg bw/day was identified. At 43.1 mg aluminium/kg bw/day, significant VOR impairment was seen in all exposed rats, regardless of animal age. Dose-related increases in brain aluminium concentrations were seen at both dose levels. In this study, three dose levels were used and water consumption was measured. The concentration of aluminium in the diet was 92 mg/kg, equivalent to an intake of 9.2 mg/kg bw/day (on the assumption that rats consume 10g diet/100g body weight/day (Harkness and Wagner, 1989)). Kaur *et al* (2006) reported impaired motor performance in male rats treated "intragastrically"[44] with 10 mg aluminium/kg bw/day as aluminium lactate for 12 weeks, the only dose used. However, gross behavioural effects were also reported, which is inconsistent when compared with

[44] It is not entirely clear what is meant by "intragastrically". We have assumed it means by gavage administration.

findings at this dose level in other studies. Alterations were reported in brain protein kinase, phosphoprotein phosphatase, chemical phosphorylation status and brain neurofilaments. Luo *et al* (2007) demonstrated learning and memory deficits, as determined by the Morris water maze test, in rats receiving 1600 ppm aluminium chloride[45] in drinking water for 5 to 8 months (equivalent to 17.9 to 21.5 mg aluminium/kg bw/day on the assumption that rats consume 10-12 ml/100g/day (Harkness and Wagner, 1989)). No effect on learning ability was reported in a study in which aluminium was administered to rats by intraperitoneal injection, despite significantly increased brain aluminium concentrations, although the time taken to undertake the trial was increased (Struys-Ponsar *et al*, 1997).

6.48 Zhang *et al* (2003), in a study to evaluate the protective effects of the herbal medicine *Dipsacus asper Wall* extract against the cognitive impairment and overexpression of hippocampal β-amyloid protein induced by chronic aluminium exposure in rats, found that treatment with a single dose of aluminium chloride in drinking water (equivalent to 61-73 mg aluminium/kg bw/day on the assumption that rats consume 10-12 ml/100g/day (Harkness and Wagner, 1989)) caused impaired performance in a passive avoidance test. Golub and Germann (2001) administered aluminium in a suboptimal diet to pregnant mice, and to their pups from weaning to 35 days old. The control concentration of aluminium in the diet was 7 mg/kg, said to give an intake of <1 mg aluminium/kg bw/day. Pups suffered retarded growth at 500 mg aluminium/kg diet (said to be approximately 50 mg/kg bw/day) and above and showed subtle deficits in several neurobehavioural parameters at 1000 mg/kg bw/day (100 mg/kg bw/day) when tested at more than 90 days of age.

Potential mechanisms of aluminium neurotoxicity

6.49 Several studies have investigated the possible mechanisms involved in the causation of aluminium neurotoxicity. Neurobehavioural responses to aluminium may be due to effects other than, or in addition to, reduced cholinergic activity (Cheroret *et al*, 1992). In rats given aluminium chloride (320 mg/kg bw/day; 65 mg aluminium/kg bw/day based on the molecular weight of the unhydrated salt) orally for 4 days, brain acetylcholinesterase activity increased after 4 days but decreased after 60 days administration (Kumar, 1998). Lower doses were not studied. Oral administration to rats by gavage for 90 days of 91.8 mg aluminium/kg bw/day as the lactate caused decreases in both ATPase and acetylcholinesterase activities, detectable at 2 weeks after the exposure but not immediately after exposure (Kohila *et al*, 2004).

6.50 Sarin *et al* (1997a) administered oral aluminium lactate (25 mg aluminium/kg body weight) by gavage every other day for one year to monkeys. There was evidence of decreased lipid concentrations in the brain together with lipid peroxidation and inhibition of the enzyme calcium-ATPase. The findings suggested an increase in intracellular calcium concentrations that may be responsible for altering neuronal excitability. The treatments also produced a decrease in total lipid, glycolipid and phospolipid content and an increase in cholesterol content in the brain. The associated membrane changes may be responsible for decreased activities of the enzymes sodium potassium-ATPase and acetylcholinesterase, and 2'3'-cyclic nucleotide phosphohydrolase in the brain (Sarin *et al*, 1997b). Alterations in calcium-

[45] Described as 'analytical grade' aluminium chloride, which is aluminium chloride hexahydrate $AlCl_3.6H_2O$.

mediated homeostatic mechanisms were also reported after administration of 10 mg aluminium/kg bw/day to rats by gavage as aluminium lactate for 12 weeks (Kaur and Gill, 2005). Other studies have demonstrated the ability of aluminium to alter membrane function at the blood-brain barrier, potentially altering access to the brain of nutrients, hormones and foreign compounds (e.g. Banks and Kastin, 1985).

6.51 After administration to rats of 20 mg aluminium/kg bw/day as aluminium chloride added to the diet for 90–100 days, both brain and liver mitochondrial respiratory activity were affected dependent on the substrate provided (Swegert *et al*, 1999). This effect may be related to the reported ability of aluminium to replace other metal ions associated with various enzymes (Deloncle and Guillard, 1990). However, no toxicological implications of these biochemical changes were established.

6.52 El-Demerdash *et al* orally administered 34 mg aluminium/kg bw as aluminium chloride to a group of seven male rats every other day for 30 days (El-Demerdash *et al*, 2004). The dose was stated to be 1/25 of the rat oral LD_{50} for aluminium and the comparison indicates that the dose is expressed as aluminium rather than aluminium chloride, although this is not completely clear from the paper. Compared to a control group, aluminium chloride significantly increased markers of lipid peroxidation (TBARS) in rat plasma, liver, brain, testes and kidney. The activity of GST and levels of sulphydryl groups were significantly decreased in all tissues except brain. Effects were reported on the levels of a number of enzymes in plasma and tissues and of other blood parameters. In brain, the activity of LDH was significantly increased and activities of phosphorylase and acetylcholinesterase decreased. Vitamin E or selenium in combination with aluminium alleviated its effects on the parameters studied. In a related study, similar changes were found in a group of 6 male rabbits orally administered the same dose of aluminium chloride by gavage on alternate days for 16 weeks (Yousef, 2004). In addition, significant changes in levels of several haematology parameters were reported in these animals. Ascorbic acid ameliorated the effects of aluminium. No lower dose levels of aluminium were used in either of these studies.

6.53 According to Rodella et al (2008), dysfunction of the endoplasmic reticulum is thought to be involved in the pathogenesis of Alzheimer's disease. These authors reported a deposition of β-amyloid and a reduction in the expression of GRP78, a stress-response protein induced by conditions that adversely affect endoplasmic reticulum function, in the brain cortex of mice following exposure to 2.5% aluminium sulphate in tap water for 12 months (equivalent to 296 mg aluminium/kg bw/day on the assumption that mice consume 15 ml/100g/day (Yale School of Medicine, 1999)). There are a number of difficulties in interpreting this study, namely, Rodella and colleagues have used a supposedly sensitive immuno-cytochemical technique to show small amounts of amyloid-like protein but the paper gives no information about amyloid in other organs to see how advanced generalised amyloid is in the mice. The paper lacks detail on the cross reactivity of the specific antibody used for amyloid in the study and it does not provide information on the pathology of the mice; this also makes interpretation difficult.

6.54 *In vitro* studies have shown that concentrations of 4.2 mg/l aluminium and above can elevate intracellular free calcium through effects on calcium ATPases (Gandolfi *et al*, 1998). However, there was no evidence of such changes *in vivo*

(Anghileri *et al*, 1994) and it appears that effects on rat hippocampal neurons are independent of calcium receptor activation (Brenner and Yoon, 1994).

6.55 Matja (2000) showed that aluminium potentiated glutamate-induced neuronal lesions associated with excitation of rat hippocampal neurons in vitro. The potentiation may involve interference with glutamate metabolism since aluminium increased the concentration of glutamine in the hippocampus and neocortex of rat brain (Struys-Ponsar *et al*, 2000).

6.56 Christen (2000) reviewed the evidence that oxidative and inflammatory effects of aluminium may be important in the mechanism of toxicity. There is evidence that aluminium is able to enhance the iron-induced production of reactive oxygen species (Xie *et al*, 1996; Mundy *et al*, 1997; Campbell *et al*, 1999; Xie and Yokel, 1996) and, consequently, lipid peroxidation. However, there are conflicting findings as to whether this occurs *in vivo* (Swain and Chainy, 1998; Xie *et al*, 1995). There is evidence of the involvement of glial cells and of an inflammatory response in the brain in response to aluminium both *in vitro* and *in vivo* in rodents and rabbits (Campbell *et al*, 2001; Platt *et al*, 2001; Tsunoda and Sharma, 1999; Yokel and O'Callaghan, 1998). Exley (1999) has also suggested interference with ATP receptors.

6.57 There is evidence that chelating agents, including desferrioxamine, can lower the concentration of aluminium in brain, enhance its excretion in rats and decrease neuronal damage in rabbits (Florence *et al*, 1995; Gomez *et al*, 1999; Savory *et al*, 1994). These studies are insufficient to indicate a role for aluminium as a causative factor in Alzheimer's disease. However, after sustained administration, desferrioxamine may slow the clinical progression of the dementia associated with Alzheimer's disease (McLachlan *et al*, 1991).

6.58 The morphological changes seen in the brains of animals are different from the neurofibrillary tangles that occur in Alzheimer's disease in humans although Huang *et al* (1997) found that brain sections in rabbits stained positive for three proteins that occur in neurofibrillary tangles in the brains of patients with Alzheimer's disease. Strong *et al* (1996) suggested that the aluminium-induced changes are produced, at least in part, by increased phosphorylation of a neurofilament tau protein. The aluminium exposure that occurred in the past in some renal dialysis patients has also been associated with increased phosphorylation of the tau protein (Harrington *et al*, 1994) although no neurofibrillary tangle formation was found in these patients at *post mortem* (Candy *et al*, 1992; Edwardson *et al*, 1992; Wisniewski, 1994). A number of studies *in vitro* show that aluminium can cause the aggregation of β-amyloid protein and modification of the tau protein (Fasman *et al*, 1995; Bondy and Truong, 1999). However the effect on β-amyloid protein is not unique to this metal. It is likely that there are a number of mechanisms whereby aluminium can disturb neurofilament biochemistry (Shea *et al*, 1997).

6.59 Cytoplasmic filamentous inclusions known as Lewy bodies occur in Parkinson's disease and also in a proportion of Alzheimer's disease cases (Jellinger *et al*, 2004; Mikolaenlo *et al*, 2005). The major component of Lewy bodies is the protein α-synuclein. Aluminium and other metals cause significant accelerations in the rate of α-synuclein fibril formation *in vitro* (Uversky *et al*, 2001). In other *in vitro*

studies, aluminium changed the conformation of the non β-amyloid component of the amyloid plaques found in Alzheimer's disease patients, which is derived from α-synuclein (Paik *et al*, 1997; Khan *et al*, 2005).

6.60 It has been considered that the disturbance of mitochondrial free calcium homeostasis by aluminium is mediated by endoplasmic reticulum stress and leads to neuronal cell death by a programmed mechanism (Savory *et al*, 2003).

Summary of neurotoxicity

6.61 Considering information derived from mechanistic studies together with information from epidemiology as discussed above, the evidence would suggest that aluminium exposure does not cause Alzheimer's disease, although it has not been established whether aluminium may contribute indirectly in some cases.

6.62 Aluminium has been found to be neurotoxic in animals and a number of potential mechanisms of action exist. The most sensitive neurological responses reported in animals in repeated-dose studies are given in Table 47. However, it should be noted that many of these studies are of poor quality or report insufficient measurements to aid hazard assessment. Several studies only examined effects at a single dose of aluminium and, therefore, provide no information about the dose-response relationship. In some cases, it is not clear whether the stated dose levels refer to elemental aluminium or to the aluminium compound administered. Of the studies listed in Table 47, only that by Mameli *et al* (2006) measured the concentration of aluminium in the rat diet.

6.63 The study by Kaur *et al* (2006) reported impaired motor performance at 10 mg/kg aluminium/day, the only dose level administered, but there are features of this study which give cause for concern about the reliability of the results (see paragraph 6.47 and Table 47). In comparison, the study by Mameli *et al* (2006), which was of good quality, showed a clear NOAEL of 21.5 mg administered aluminium/kg bw/day for functional neurotoxic effects (see paragraph 6.47 and Table 47). Additional intake of aluminium from the diet in this study was estimated to be 9.2 mg/kg bw/day, giving an actual NOAEL of 30.7 mg/kg bw/day. The study by Luo *et al* (2007) demonstrated learning and memory deficits in rats receiving 17.9-21.5 mg aluminium/kg bw/day in drinking water for 5 to 8 months. Only one dose was given in the study and no information was provided on the aluminium intake from the diet (paragraph 6.47 and Table 47). The study by Somova *et al* (1996, 1997) reported spongiform changes and neurofibrillary degeneration at 20 mg aluminium/kg bw/day and indicated an apparent NOAEL of 5 mg/kg bw/day, but interpretation of the results of this study is difficult because non-dose-related reductions were seen in body weight and haematological parameters (see paragraph 6.38 and Table 47). Kaur and Gill (2005) reported alterations in brain biochemical parameters at 10 mg aluminium/kg bw/day but the study is limited and it is not clear that these effects are adverse (see paragraph 6.50 and Table 47). Changes in brain biochemistry may be temporary and without any long-term consequences. The values identified are likely to vary according to the salt form in which aluminium is administered, because of the differences in absorption efficiency of different salts noted above. Neither a NOAEL nor a LOAEL has been established for single, or very short term exposures.

Table 47: The neurological responses observed at the lowest aluminium exposures in animal studies

Neurological effect	Species	Test substance: dose method and level	Notes	Reference
Increased sensitivity to flicker	Rat	Aluminium chloride: gavage, 28 days LOAEL[a]: 45 mg/kg bw /day aluminium? NOAEL[b]: 22.5 mg/kg bw/day aluminium?	Other behavioural tests were negative. Results of study difficult to interpret.	Bowdler *et al*, 1979
Impairment of the vestibulo-ocular reflex	Rat	Aluminium chloride: drinking water, 90 days LOAEL: 43.1 mg/kg bw/day aluminium NOAEL: 21.5 mg/kg bw/day aluminium Additional intake of aluminium from the diet estimated to be 9.2 mg/kg bw/day	Good quality paper: 3 dose groups; intakes of aluminium chloride measured; intake via diet discussed; methodology and results clearly described.	Mameli *et al*, 2006
Learning and memory deficits	Rats	Aluminium chloride: drinking water, 5 to 8 months Effects seen at 17.9 to 21.5 mg aluminium/kg bw/day	Purpose of study was not specifically to examine the effects of aluminium. Only one dose used.	Luo *et al*, 2007
Spongiform changes and neurofibrillary degeneration	Rat	Aluminium chloride: drinking water, 6 months LOAEL: 20 mg/kg bw/day NOAEL: 5 mg/kg bw/day	The reference is ambiguous as to whether the dose refers to the metal or salt. We have assumed it to be the metal. Non dose-related reductions on body weight and haematological parameters reported at both 5 and 20 mg/kg bw/day: interpretation of results difficult.	Somova *et al*, 1996, 1997
Degeneration of nerve cells	Rat	Potassium aluminium sulphate: drinking water, 21 days LOAEL: 28.6 mg/kg bw/day aluminium.	Potential artefacts	Roy *et al*, 1991
Brain lipid changes	Monkey	Aluminium lactate: gavage, alternate days for 1 year Effects seen at 25 mg/kg bw aluminium on alternate days	Only 3 animals and one dose level.	Sarin *et al*, 1997
Alterations in calcium-ATPase activity, calpain activity and calcium concentrations in brain.	Rat	Aluminium lactate: gavage, for 12 weeks Effects seen at 10 mg/kg bw/day aluminium	Only 7 rats/group and one dose level.	Kaur and Gill, 2005

Impaired motor performance. Alterations in brain enzymes , phosphorylation status and brain neurofilaments.	Rat	Aluminium lactate: “intragastric”, 12 weeks Effects seen at 10 mg/kg bw aluminium	Route of administration unclear. Only 6 rats/group and one dose level. Gross behavioural effects reported in treated rats: inconsistent with results of other studies.	Kaur *et al*, 2006
Increase in indicators of lipid peroxidation and changes in other biochemical parameters	Rat	Aluminium chloride: oral administration on alternate days for 30 days. Effects seen at 34 mg/kg bw aluminium on alternate days	Only 7 rats/group and one dose level.	El-Demerdash, 2004
Increase in indicators of lipid peroxidation; changes in other biochemical parameters and in haematological parameters	Rabbit	Aluminium chloride: oral administration on alternate days for 16 weeks. Effects seen at 34 mg/kg bw aluminium on alternate days	Only 6 rabbits/group and one dose level.	Yousef, 2004.

a: LOAEL = lowest observed adverse effect level
b: NOAEL = no observed adverse effect level

Effects on bone

6.64 Osteomalacia, characterised by bone softening, bone pain and an increased incidence of spontaneous fractures, has been reported in otherwise healthy infants treated for azotemia with more than 100 mg aluminium/kg bw/day for several months from the first month of life, and in adults following ingestion of several grams of aluminium-containing antacids per day (ATSDR, 2008; Woodson, 1998; Andreoli *et al*, 1984; Dent and Winter, 1974). The occurrence of osteomalacia has also been documented in patients with chronic renal failure (IPCS, 1997). Osteomalacia occurs in a number of animal species if aluminium is given by injection such that concentrations reach 100 μg/g bone ash. This is more than 10 times the normal human bone aluminium concentration (IPCS, 1997). One paper reported that aluminium can inhibit parathyroid hormone secretion *in vitro*, implying the potential for lowered calcium release from the bone into blood (Smans *et al*, 2000). A study by Li *et al* (2011) found that the bone mineral density of the femoral metaphysis was significantly lower in rats receiving 430 mg/L aluminium chloride[46] in drinking water for up to 150 days (equivalent to 48.1 mg aluminium/kg bw/day) than in control rats.

Aluminium and carcinogenesis

6.65 Aluminium forms complexes with DNA (Rao and Divakar, 1993) and can inhibit the ADP-ribosylation involved in DNA repair (Crapper McLachlan *et al*, 1983). However, various studies have shown an absence of mutagenicity of aluminium in bacterial and mammalian cells (IPCS, 1997). Aluminium has been shown to produce chromosomal aberrations in rats following repeated intraperitoneal dosing (Manna and Das, 1972; Roy *et al*, 1991b). Aluminium chloride[47] (34 mg/kg bw) was reported to increase micronucleus formation in hepatocytes following oral dosing of rats for 30 days (Turkez *et al*, 2010). Rui and Yongjian (2008) demonstrated induction of nDNA damage in a dose-dependent manner, as determined by the COMET assay. The increased formation of 8-hydroxy 2-deoxyguanosine (8-OHdG) was also measured in the mitochondrial DNA isolated from brain cells of mice following oral dosing of aluminium chloride at concentrations up to 300 mg/kg bw/day for 100 days.

6.66 IPCS (1997) concluded, on the basis of limited early studies, that there is little evidence that aluminium causes cancer. Although carcinomas have been reported in the lungs and at sites of subcutaneous administration, these effects have been attributed to a chronic foreign body reaction and not to aluminium *per se* (Haugen *et al*, 1983; IPCS, 1997).

Reproductive and developmental toxicity

6.67 There is no information on the reproductive toxicity of aluminium in humans (IPCS, 1997).

6.68 Borak and Wise (1998) reviewed fourteen studies in which aluminium was given to adult female experimental animals during pregnancy and/or lactation and the

[46] Described as 'analytical grade' aluminium chloride, which is aluminium chloride hexahydrate $AlCl_3.6H_2O$.
[47] Hydration form unknown.

concentration of the metal was measured in the offspring. Fetal aluminium concentrations were not increased in 6 of 7 studies and pup aluminium concentrations were not increased in 4 of 5 studies in which they were measured. There was no association between aluminium concentrations in fetuses and/or pups and either dose, the nature of the aluminium compound, or the route of administration of aluminium to the dam.

6.69 In a series of poorly documented studies in rats, guinea pigs and rabbits, decreased serum alkaline phosphatase activity was reported within 3 hours of oral administration of aluminium (as aluminium chloride), with a minimum effective dose of between 9 and 17 mg Al/kg bw depending on the species (Krasovskii *et al*, 1979). However, this change was not linked to a toxic response. Some ill-defined effects on spermatozoa and kidney were mentioned with no reference to the dose levels at which they occurred. After 6 months of daily exposure to aluminium, changes in the number and motility of spermatozoa and histological changes in the testis were reported at 2.5 mg Al/kg bw/day. Unspecified effects on development and conditioned refluxes were also reported at this dose level but not at lower doses. In the absence of functional effects on reproduction at much higher doses (see below) and given the poor quality of the paper, these findings are difficult to interpret. Bataineh *et al* (1998) reported suppressed sexual behaviour and reduced aggression but no effect on the fertility of male rats receiving 1000 ppm aluminium chloride in drinking water for 12 weeks (100-120 mg/kg bw/day; equivalent to 11.2 to 13.4 mg aluminium/kg bw/day on the assumption that rats consume 10-12 ml/100g/day (Harkness and Wagner, 1989) and the doses of aluminium chloride refer to the hydrated salt). No other dose levels were administered. The rats were reported to have a mean body weight 31% less than that of a control group at the end of treatment and it is likely that the adverse effects reported were due to non-specific toxicity. When male rats were given 34 mg aluminium chloride/kg bw/day (hydration form unknown) orally for up to 60 days, serum testosterone levels were reported to be significantly decreased compared to controls at 30, 45 and 60 days (Moselhy *et al*, 2012). Aluminium treatment was also reported to cause a significant increase in testicular malondialdehyde (MDA) levels at day 60, and effects on sperm motility, viability and morphology. Histopathological examinations revealed a number of abnormalities in the reproductive organs.

6.70 In a study of reproductive toxicity (Domingo *et al*, 1987b), male and female rats were given aluminium nitrate by gavage at doses of 13-52 mg aluminium/kg/day for 60 days in males and for 14 days in females before mating and then up to lactation in females. There were no effects on reproductive capacity even at the highest dose. A LOAEL was found to be 26 mg/kg/day with respect to pup birth rate and postnatal growth. Developmental effects of aluminium (given by gavage as the nitrate) in rats were seen at the lowest dose administered (13 mg aluminium/kg/day), thus preventing the derivation of a NOAEL. The effects seen at this dose included decreased ossification, lowered fetal weight, and an increased incidence of skeletal abnormalities and malformations. The dose dependency suggests that the effects were not due to maternal toxicity (Paternain *et al*, 1988). In comparison to the above, no adverse maternal, embryotoxic or teratogenic effects were seen when aluminium was administered by gavage as aluminium hydroxide to pregnant mice on days 6-15 of gestation at doses up to 92 mg aluminium/kg bw/day (Domingo *et al*, 1989c).

6.71 Bernuzzi *et al* (1989,1989a) reported impaired grip strength in the 6 day old offspring of dams fed 100 mg aluminium/kg bw/day and above via the diet as the lactate throughout gestation. No effects on maternal or fetal weight were reported. Donald *et al* (1989) reported that pup performance was significantly affected in a series of postweaning neurobehavioural tests when dams were fed $\geq$500 ppm aluminium in the diet as the lactate (100-210 mg aluminium/kg bw/day), the lowest dose administered. There were no effects on maternal or fetal weight or mortality. In a small study by Muller *et al* (1990), the administration of 400 mg aluminium/kg bw/day as the lactate in the diet of pregnant rats resulted in a reduced performance by the pups in tests of locomotor development and of operant conditioning, in the absence of any observed effect on the dams. Domingo *et al* (1987c) reported that, when given to rats during the third trimester of pregnancy, aluminium nitrate produced a decrease in pup body weights at birth. Effects were seen at the lowest dose tested (13 mg aluminium/kg bw/day). It should be noted that aluminium salts would be expected to produce higher peak plasma concentrations when given by gavage than if the same dose was administered via drinking water. Therefore, the LOAELs are anticipated to be higher if exposure is via drinking water. This is supported by the findings of Domingo *et al* (1987a).

6.72 Clayton *et al* (1992) gave pregnant mice aluminium sulphate (750 mg/l, equivalent to 10.8 mg aluminium/kg bw/day) in drinking water (pH 4.1-4.3) on days 10-17 of gestation. Choline acetyltransferase activity was assessed in pups sacrificed at either 3.5 or 16 weeks. Both increases and decreases in activity were seen in some regions of the brain. In the absence of a dose response relationship, these findings are difficult to interpret.

6.73 In a two-generation reproductive toxicity study, Hirata-Koizuma *et al* (2011a) gave male and female rats aluminium sulphate in drinking water at 0, 120, 600 or 3000 ppm. Significantly reduced water consumption was seen in all treated groups compared to controls in the F0 generation and body weight was transiently decreased in the 3000 ppm group. At this dose, they reported decreased body weight gain and liver and spleen weights in the F1 and F2 offspring and slight retardation of sexual development in the F1 females (delayed vaginal opening), attributed to inhibition of growth. No other compound-related changes were reported in other reproductive/developmental parameters, including developmental neurobehavioral endpoints. The authors concluded that the NOAEL of aluminium sulphate in this two-generation study was 600 ppm (which they calculated to be 41.0 mg aluminium sulphate/kg bw/day) for parental systemic toxicity and reproductive/developmental toxicity. The total ingested dose of aluminium from drinking water and food (standard rat diet, containing 25-29 ppm of aluminium) combined for this 600 ppm group was calculated to be 8.06 mg aluminium/kg bw/day. In a second two-generation reproductive toxicity study, Hirata-Koizuma *et al* (2011b) gave aluminium ammonium sulphate to male and female rats in drinking water at 0, 50, 500 or 5000 ppm. Water consumption was significantly reduced in all treated groups in F0 males, and in F0 females and F1 males and females in the 500 and 5000 ppm groups. At 5000 ppm, they observed retardation of sexual development in the F1 females, attributed to inhibition of growth, and decreased body weight gain and liver, spleen and thymus weights in the F1 and F2 offspring. No other compound-related changes were observed in reproductive/developmental parameters, including developmental neurobehavioral endpoints. The authors concluded that the NOAEL was 500 ppm

(33.5 mg aluminium ammonium sulphate/kg bw/day), primarily based on the effect on preweaning body weight gain. The total ingested dose of aluminium from drinking water and food in this 500 ppm group was calculated to be 5.35 mg aluminium/kg bw/day.

6.74 In a well-designed, double-blind, vehicle-controlled, randomized twelve-month neurodevelopmental toxicity study, Poirier et al. (2011) administered aluminium citrate in drinking water at doses of 30, 100 and 300 mg aluminium/kg bw/day to groups of pregnant Sprague-Dawley rats. The major treatment-related effect observed in the offspring was renal damage (hydronephrosis, urethral dilatation, obstruction and/or presence of calculi). There was evidence of a dose-response relationship between neuromuscular measurements (hindlimb and forelimb grip strength) and aluminium in both males and females, although some of the effects may have been secondary to body weight changes. Aluminium treatment did not cause cognitive impairment as measured using the startle response, T-maze or Morris Water Maze tests. Overall, the authors concluded that the study indicated a LOAEL of 100 mg aluminium/kg bw per day and a NOAEL of 30 mg/kg bw per day.

Effects on the thyroid gland

6.75 Thyroid disease was among the less commonly-reported conditions attributed to the contamination incident in our collection of evidence from private individuals (see Table 31). In the consultation exercise, we were asked why the draft report had made a specific recommendation on monitoring of rates of joint problems but not of rates of thyroid problems. Also, one response implied that there were papers in the scientific literature covering the role or putative role of aluminium in thyroid disease. We were unable to find any papers in a search of the standard scientific database but a relevant reference, not cited in this database, was submitted in the list of 548 hyperlinks to references received from another respondent. This reported a study in which rats were fed with diet containing 1620 mg/kg aluminium chloride for 40 days (equivalent to 33 mg aluminium/kg bw/day on the assumption that rats consume 10 g diet/100 g body weight/day (Harkness and Wagner, 1989) and that the dose of aluminium chloride quoted is of the unhydrated salt) (Taheri *et al*, 2004). At the end of this period, the serum aluminium concentrations of the test and control rats did not differ significantly. Serum tri-iodothyronine concentrations were not affected but thyroxine concentrations were significantly reduced compared to a control group. Although this study shows the potential for aluminium to affect thyroid function, lower doses were not studied and thus a dose-response relationship could not be determined.

Other effects

6.76 In a study of immune parameters, Graske *et al* (2000) gave a group of 13 volunteers (4 males, 9 females) 10 ml antacid (aluminium hydroxide) three times daily for 6 weeks (stated to be equivalent to 29.5 mg aluminium/kg bw/day for a 60 kg adult). A group of 2 males and 3 females were used as controls. Assessment of parameters of cell-mediated immunity showed a significantly smaller population of a certain T-cell subset (CD8+CD45R0+). The urinary aluminium concentration in the test subjects was approximately 10- to 20-fold higher than in the control group during exposure. The authors comment that this indicates that ingestion of an aluminium-

containing antacid is associated with an aluminium absorption far above that from food or drinking water.

6.77 Gherardi *et al*, 2001 proposed that a syndrome of macrophagic myofasciitis might be caused by aluminium hydroxide present in vaccines. The symptoms of his description of the condition include fatigue and muscle and joint pain. The WHO Global Advisory Committee on Vaccine Safety (GACVS) has considered these data and advised that there is no evidence of a health risk from aluminium-containing vaccines (http://www.who.int/vaccine_safety/topics/aluminium/statement_112002/en/index.html October 2008).

6.78 Contact sensitivity to aluminium has been reported but is extremely rare (IPCS, 1997) (see Chapter 8).

Current recommended upper intake levels

6.79 In 2006, JECFA set a Provisional Tolerable Weekly Intake (PTWI) for aluminium of 1 mg/kg body weight. JECFA noted that the available studies had many limitations and considered that they were not adequate for defining the dose-response relationships. The Committee therefore based its evaluation on the combined evidence from several studies. It commented that "the relevance of studies involving administration of aluminium compounds by gavage was unclear because the toxicokinetics following gavage were expected to differ from toxicokinetics following dietary administration, and these gavage studies generally did not report total aluminium exposure including basal levels in the feed." It concluded that the studies conducted with dietary administration of aluminium compounds were most appropriate for the evaluation. It identified the smallest Lowest Observed Effect Levels[48] for aluminium in a number of different dietary studies in mice, rats and dogs to be in the range of 50-75 mg/kg bw/day and applied an uncertainty factor of 300 to the lowest level. JECFA noted that the PTWI is likely to be exceeded to a large extent by some population groups, particularly children, who regularly consume foods that include aluminium-containing additives. It also noted that dietary exposure to aluminium is expected to be very high for infants fed on soya-based infant formula (JECFA, 2007).

6.80 In 2011, the WHO published new guidelines for Drinking Water Quality, which included a review of the guideline value for aluminium (WHO, 2011). WHO commented that "a health-based value derived from the 2006 JECFA PTWI of 1 mg/kg bw would be 0.9 mg/L, based on the allocation of 20% of the PTWI to drinking water and assuming a 60 kg man drinking 2 litres of water a day. However, there remain uncertainties as to the extent of aluminium absorption from drinking-water, which depends on a number of parameters, such as the aluminium salt administered, pH (for aluminium speciation and solubility), bioavailability and dietary factors." The guidelines recognise the beneficial effects of the use of aluminium as a coagulant in water treatment to reduce microbial contamination. Taking this into account and considering the potential health concerns (i.e. neurotoxicity) of aluminium, a practicable level was derived based on optimisation of the coagulation

[48] JECFA used the term 'Lowest Observed Effect Level' instead of 'Lowest Observed Adverse Effect Level

process in drinking-water plants using aluminium-based coagulants, to minimize aluminium levels in finished water.

6.81 In June 2011, JECFA reviewed new data on aluminium which had been published or submitted to the committee since the previous evaluation. It noted that the recent evidence did not show effects of aluminium on reproductive outcomes. The new studies supported previous observations of neurodevelopmental effects in experimental animals, but the committee commented that there continued to be a lack of consistency regarding the reported effects, and there are some limitations to all of the studies. JECFA noted that the new data did not substantially change the LOAEL range of 50–75 mg/kg bw per day but the study by Poirier et al (2011, reviewed in paragraph 6.74 above) also provided a NOAEL of 30 mg/kg bw per day and that this was an appropriate basis for establishing a PTWI for aluminium compounds (JECFA, 2012). It concluded that, because long-term studies on the relevant toxicological end-points had become available since the sixty-seventh meeting, there was no longer a requirement for an additional safety factor for deficiencies in the database. Therefore, the committee established a PTWI of 2 mg/kg bw from the NOAEL of 30 mg/kg bw per day by applying a safety factor of 100 for interspecies and intraspecies differences. The previous PTWI of 1 mg/kg bw was withdrawn.

Determination of the dose of aluminium which produces no effect

6.82 We have considered the toxicological database reviewed above in order to identify the lowest dose of aluminium which has produced a toxicological effect. We identified neurological effects, and reproduction and development as the most sensitive endpoints. In paragraph 6.63 we identified a NOAEL of 21.5 mg administered aluminium/kg bw/day for functional neurotoxic effects from the study by Mameli *et al* (2006) in which aluminium was given in drinking water as the chloride for 90 days. The additional intake of aluminium from the diet in this study was estimated to be 9.2 mg/kg bw/day, giving a total intake at the NOAEL of 30.7 mg/kg bw/day. A LOAEL of 13 mg aluminium/kg bw/day for developmental and fetotoxic effects was reported by Domingo *et al* (1987b) but a study with aluminium hydroxide showed no adverse effects at doses up to 92 mg aluminium/kg bw/day (Domingo *et al*, 1989c) (see paragraph 6.70). In a number of studies in which pregnant rats were exposed during gestation and, in some cases, during lactation as well, neurodevelopmental effects were seen in the pups of pregnant rats exposed to doses of 100 mg aluminium/kg bw/day and above (Donald et al, 1989; Golub and Germann, 2001, Bernuzzi, 1989, 1989a). Golub and Germann (2001) identified a NOAEL for neurodevelopmental effects of 50 mg aluminium/kg bw/day but NOAELs were not identified in the other studies. The study by Poirier *et al* (2011) identified a NOAEL of 30 mg aluminium/kg bw/day when given to pregnant rats in drinking water as the citrate (paragraph 6.73). Above this level, renal damage and neuromuscular effects were reported in the offspring. The aluminium level in the diet was less than 0.01 mg per g of diet so intake from this source would have been low.

6.83 A number of other studies have reported effects at doses lower than the NOAELs cited above. Two-generation studies by Hirata-Koizumi et al (2011a, b) on aluminium sulphate and aluminium ammonium sulphate reported decreased body weight gain in the parent generation, and decreased body weights and retardation of sexual development in the offspring at the highest dose level. The NOAELs were

identified as 8.06 and 5.35 mg aluminium/kg bw/day, including the intake from the diet. However, there were significant reductions in drinking water consumption by the parent generation at this level, attributed to its unpleasant taste, and this is likely to have contributed to these developmental delays in the offspring. No other developmental effects were seen in the offspring, nor was there any effect in postnatal neurobehavioural tests. The study by Luo *et al* (2007) demonstrated learning and memory deficits at approximately 20 mg aluminium/kg bw/day but only one dose level was given and, therefore, no information on dose response. Similarly, the study by Practico *et al* (2002) administered only a single dose of 0.3 mg/kg bw/day aluminium for 9 months when they reported an increase in markers of oxidative stress and amyloid β peptide formation and deposition in the brains of transgenic mice. Moreover, the relevance of a NOAEL from a study in transgenic mice for a risk assessment in humans is not clear. Moselhy *et al* (2012) reported effects on serum testosterone levels, sperm motility and morphology, and male reproductive organs at 34 mg aluminium chloride/kg bw/day but only one dose level was administered and the hydration level of the salt was not given, making it impossible to determine the dose of aluminium. Finally, a number of studies have identified biochemical effects in animal studies at lower levels of aluminium exposure than those in paragraphs 6.82, but it is not clear that these would result in adverse toxicological effects in humans (see, for example, Sarin *et al*, 1997a,b; Kaur and Gill, 2005; Becaria *et al*, 2006).

6.84 We conclude that neurological effects are the most sensitive end point and, in our risk assessment in Chapter 7, we have used 30.7 mg/kg bw/day as the NOAEL for neurotoxic effects.

Copper

Introduction

6.85 An extensive review of existing research and a risk assessment of copper has been made by the Food Standards Agency's Expert Group on Vitamins and Minerals (EVM) in the context of recommending a safe upper level for total daily consumption of copper over a lifetime (Expert Group on Vitamins and Minerals, 2003). The review paper on which the assessment was made is available on the Food Standards Agency's website and gives details of the references which were used (http://www.food.gov.uk/multimedia/pdfs/reviewofcopper.pdf). We have used this review in our assessment of copper for this report.

6.86 Copper entered the water supply as a result of the effect of the acidic water on copper piping and fittings (see Chapter 3).

General information

6.87 Copper (Cu) is an element that occurs in copper compounds in two valency states: cuprous (Cu^{2+}) and cupric (Cu^{3+}). Copper is an essential element for man, the human adult requirement being in the region of 1.2 mg/day. Normally the human body is very efficient at maintaining copper balance through the action of homeostatic mechanisms, and toxic amounts only accumulate in individuals with genetic defects in

these mechanisms such as those present in patients with Wilson's disease or Menke's disease (see below) (Expert Group on Vitamins and Minerals, 2003).

6.88 Food is the major source of copper intake, with high concentrations being found in nuts, shellfish and offal. The upper bound[49] mean intake from food and beverages by adults, estimated from the 1991 Total Diet Study for the UK population was 1.44 mg/day, which is equivalent to an intake of 0.024 mg/kg/day based on a mean body weight of 60 kg (Ministry of Agriculture, Fisheries and Food, 1998a). No data were found for other age groups. Mean level intakes from the 2006 Total Diet Study were 0.02 mg/kg bw/day for adults, 0.03 mg/kg bw/day for young people and 0.05 mg/kg bw/day for toddlers, based on mean body weights of 60, 41.5 and 14.5 kg, respectively (Rose *et al*, 2010). High level intakes in this survey were estimated to be 0.03 mg/kg bw/day for adults, 0.05 mg/kg bw/day for young people and 0.08 mg/kg bw/day for toddlers. Copper is also present in dietary supplements, at doses up to 2 mg/day, and in licensed medicines with a maximum recommended dose of 4 mg/day (Expert Group on Vitamins and Minerals, 2003).

6.89 The 1984 WHO Guideline Value for Drinking Water Quality for copper was 1 mg/l based on undesirable staining of fixtures, fittings, utensils and laundry (WHO, 1984). The current EU and UK standard is 2 mg/l (SI No 3184, 2000), in line with the revised WHO provisional Guideline Value of 2 mg/l, set to protect against acute gastrointestinal effects (nausea, vomiting and diarrhoea) consequent upon the consumption of higher concentrations of copper in water (WHO 1998, 2003). These effects are more dependent on the concentration of copper than on the total dose ingested (WHO, 2003; Araya *et al*, 2003).

6.90 Above a certain concentration, dissolved copper imparts an unpleasant, metallic taste to water. The concentration at which the unpleasant taste becomes noticeable varies between individuals. A study by Zacarias *et al* (2001) found that 50% of 61 volunteers could first detect the taste of copper in tapwater at concentrations between 2.4 and 2.6 mg/l when present as the sulphate or chloride. The concentration at which all the volunteers perceived a taste was 8 mg copper/l.

The absorption, distribution and excretion of copper in man

6. 91 Copper in drinking water is absorbed from the gastrointestinal tract bound to specific proteins in the Cu^{2+} form. Following absorption, copper is distributed in two phases, the first to the liver and then to other tissues. Copper is distributed in the blood bound to the carrier proteins albumin, transcuprein and caeruloplasmin. Homeostasis is maintained largely by the degree of excretion, which is mainly via the bile (Expert Group on Vitamins and Minerals, 2003).

6.92 Under certain conditions, copper may be absorbed through the skin, for example, when administered in lipophilic formulations or when applied with a cupriphore (Beveridge *et al*, 1984; Fairlie and Whithouse, 1991). However, normal skin acts as a barrier to absorption of hydrophilic compounds such as copper sulphate.

[49] The estimated intake calculated from the upper bound mean concentrations in food; that is, where individual sample analyses are less than the limit of detection, the result is expressed as equal to the limit of detection (upper bound) and the mean calculated accordingly.

6.93 Copper can cross the placenta; the neonate having copper reserves accumulated during the third trimester of pregnancy (Expert Group on Vitamins and Minerals, 2003). Copper is present in human milk (Woolridge *et al*, 2004).

The toxicity of copper

Human data

6.94 Acute copper toxicity is rare, but it has been reported in humans who have consumed contaminated beverages or food. Symptoms include salivation, abdominal pain, nausea, vomiting and diarrhoea. The threshold for symptoms varies between individuals, and with the concentration and the form of exposure (Olivares *et al*, 2001; Araya *et al*, 2003). Intakes of 25-75 mg copper have been reported to be emetic but lower intakes have resulted in the same symptoms when taken on an empty stomach. Vomiting is usually so prompt a response that systemic toxicity does not occur (Expert Group on Vitamins and Minerals, 2003).

6.95 There are few reports of chronic copper toxicity, except in individuals with inherited disorders of copper metabolism causing accumulation of copper in the body, such as Wilson's disease. In normal individuals, daily intakes of 2-32 mg copper in drinking water have been reported to cause symptoms of gastric irritation (US Environmental Protection Agency, 1987). However, according to WHO (2004), the data on the gastrointestinal effects of copper must be used with caution since the effects observed are dependent on the pattern of ingestion, such as duration of exposure and the concentration of ingested copper, to a greater extent than the total mass or dose ingested in a 24-hour period.

6.96 Studies which examined the incidence of cancer in populations exposed to different concentrations of copper have shown no evidence of an association (International Programe on Chemical Safety (IPCS), 1998).

6.97 Indian childhood cirrhosis (ICC) is a fatal disorder associated with the accumulation of massive amounts of copper in the liver. Copper accumulation in ICC has been attributed to boiling and storing milk in copper and brass vessels although genetic predisposition occurs. Isolated cases of idiopathic copper toxicosis, identical in nature to ICC, have also been reported in non-Indian communities in the US and Europe.

6.98 Allergic skin reactions to copper are rare and are usually associated with the presence of other metal allergies. No other types of allergic reactions have been reported (Karlberg *et al*, 1983; Morris and English, 1998; Pevny and Binzenhofer, 1984; Wohrl *et al*, 2001; Zabel *et al*, 1990).

Animal data

6.99 Copper toxicity is highly species dependent. For example, while pigs and rats are relatively tolerant of copper, sheep develop copper toxicosis at low dietary intakes. In standard repeat dose toxicity studies with copper sulphate in rodents, lesions were seen in the forestomach (attributed to irritation), and kidney and liver damage and anaemia were also found. There is limited evidence that exposure to

copper compounds can affect reproduction in animals, although the results are inconsistent (IPCS, 1998). Limited data indicate that copper compounds can produce developmental effects in laboratory rodent studies. In one study in mice using copper sulphate administered in the feed, congenital anomalies were seen at doses above 53 mg copper/kg bw/day (Lecyk, 1980).

6.100 In the Long-Evans Cinnamon rat, which is a rodent model of Wilson's disease characterised by caeruloplasmin deficiency, hepatic copper accumulation and hepatocellular injury are seen, together with a high incidence of hepatocellular carcinoma (Expert Group on Vitamins and Minerals, 2003). There are insufficient data in normal laboratory animals to draw conclusions about the carcinogenicity of copper (IPCS, 1998).

Effects of copper in animal models of Alzheimer's disease

6.101 In view of the reports of cognitive impairment in some individuals following the pollution incident, it is necessary for us to comment upon papers suggesting a link between copper and the pathogenesis of Alzheimer's disease. It has been known for some time that β-amyloid, the peptide that aggregates in the brain to form senile plaques in Alzheimer's disease, can bind copper. It has been suggested that the normal physiological role for β-amyloid may be to transport copper out of the brain to prevent the accumulation of toxic amounts. However, a study by Sparks and Schreurs (2003) suggested that trace amounts of copper in drinking water could induce both β-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. This led to speculation that chelation therapy to lower the concentration of copper in the brain could counteract the development of pathology typical of Alzheimer's disease.

6.102 Two subsequent reports have contained different conclusions. Studies by Bayer *et al* (2003) have shown that increased dietary copper intake lowers the concentration of β-amyloid and the number of amyloid plaques in a transgenic mouse model of Alzheimer's disease. In addition, Phinney *et al* (2003) reported that, in a different transgenic mouse model of Alzheimer's disease, there were lower amounts of β-amyloid in the brain and fewer amyloid plaques if a mutant copper transporter gene, which increases copper levels in the brain, was also expressed. These data suggest that copper may protect against the development of amyloid deposits in the human brain.

Current recommended upper intake levels

6.103 The EVM identified a No Observed Adverse Effect Level (NOAEL) for copper of 16 mg/kg bw/day from a 13-week study in rats and applied an uncertainty factor of 100 to generate a Safe Upper Level for total daily consumption by humans over a lifetime of 0.16 mg/kg bw/day (equivalent to 10 mg/day for a 60 kg adult). JECFA has set a provisional tolerable daily intake for copper of 0.5 mg/kg bw/day (WHO, 1982).

Zinc

Introduction

6. 104 A comprehensive review and risk assessment of zinc was made by the Food Standards Agency's Expert Group on Vitamins and Minerals (EVM) in the context of recommending a safe upper level for total daily consumption of zinc over a lifetime (Expert Group on Vitamins and Minerals, 2003). The review paper on which the assessment was made is available on the Food Standards Agency's website and gives details of the references which were used (http://www.food.gov.uk/multimedia/pdfs/reviewofzinc.pdf). We have used this review in our assessment of zinc for this report (Expert Group on Vitamins and Minerals, 2003).

6.105 Zinc entered the water supply as a result of the effect of the acidic water on galvanised pipes and fittings (see Chapter 3).

General information

6.106 Zinc (Zn) is an abundant metallic element which forms a range of compounds as divalent zinc (Zn^{2+}). It is an essential element with diverse functions in the human body. In the UK, the Reference Nutrient Intake (RNI) is 5.5-9.5 mg/day for males and 4.0-7.0 mg/day for females (Expert Group on Vitamins and Minerals, 2003).

6.107 Meat and cereal products are rich in zinc and zinc salts are also available in food supplements. Zinc compounds are present in a number of licensed medicines and are used in the treatment and prevention of zinc deficiency. Topical applications are also available. The maximum daily dose of zinc in products available from a pharmacist is 150 mg (Expert Group on Vitamins and Minerals, 2003).

6.108 The upper bound mean intake of zinc from food and beverages by adults, estimated from the 1991 Total Diet Study for the UK population was 10 mg/day, which is equivalent to an intake of 0.17 mg/kg bw/day based on a body weight of 60 kg. The lower bound intake was 9.8 mg/day (equivalent to 0.16 mg/kg bw/day) (Ministry of Agriculture, Fisheries and Food, 1998a). No data were found for other age groups. Mean intakes for zinc from food and beverages, estimated from the 2006 Total Diet Study for the UK population, were 0.14 mg/kg bw/day for adults, 0.23 mg/kg bw/day for young people and 0.39 mg/kg bw/day for toddlers, based on mean body weights of 60, 41.5 and 14.5 kg, respectively (Rose *et al*, 2010). High level intakes in this study were estimated to be 0.27 mg/kg bw/day for adults, 0.48 mg/kg bw/day for young people and 0.78 mg/kg bw/day for toddlers.

6.109 The 1984 WHO Drinking Water Quality Guideline Value for zinc was 5 mg/l (WHO, 1984). This was revised to 3 mg/l in 1996 (WHO, 1996). Drinking water containing zinc at concentrations above 3 mg/l tends to have an opalescent appearance and at concentrations above 4 mg/l in water it can impart an unpleasant taste (WHO, 1996). There is currently no EU or WHO drinking water standard for zinc as it rarely occurs in drinking water at concentrations which cause concern.

The absorption, distribution and excretion of zinc in humans

6.110 Zinc is absorbed from the gastrointestinal tract both by a passive diffusion process through the gut wall and via an unspecified membrane carrier process (Expert Group on Vitamins and Minerals, 2003). The bioavailability of zinc varies widely

(IPCS, 2001). Homeostatic mechanisms operate to regulate zinc absorption and increased intake of zinc is accompanied by decreased absorption and increased excretion. Individuals with adequate zinc status absorb approximately 20-30% of all ingested zinc, while greater proportions of dietary zinc are absorbed by zinc-deficient subjects if it is presented in a bioavailable form (IPCS, 2001). Zinc and copper are mutually antagonistic, each interfering with the gastrointestinal uptake of the other thus potentially leading to imbalance (Expert Group on Vitamins and Minerals, 2003). Similarly, zinc and iron compete for gastrointestinal absorption and excess zinc may also decrease magnesium and calcium uptake. Zinc is excreted largely via the faeces.

6.111 Zinc can cross the placenta and is found in human milk (IPCS, 2001; Woolridge *et al*, 2004).

The toxicity of zinc

Human data

6.112 Zinc is considered to be relatively non-toxic. Symptoms of zinc toxicity are associated with the ingestion of large amounts of zinc, usually through accidental ingestion or overdose (IPCS, 2001).

6.113 Acute toxicity following massive ingestion of zinc is usually characterised by abdominal pain, dizziness, nausea, vomiting and diarrhoea. The lowest estimated dose cited by IPCS (2001) as causing these effects was 325 mg. Nausea and abdominal cramping have also been reported following a single 50 mg dose of zinc sulphate, equivalent to 20 mg of zinc (Freeland-Graves *et al*, 1980; Henderson *et al*, 1995 and 1996). Prolonged intake of high doses of zinc as food supplements can produce a secondary deficiency of copper (Expert Group on Vitamins and Minerals, 2003).

6.114 The long term toxic effects of zinc are largely a consequence of zinc-induced copper deficiency following prolonged intake of high doses. Dietary zinc supplementation at a dose of 20 mg/day did not result in adverse effects on pregnancy progress or outcomes in healthy pregnant women in a number of large, controlled trials (IPCS, 2001). A number of studies in which subjects were given up to 24 mg zinc/day for up to 30 days showed varying effects on copper balance and excretion (IPCS, 2001). However, in case studies where severe haematological effects have resulted from long-term, excessive zinc intake (between 150 mg/day and 2 g/day), the haematology returned to normal after cessation of zinc intake, whether or not the diets were supplemented with copper (IPCS, 2001).

Animal data

6.115 High doses of zinc (1-2 g/day for 2 or more weeks) can cause pancreatic toxicity, anaemia and reproductive toxicity in laboratory animals (IPCS, 2001; Expert Group on Vitamins and Minerals, 2003).

Current recommended upper intake levels

6.116 The EVM identified a Lowest Observed Adverse Effect Level (LOAEL) for zinc of 50 mg/day from a number of human studies and applied an uncertainty factor of 2 to generate a Safe Upper Level for total daily consumption over a lifetime of 25 mg zinc/day for *supplemental* zinc (i.e. over and above the normal intake from the diet). JECFA has set a provisional tolerable daily intake for zinc of 1 mg/kg bw/day (WHO, 1982).

Lead

Introduction

6.117 Lead entered the water supply as a result of the effect of the acidic water on service pipes made of lead and, if houses had lead plumbing, on pipes within the properties(see Chapter 3).

General Information

6.118 Lead (Pb) is a metal found in small amounts (10-20 mg/kg) in the earth's crust and is usually present in inorganic lead compounds in the divalent state (Pb^{+2}).

6.119 Outside the workplace, the major source of lead for adults is food and drink, in which lead is present as a contaminant. Children may also be exposed via flakes of lead paint or from dust in houses containing lead paint. The mean upper bound intake of lead from food and beverages by adults, estimated from the 1991 Total Diet Study was 0.028 mg/day (Ministry of Agriculture, Fisheries and Food, 1998b) which is equivalent to an intake of 0.0005 mg/kg bw/day based on a body weight of 60 kg. The lower bound intake was 0.015 mg/day (0.00025 mg/kg bw/day). No data were found for other age groups. Upper bound mean intakes from food and beverages, estimated from the 2006 Total Diet Study for the UK population, were 0.0001 mg/kg bw/day for adults, 0.0002 mg/kg bw/day for young people and 0.0003 mg/kg bw/day for toddlers, based on mean body weights of 60, 41.5 and 14.5 kg, respectively (Rose *et al*, 2010). Upper bound high level intakes in this study were estimated to be 0.0002 mg/kg bw/day for adults, 0.0003 mg/kg bw/day for young people and 0.0004 mg/kg bw/day for toddlers.

6.120 The 1984 WHO Guideline Level for lead in drinking water was 0.05 mg/l. The current standard is 0.025 mg/l, and this will be lowered to 0.01 mg/l by the year 2013 (SI No 3184, 2000). These standards are set on health grounds, in order to protect against the effects of lead on the neurological and behavioural development of infants and children (see below).

The absorption, distribution and excretion of lead in humans

6.121 The extent and rate of intestinal absorption of lead can be affected by its chemical form and by the nutritional status and age of the individual. The degree of absorption of lead ingested with food is around 5% in adults, increasing to about 50% under fasting conditions. A number of studies have reported lead absorption from the diet in young children and infants to be as high as 50%. Low concentrations of calcium, iron, copper, zinc or phosphorus in the diet can increase lead absorption, as can high amounts of fats (IPCS,1995).

6.122 The distribution of lead within the body is independent of the route of absorption. It is transported in the blood via the red blood cells. Blood lead (PbB) concentrations are used as a measure of body burden and absorbed (internal) dose of lead. Lead is initially distributed to soft tissues, particularly the liver and kidneys, then it is redistributed and is either excreted or accumulates in bone. The half-life of lead in blood and soft tissues is between 28 and 36 days, but is much longer in bone. In adults, over 90% of the total body burden is found in bone, where it is largely inert. In growing children, the high turnover rate of bone mineral can release lead and prolong exposure of sensitive target sites to lead. Transfer of lead to the human fetus occurs throughout pregnancy (IPCS,1995).

The toxicity of lead

Human data

6.123 Lead ingestion is associated with a wide range of adverse effects in humans depending on the concentration and duration of exposure. These range from the inhibition of enzymes to the production of marked morphological changes and death. Effects on the haematopoetic system, which result in decreased haemoglobin synthesis and anaemia, have been observed in children with PbB concentrations above 40 micrograms per decilitre (µg/dl). Exposure to lead increases blood pressure, an effect for which no No Adverse Effect Level (NOAEL) has been determined. PbB concentrations above 40 µg/dl are associated with nephropathy, peripheral neuropathy, and psychological and neurobehavioural dysfunction. There is qualitative evidence that lead is toxic to the reproductive system in both males and females. Altered sperm morphology and function have been reported at PbB concentrations above 40 µg/dl. There are insufficient data to estimate the dose-relationship for adverse reproductive effects in women (IPCS, 1995). There is some evidence that high prenatal exposure to lead may impair fetal growth (JECFA, 2011).

6.124 An evaluation of the carcinogenicity of lead by the International Agency for Research on Cancer (IARC, 2004) classified inorganic lead compounds as *probably carcinogenic to humans* (IARC Group 2A). The IARC Working Group which made this evaluation considered that there was limited evidence in humans for the carcinogenicity of inorganic lead compounds, based on a review of occupational cohort studies. Increases in incidence of stomach, lung and kidney cancer were reported, but not consistently. Mean blood lead concentrations in the exposed cohorts in these studies, where reported, were from 35 to 63 ug/dL; few data were provided on exposure levels. Organic lead compounds were considered “not classifiable as to their carcinogenicity to humans” (IARC Group 3).

6.125 The most important adverse effect of lead at low doses is on intellectual and cognitive development in children. Cross-sectional and prospective epidemiological studies of the effect of lead neuropsychological development in children provide no evidence of a threshold for the effect of lead (IPCS, 1995). A study by Canfield *et al* (2003) adds to this evidence. The policy on lead in the developed world has been to lower exposure wherever possible and, as a result, PbB concentrations in children have fallen substantially in recent decades (IPCS, 1995). However, the effect of lead on intellectual and cognitive development is small compared to the major

determinants: socio-economic status and the quality of the care-giving environment (Al-Saleh *et al*, 2001; Institute for Environment and Health, 2003).

Animal data

6.126 Lead has been shown to cause a range of adverse effects in all species of experimental animals studied. These include effects on the haematopoeitic, nervous, renal, cardiovascular, reproductive and immune systems. Lead also adversely affects bone homeostasis. Impaired learning/memory abilities have been reported in rats with PbB concentrations exceeding 13-15 µg/dl and in non-human primates at PbB concentrations exceeding 15 µg/dl. According to IPCS (1995), lead is a renal carcinogen in rats and mice at exposures below the maximum tolerated dose of 200 mg lead/l (as lead acetate) in drinking water (IPCS, 1995). The2004 IARC evaluation (see above) considered that there was sufficient evidence for the carcinogenicity of inorganic lead compounds to experimental animals. The Working Group commented that "extensive experimental data shows that various water-soluble and –insoluble lead compounds can induce kidney tumours in rodent. In addition, one study showed that renal tumours can occur in the absence of lead-induced nephropathy. It is also noteworthy that the induction of brain gliomas, which are rarely spontaneous, occurred after oral exposure to lead in rats" (IARC, 2004).

Genetic toxicity

6.127 With regard to genetic toxicity, the IARC Working Group (see above) commented "Humans occupationally exposed to lead show evidence of genotoxicity as measured in a variety of assays. In some studies, these effects were correlated with blood lead concentrations. However, all the human genotoxicity studies involved co-exposure to lead and other compounds, making it difficult to attribute genetic and other effects to lead alone." It went on to conclude: "There is, however, little evidence that (lead) interacts directly with DNA at normally encountered blood lead concentations. The genetic toxicity of lead appears to be mediated in part by increases in, and modulation of, reactive oxygen species. In addition, lead interacts with proteins, including those involved in DNA repair. This latter mechanism might be responsible for enhancing the genotoxicity of other agents. These properties could result in mutation, changes in gene expression and cell proliferation, all of which would contribute to a carcinogenic response if exposure is sustained" (IARC, 2004).

Current recommended upper intake levels

6.128 JECFA has evaluated lead on a number of occasions. At its 73rd meeting, JECFA reconsidered lead and estimated that "the previously established PTWI of 25 µg/kg bw is associated with a decrease of at least 3 IQ points in children and an increase in systolic blood pressure of approximately 3 mmHg (0.4 kPa) in adults. These changes are important when viewed as a shift in the distribution of IQ or blood pressure within a population." The Committee therefore concluded that the PTWI could no longer be considered health protective, and it was withdrawn. Because the dose–response analyses do not provide any indication of a threshold for the key effects of lead, the Committee concluded that it was not possible to establish a new PTWI that would be considered to be health protective (JECFA, 2011).

Manganese

Introduction

6.129 An extensive review of research and a risk assessment of manganese wasmade by the Food Standards Agency's Expert Group on Vitamins and Minerals (EVM) in the context of recommending a safe upper level for total daily consumption of manganese over a lifetime (Expert Group on Vitamins and Minerals, 2003). The review paper on which the assessment was made is available on the Food Standards Agency's website and gives details of the references which were used (http://www.food.gov.uk/multimedia/pdfs/evm9922p.pdf). We have used this review in our assessment of manganese for this report.

6.130 Sediments containing deposits of manganese oxide in the mains water supply may have been disturbed by the flushing programmes, resulting in increased concentrations in water at the tap (see Chapter 3).

General Information

6.131 Manganese (Mn) is an abundant metal occurring naturally as manganese salts in the environment and groundwater, and as a result of anthropogenic contamination of soils, sediments and water. Manganese can exist in a variety of oxidation states of which the two most biologically important are the divalent (Mn^{2+}) and trivalent (Mn^{3+}) forms (EVM, 2003). Manganese is an essential element for humans and is a component of a number of enzymes.

6.132 Manganese is present in foods, mainly nuts, vegetables, grains, legumes and tea. It is prescribed in licensed medicines, in combination with other substances, for use in the prevention and treatment of nutrient deficiencies and other related conditions. Manganese is also present in a number of dietary supplements in amounts up to 10 mg. The upper bound mean intake from food and beverages by adults, estimated from the 1991 Total Diet Study for the UK population was 6.2 mg/day which is equivalent to an intake of 0.1 mg/kg bw/day based on a body weight of 60 kg. The lower bound mean intake was 6.1 mg/day (0.1 mg/kg bw/day) (Ministry of Agriculture, Fisheries and Food, 1998b). No data were found for other age groups. Mean intakes from food and beverages, estimated from the 2006 Total Diet Study for the UK population, were 0.07 mg/kg bw/day for adults, 0.11 mg/kg bw/day for young people and 0.17 mg/kg bw/day for toddlers, based on mean body weights of 60, 41.5 and 14.5 kg, respectively (Rose *et al*, 2010). Upper bound high level intakes in this study were estimated to be 0.12 mg/kg bw/day for adults, 0.20 mg/kg bw/day for young people and 0.31 mg/kg bw/day for toddlers.

6.133 At concentrations in water above 0.1 mg/l, manganese imparts an undesirable taste to beverages and stains plumbing fixtures and laundry. When Mn^{2+} compounds are oxidised, manganese dioxide is precipitated. At concentrations as low as 0.02 mg/l, manganese can form a coating on water pipes that can later slough off as a black precipitate (WHO, 2003). The WHO Guideline Value in 1988 was 0.1 mg/l, based on staining of plumbing fixtures and laundry (WHO, 1984). The current UK and EU standard for the maximum concentration of manganese in drinking water is 0.05 mg/l

(SI No 3184, 2000). In 2003, WHO proposed a provisional health-based guideline value of 0.4 mg manganese/l (WHO, 2003).

The absorption, distribution and excretion of manganese in humans

6.134 Absorption of manganese takes place in the small intestine via a carrier mediated mechanism and, in adults, is low compared with the amount ingested (3-8%). Absorption in infants is thought to be higher (Keen *et al*, 1986). The chemical form of manganese may influence its absorption. Administration of 24.3 mg manganese/kg bw once a week as the chloride to rats resulted in a 68% increase in manganese concentrations in blood and a 22% increase in manganese concentrations in brain, but the same dose of manganese administered as the dioxide did not increase the concentrations in blood or brain (Roels *et al*, 1997).

6.135 In portal blood, manganese may bind to albumin and α-macroglobulin. A small proportion of manganese is oxidised to Mn^{3+} and enters the systemic circulation, possibly bound to transferrin. Manganese is present in all tissues of the body, the highest concentrations being found in the liver, kidney, pancreas, and adrenal glands (Tipton and Cook, 1963; Sumino *et al*, 1975). Manganese also accumulates in the brain, particularly in the globus pallidus, striatum and substantia nigra (Zlotkin and Buchanan, 1986; Kontur and Fechter, 1988). Studies in rats suggest that manganese homeostasis is largely maintained by control of absorption, rather than by variation in excretion (Davis *et al*, 1992).

The toxicity of manganese

Human data

6.136 Chronic occupational exposure, for example, of manganese miners and smelters, to elevated levels of inhaled manganese dusts or fumes has been associated with 'manganism', a neurological condition similar to Parkinson's disease (ATSDR, 2000; Canavan *et al*, 1934; Cook *et al*, 1974; Roels *et al*, 1999).

6.137 When ingested by the oral route, manganese is generally regarded as a nonoxic element, although case reports of oral exposure to high doses of manganese have described neurological impairment. However, the quantitative and qualitative details of exposure necessary to establish direct causation of neurotoxicity are lacking (WHO, 2003).

6.138 An epidemiological study in Greece investigated the possible correlation between exposure to manganese in drinking water for more than 10 years and neurological effects in elderly people (Kondakis *et al*, 1989). Three groups of adults were studied. The report provided no data on water consumption but, on the assumption that subjects drank 2 l water/day, it can be estimated that the three groups would have had intakes of 0.007-0.03, 0.16-0.5 and 3.6-4.6 mg manganese/day (equivalent to up to 0.08 mg manganese/kg bw/day for a 60 kg individual). Progressive increases of the manganese concentration in drinking water were associated with increases in adverse neurological scores and in manganese concentrations in hair. The differences were statistically significant between the high and low concentration areas. No relationship was found between blood and hair

manganese concentrations, nor between blood manganese and neurological score. The authors concluded that progressive increases in the manganese concentration in drinking water are associated with a progressively higher prevalence of neurological signs of chronic manganese poisoning.

6.139 Another study investigated the potential neurological effects of manganese in two groups of individuals in a rural area of Germany who were drinking water from separate wells for up to 40 years (range 10-40 years) (Vieragge *et al*, 1995). No estimates were provided of the amount of water consumed nor of the manganese content of the diet, but the cohorts were considered to be comparable. No significant differences in blood manganese concentrations were found between the two groups. The authors found no neurological effects at a concentration of at least 0.3 mg/l manganese in the water. The higher exposure group contained 41 subjects and had an estimated exposure of 0.6-4.3 mg manganese/day from water (up to 0.07 mg manganese/kg bw/day for a 60 kg individual). The lower exposure group contained 74 subjects and had an estimated exposure of less than 0.1 mg manganese/day from water (less than 0.002 mg manganese/kg bw/day for a 60 kg individual). No neurological impairment was detected and there was no difference between the groups in any neurological parameters.

6.140 The EVM noted that a major limitation of both these studies was the failure to provide quantitative data on water consumption or on the intake of manganese from the diet. They also noted that the lowest concentration at which effects were seen in Kondakis *et al* (1989) is apparently lower than occupational exposure levels to manganese at which no adverse effects are seen. The authors had considered that this may be due to the increased sensitivity of the ageing brain to manganese (EVM, 2003).

Animal data

6.141 Manganese is of low acute toxicity in animals. In three separate studies, the survival of rats and mice was not affected by concentrations of 50 g manganese/kg diet for 14 days (reviewed in US DHHS, 1997; NTP, 1993). However, neurotoxic effects have been observed in mice fed concentrations of 2000 mg manganese/kg in the diet for 1 year (Komura and Sakamoto, 1992). High doses (1-2 mg manganese per kg of body weight per day) have resulted in anaemia as a result of iron sequestration, observed to occur in rabbits, pigs and cattle by Hurley and Keen (1987). Fertility was lowered by high doses of manganese (in the region of 150 mg/kg bw/day and above) but other reproductive parameters were unaffected (Laskey *et al*, 1982).

Current recommended upper intake levels

6.142 The Food and Nutition Board of the US Institute of Medicine (IOM) cited 11 mg manganese/day as a No Observed Adverse Effect Level (NOAEL). This was based on the fact that 10.9 mg/day was the upper intake level identified by Gregor (1999) for adults eating typically western and vegetarian diets (IOM 2001, cited in WHO, 2003). The IOM NOAEL is the basis of the proposed provisional health-based guideline value for drinking water of 0.4 mg manganese/l (WHO, 2003).

6.143 The EVM concluded that the data were insufficient to establish a Safe Upper Level for manganese. However, it estimated an acceptable total manganese intake to be 12.2 mg/day for the general population (equivalent to 0.2 mg/kg bw in a 60 kg adult), based on the NOAEL in a study by Vieregge et al (1995) and a dietary intake of 8.2 mg/day. It also estimated an acceptable total manganese intake of 8.7 mg/day (equivalent to 0.15 mg/kg bw in a 60 kg adult) for older people, based on the NOAEL in the Kondakis *et al* (1989) and the same dietary intake (EVM, 2003).

6.144 The COT, when it considered manganese in the context of population exposures from the 2006 Total Diet Study (TDS), concluded that there was insufficient information to determine whether there are risks associated with dietary exposure to manganese. It added "However, the population exposures to manganese have remained fairly constant since manganese was first included in a TDS in 1983 (4.6 mg/kg) to the 2006 TDS (5.24 mg/day), and there is no basis for assuming any concern to health" (COT, 2008).

Iron

Introduction

6.145 An extensive review of existing research and a risk assessment of iron was made by the Food Standards Agency's Expert Group on Vitamins and Minerals (EVM) in the context of recommending a safe upper level for total daily consumption of iron over a lifetime (Expert Group on Vitamins and Minerals, 2003). The review paper on which the assessment was made is available on the Food Standards Agency's website and gives details of the references which were used (http://www.food.gov.uk/multimedia/pdfs/evm-01-12r.pdf). We have used this review in our assessment of iron for this report.

6.146 Sediments containing deposits of iron oxide in the mains water supply may have been disturbed by the flushing programmes, resulting in increased concentrations in water at the tap (see Chapter 3).

General Information

6.147 Iron (Fe) is a transition metal that is present in all biological systems. It occurs naturally in the environment in certain minerals and soils. It exists in solid form either as the free element or in iron-containing compounds. In aqueous solution, it can exist in one of two oxidation states, the ferrous form (Fe^{2+}) and the ferric form (Fe^{3+}) and it can rapidly convert between these two oxidation states (EVM, 2003).

6.148 Iron is an essential element for man. Most iron within the body is present as haem proteins and in enzymes, where it is present as a key component.

6.149 Dietary iron is present in a variety of foods including meat, fish, beans, nuts, whole grains and dark green leafy vegetables. It can be categorised into two forms, depending on the source. About 90% of dietary iron is in the form of iron salts and is referred to as 'non-haem iron'. The other 10% is in the form of 'haem-iron' and comes mainly from the haemoglobin and myoglobin of meat. Flour and many

breakfast cereals are fortified with iron to prevent iron deficiency in humans (Schumann *et al*, 1998) and iron is also taken as a dietary supplement.

6.150 The upper bound[50] mean intake of iron from food and beverages by adults, estimated from the 1991 Total Diet Study for the UK population, was 12.4 mg/day, which is equivalent to an intake of 0.21 mg/kg bw/day based on a body weight of 60 kg . No data were found for other age groups. The mean dietary intake of iron (both haem and non-haem iron) in the National Diet and Nutrition Survey (NDNS) carried out between February 2008 and March 2009 was 12.3 mg/day for men and 10 mg/day for women. An average of the mean total intakes of iron from food in adolescents aged 11–18 years is 11.1 mg/day for males and 8.5 mg/day for females; in toddlers aged 1.5–3.0 years it is 6.2 mg/day and in infants aged 6–12 months is 8.1 mg/day (1986 data) (Food Standards Agency, 2010; Expert Group on Vitamins and Minerals, , 2002).

6.151 The WHO Guideline Value for iron in drinking water in 1988 was 0.3 mg/l, based on staining of laundry and sanitary ware and upon unpalatability (WHO, 1984). The current UK and EU standard for the maximum concentration of iron in drinking water is 0.2 mg/l (SI No 3184, 2000). This value is 10 times lower than the current WHO Guideline Value of 2 mg/l (WHO, 2003).

The absorption, distribution and excretion of iron in humans

6.152 Absorption of iron takes place in the intestine and the amount absorbed depends on the amount required by the body. This ability to alter the amount absorbed from the diet provides an effective way of regulating the amount of iron in the body. Thus, the absorption of non-haem iron is highly variable and is dependent on an individual's iron status and upon other components of the diet (Skikne and Baynes, 1994). In contrast, haem iron is well absorbed and absorption is less strongly influenced by an individual's iron stores or other constituents of the diet (Yip and Dallman, 1996). Haem iron uptake occurs via a specific haem receptor (Grasbeck *et al*, 1979), whilst the uptake of non-haem iron appears to be dependent on the presence of an acidic environment to aid solubilisation (Bezwoda *et al*, 1978). About 15% of the total iron ingested is absorbed (FAO, 1988). Women and children absorb more than men because, in general, they have lower stores of iron in the body.

6.153 Once absorbed through the intestinal mucosa, iron is transported around the body by the plasma transport protein transferrin. Approximately 80% of the iron transported is delivered to the bone marrow as a raw material for the production of red blood cells (Ponka, 1999). Transferrin also aids in the uptake of iron by other tissues via endocytotic mechanisms (EVM, 2002). Most iron in the body is found in red blood cells and most of this is recycled following red blood cell degradation and thus little iron is excreted. Substantial loss of iron can occur through bleeding, which tends to be highest in menstruating women.

[50] The estimated intake calculated from the upper bound mean concentrations in food; that is, where individual sample analyses are less than the limit of detection, the result is expressed as equal to the limit of detection (upper bound) and the mean calculated accordingly.

The toxicity of iron

Human data

6.154 Most cases of acute iron poisoning occur in children, following accidental ingestion of iron supplements intended for adults (Litovitz *et al*, 1994). The symptoms are largely gastrointestinal and include constipation, nausea, diarrhoea and vomiting. Acute toxic effects have been reported in children ingesting a 20 mg/kg body weight dose, with lethality occurring at doses between approximately 200 and 300 mg/kg body weight (Department of Health, 1991). The lethal dose in adults is reported to be 1400 mg/kg body weight (Eriksson *et al*, 1974; Department of Health, 1991)

6.155 Chronic iron toxicity or 'iron overload' arises following an increase in total body iron which can be either primary or secondary. Primary iron overload arises due to defects in iron metabolism which result in deregulation of the absorption of iron from the diet. As a result, excess iron accumulates in major organs of the body. Such increases in iron absorption tend to occur in individuals with a genetic condition known as hereditary haemochromatosis (HHC) – an autosomal recessive disorder, and the most common genetic disorder in Caucasians (Merryweather-Clarke *et al*, 1997). The overall prevalence of HHC is reported to be 1 in 250 of the Caucasian population and the majority of HHC patients develop symptoms between the ages of 40 and 60 years. In subjects who are heterozygous for the condition (up to 1 % of the population), a small increase in iron storage may occur (Bulaj *et al*, 1996).

6.156 Severe iron overload arises in adults who have an excess total body iron of 10g or more, and is associated with irreversible tissue damage, including cirrhosis of the liver, hepatocellular carcinoma, heart failure and diabetes (Pippard, 1994).

6.157 Secondary iron overload refers to an increase in iron absorption which is not genetically determined. Individuals suffering from hereditary anaemias, such as thalassemia or sideroblastic anaemia, who require repeated blood transfusions and frequent treatment with iron salts, may develop iron overload and toxicity (Pippard, 1994).

6.158 A number of epidemiological studies have found associations between markers of increased body iron stores and an increased risk of cardiovascular disease and cancer in the general population, although the validity of these results is debatable (EVM, 2002; Deugnier *et al*, 1998). No studies were located which have investigated an association between exposure to iron from drinking water and adverse health effects.

Animal data

6.159 In general, animal models of iron overload are of limited value because the high doses used to produce them have little relevance to human populations.

6.160 Reproductive studies in female Sprague-Dawley rats treated with 20 mg/kg bw/day iron for 6 weeks, repeated in four successive generations, produced no significant adverse effects in the offspring (Fisch *et al*, 1975). However, evidence of

teratogenicity has been observed in pregnant mice treated with 6.25 mg iron gluconate (Kuchta, 1982). Studies of the carcinogenicity of iron in laboratory animals have used mainly animals previously exposed to chemical carcinogens, which therefore invalidates their use for determining the carcinogenic effects of iron alone. Mitotic and nuclear changes have been observed in colonic and hepatocellular epithelia following supplementation of animal diets with carbonyl-iron (Lund *et al*, 1998; Pigeon *et al*, 1999).

Current recommended upper intake levels

6.161 The EVM concluded that the data were insufficient to establish a Safe Upper Level for iron. It advised that, for guidance purposes, a supplemental intake of approximately 17 mg/day (equivalent to 0.28 mg/kg bw/day for a 60 kg adult) would not be expected to produce adverse effects in the majority of people. This was derived from the fact that a supplement dose of 50 mg iron/day is the lower end of the range found to be associated with adverse gastrointestinal effects in iron-replete individuals from developed countries who were not suffering from hereditary haemochromatosis (Brock *et al*, 1985; Coplin *et al*, 1991). The application of an uncertainty factor of three was considered to be sufficient, resulting in the value of 17 mg iron/day (EVM, 2003).

6.162 JECFA has set a provisional maximum tolerable daily intake for iron of 0.8 mg/kg bw/day (WHO, 1983).

Metal-metal interactions

Introduction

6.163 It had been suggested to us that adverse effects on health may have been caused by a combination of two or more of the metals which contaminated the water during the Lowermoor incident. We asked our secretariat to review the information in the scientific literature on biological interactions between the metals of concern ie aluminium, copper, zinc, lead, manganese and iron.

6.164 The approach used was to consider pairwise combinations of these 6 metals. As aluminium was the major pollutant, the review focussed on combinations of aluminium with each of the other metals. Studies of the interactions of lead with the nutritionally essential metals (copper, zinc and iron) were also reviewed. The review covered all types of interactions, and considered studies which had employed exposure by the oral route.

6.165 An overview of the relevant data is given below and the detailed reviews, with references, can be found at Appendices 28 and 29.

Interactions with aluminium

6.166 Few studies have examined the effects of combined exposure to aluminium and lead. One epidemiological study suggested a possible association between decreased visual-motor performance and high hair concentrations of aluminium and lead in children (although the concentrations were said to be within the usual range

found in children) (Marlowe *et al*, 1985). However, this study must be considered unconvincing since no reliable exposure data are provided. Hair concentration is not a reliable means by which to assess quantitative exposure to metals (Poon *et al*, 2004; ATSDR, 2001; Yoshinga *et al*, 1990). An experimental study examined the effects of treating rats with 50 mg/kg/day aluminium chloride and/or 125 mg/kg/day lead acetate in drinking water in a number of behavioural tests. A significant reduction in the Forced Locomotor Activity test was seen earlier in rats receiving both aluminium chloride and lead acetate than in rats receiving aluminium or lead salts alone (Shakoor *et al*, 2003).

6.167 There was little information on biological interactions of aluminium and copper. A case-report described severe copper deficiency in a woman who had taken massive doses of aluminium-containing antacids for several years (Nutrition Reviews, 1984). An experimental study showed that long-term treatment of rats with moderate levels of aluminium in drinking water (approximately 6 mg/kg bw/day in excess of standard dietary intake) led to increased aluminium and decreased copper concentrations in the intestine, but the concentrations of these metals in other tissues were not changed (Fulton *et al*, 1989). In another experimental study, a 3-month exposure of mice to aluminium lactate (4.4 mg/kg/day) in drinking water significantly increased the levels of amyloid beta peptides in the brains of treated mice and co-exposure with copper sulphate (8 µM (2 ppm)) further enhanced this effect (Becaria *et al*, 2006).

6.168 A few studies have investigated the effects of dietary aluminium supplementation in experimental animals with low zinc status. However, effects were only seen after prolonged exposure to high intakes of aluminium (at least 50 mg/kg bw/day) (Wenk and Stemmer, 1982; Wenk and Stemmer, 1983; Sugawara *et al*, 1987; Liu and Stemmer, 1990a; Liu and Stemmer, 1990b; Ecelbarger and Greger, 1991). A small study in humans showed no effect of approximately 2 mg/kg bw/day dietary aluminium supplementation, for 20 days, on zinc retention in healthy adult men (Greger and Baier, 1983). There does not appear to be any evidence to suggest an adverse interaction between concurrent increased zinc and aluminium intakes.

6.169 There is evidence for an inter-relationship between iron and aluminium metabolism in the body, and for modification of iron toxicity by aluminium. In the plasma, the majority of aluminium is bound to the iron binding protein transferrin, which has a lower affinity for aluminium than for iron (Trapp, 1983; Cochran *et al*, 1984). However, animal studies indicating effects of aluminium on iron uptake or tissue concentrations report effects only with prolonged exposure and/or at higher exposures to aluminium than occurred after the Lowermoor incident (Turgut *et al*, 2004; Farina *et al*, 2005). It has been suggested that iron deficiency may promote the uptake of aluminium by the gut (Cannata *et al*, 1991; Cannata and Diaz Lopez, 1991), although it has also been reported that co-administration of iron may increase aluminium uptake (Ittel *et al*, 1996). Some authors claim that iron and aluminium share a common mechanism of uptake in the gut, and that iron deficiency may increase aluminium absorption. However, this is disputed and more recent findings suggest that iron and aluminium uptake by the gut probably occur by different mechanisms (Priest, 2004).

6.170 Aluminium and manganese are both neurotoxicants and it is possible that one might enhance the neurotoxic effect of the other. A combination of low dietary intake of calcium and magnesium with high concentrations of aluminium and manganese has been suggested as a factor in the incidence of amyotrophic lateral sclerosis and Parkinsonian dementia (ALS-PD) in specific areas of the western Pacific (Garruto *et al*, 1984). It has also been suggested that consumption of the neurotoxic seed of the false sago palm tree (*Cycas circinalis*) may play a role in the prevalence of ALS-PD in these areas; genetic component is also possible (Plato *et al*, 2002). However, studies in which small numbers of cynomolgus monkeys were given diets low in calcium, and supplemented with aluminium (150 mg/day) and manganese (50 mg/day), with or without flour prepared from unwashed seed of *Cycas circinalis*, for 41-46 months, did not reveal any associated behavioural changes or neurological deficits. These long-term exposures were much higher than would have occurred after the Lowermoor incident. A small number of studies have indicated that aluminium or manganese supplementation may affect uptake and/or retention or tissue concentrations of the other metal, but such effects have only been reported at exposure levels much higher and/or more prolonged than after the incident.

Interactions with lead

6.171 Deficiencies of nutritionally essential metals can increase the intestinal uptake and the toxicity of dietary lead. However, few data are available on the effects of co-administration of high concentrations of lead and the other metal contaminants of interest. Some studies have indicated that the administration of both zinc and copper can decrease the toxicity of lead (Border *et al*, 1976; Tephly *et al*, 1978; Dutkiewicz *et al*, 1979; Goering and Fowler, 1987). No data were identified on interactions of lead and manganese when given orally. The interactions of lead with aluminium have been described above.

Interactions between the nutritionally essential metals (copper, zinc, iron, manganese)

6.172 It is possible that iron and some similar cations may be taken up by common mechanisms in the gut and thus competition for uptake may occur. They may also bind to common binding proteins and thus one metal could affect uptake of the other into tissues or cells. In particular, high zinc intake is known to cause copper deficiency, but only after prolonged, high exposure (50 mg/day in adults for at least 4 weeks; EVM, 2002). One study reported that infants receiving a copper-supplemented formula had lower plasma zinc concentrations than usual but that these remained within the normal range (Salim *et al*, 1986). Strozyk *et al* (2009) found that copper and zinc levels in cerebrospinal fluid (CSF) were synergistically associated with CSF Aβ42 levels in ventricular fluid autopsy samples taken from a cohort of Japanese-American men participating in a population based Honolulu Asia Aging Study (HANS). Combined high zinc and high copper levels were associated with lower levels of CSF Aβ42 (β coefficient = -1.16, 95% CI [-1.60, -0.7], p trend = <0.0001) compared to low levels of both metals. There was no association with CSF Aβ42 if only one metal was elevated. no association was found between concentrations of CSF aluminium and CSF Aβ42.

6.173 Schrag *et al* (2011) investigated the levels of iron, zinc and copper in brain samples from Alzheimer's patients with or without congophilic amyloid angiopathy (CAA) and in normal aged brain tissue. Higher levels of iron were reported in brains from Alzheimer's patients with CAA, and higher levels of zinc were found in brains from the Alzheimer's patients with or without CAA, compared to the normal brain tissue. Copper levels were lower in brain samples from all Alzheimer's patients compared to normal brain samples. In a further study, levels of copper and iron were measured in serum and lymphocyte samples from 60 subjects with normal cognition, mild cognitive impairment (MCI) or early stage senile dementia (Mueller *et al*, 2012). It was reported that the presence of radiological evidence of CAA was not associated with a change in serum iron concentration. Copper levels increased in subjects with MCI who progressed to dementia compared to those who remained cognitively statble or early Alzheimer's subjects. A higher ratio of total copper to non heme iron was found in subjects with MCI who progressed to dementia than in the controls, the MCI group who remained cognitively stable over 5 years or subjects exhibiting early Alzheimer's disease.

Sulphate

6.174 Sulphate is regarded as one of the least toxic anions, and WHO (1996, 2003) concluded that there was no need to derive a health-based Guideline for Drinking Water Quality for sulphate. Nonetheless, high concentrations of sulphate in drinking water can affect the gastrointestinal tract, causing gastrointestinal irritation, diarrhoea and dehydration. Some reports suggest that cathartic effects are commonly experienced by people consuming drinking water containing sulphate in concentrations exceeding 600 mg/l, although it is reported that, with time, humans can adapt to higher concentrations (WHO, 1996). However, studies in pigs and in human volunteers suggest that a laxative effect occurs at concentrations between 1000 and 12,000 mg/l (WHO, 2003).

6.175 Dehydration has been reported as a common side effect following the ingestion of large amounts of magnesium sulphate (Epsom salts) or sodium sulphate (WHO, 1996, 2003). Thus, some subgroups within the population, such as children and older people, might be particularly vulnerable to the adverse effects of high concentrations of sulphate in drinking water due to the risk of dehydration (WHO, 2003).

6.176 High concentrations of sulphate in drinking water render it unpalatable. The taste seems to vary with the nature of the associated cation, with taste thresholds ranging from 250 mg/l for sodium sulphate to 1000 mg/l for calcium sulphate. The lowest taste threshold reported by WHO is 250 mg/l.

6.177 In view of the gastrointestinal effects, WHO (1996, 2003) recommends that health authorities are advised of water supplies which contain sulphate concentrations of more than 500 mg/l. High concentrations of sulphate can also contribute to corrosion in water distribution systems (WHO, 2003).

Acidity

6.178 The pH of a solution is a logarithmic measure of its acid or alkaline nature. pH 7 is neutral, acid solutions have a pH less than 7, alkaline solutions more than 7. Each successive pH unit represents a ten-fold change in hydrogen ion concentration[51].

6.179 The maintenance of a correct pH is very important during drinking water treatment processes. pH control is necessary in order to produce optimum coagulation (e.g. of aluminium hydroxide, see Chapter 3) to ensure clear water, and to allow effective disinfection. Although it is not the only important factor, the pH of the water entering the distribution supply is a key factor in determining the extent of corrosion of metal pipework, in both the mains and domestic plumbing. A pH of less than 8 is preferable for effective disinfection with chlorine, but water with a lower pH is more likely to be corrosive. Current WHO guidance on pH in drinking water states that a range of 6.5-9.5 is regarded as optimal, depending on the composition of the water and the nature of the construction materials in the distribution system (WHO, 2003). This guidance is based on preventing excessive corrosion.

6.180 Exposure to water of very low or high pH results in irritation to the eyes, skin and mucous membranes, and gastrointestinal irritation may occur. Redness and irritation of the eyes have been reported with water below pH 4, with the severity of these effects increasing with decreasing pH (WHO, 1996). WHO suggests that below pH 2.5 damage to epithelium (e.g. skin, the lining of the gastrointestinal tract) is irreversible and extensive. However, this conclusion can be questioned because some carbonated soft drinks have a pH in the range of 2.4 – 3.0 (British Soft Drinks Association, 2003). The severity of any such corrosive effects would, in any case, depend on the length of time for which the epithelium is exposed to an acidic solution.

Uranium

Introduction

6.181 Uranium was detected as a contaminant in a service pipe residue from the Camelford area and in residues from a kettle (Powell *et al*, 1995).

Background

6.182 Uranium is a naturally occurring material, present in rocks, soil, water, air and food. It occurs in soils at an average concentration of about 2 mg/kg. Concentrations of uranium in water in the UK are usually below 1 μg/l but in some areas (eg Dartmoor) higher concentrations are found. Uranium can occur naturally in a number of valency states but most commonly in the hexavalent form in association with oxygen as the uranyl ion (UO_2^+).

6.183 Uranium is present to some extent in all drinking water, foodstuffs and air. Estimated upper bound average dietary exposures to uranium-238 from food, as measured in the 2001 Total Diet Study, were 0.015 ug/kg bw/day for adults, 0.044 ug/kg bw/day for toddlers between 1.5 and 4.5 years and 0.041 ug/kg bw/day for

[51] Note that there is a distinction between alkaline and alkalinity. Alkalinity is a measure of the capacity of a solution to neutralise acid.

toddlers aged 3.5 to 4.5 years. Upper bound estimated high level intakes were 0.028, 0.079 and 0.065 ug/kg bw/day, respectively (FSA, 2004a). Intakes from air have been estimated as around 1 ng/day (WHO, 2004).

6.184 The current WHO Provisional Water Guideline Value for uranium is 30 µg/l (WHO, 2011).

6.185 Unlike the other metals discussed above, uranium exhibits two types of toxicity. As a chemical element, it can be harmful because of its chemical toxicity, like the other chemicals discussed above. It is also a radioactive element and this is also a potential source of toxicity.

Kinetics and metabolism

6.186 The average human gastrointestinal absorption of uranium is reported to be 1-2% (WHO, 2004). Absorption from the gastrointestinal tract is rapid, as is clearance from the bloodstream and the uranium subsequently accumulates mainly in the skeleton, where the uranyl ion replaces calcium in the hydroxyapatite complex of bone crystals. WHO (2004) estimated that the total body burden of uranium in humans is 40 µg, with approximately 40% of this present in the skeleton and 10%, 4%, 1% and 0.3% in the blood, lungs, liver and kidneys, respectively. However, the Royal Society (2002) states that normal healthy adults may retain as much as 90 µg of uranium in the body from usual intakes of food and water and that it is retained principally in the kidneys and skeleton.

6.187 The average gastrointestinal absorption of soluble uranium has been reported to be 1-2% in humans, although this will depend on speciation (COT, 2006). Once absorbed, excretion is mainly via the urine, the rate depending in part on the pH of tubular urine. Under alkaline conditions, most of the uranyl hydrogen carbonate complex is stable and is excreted. If the pH is low, the complex dissociates to a variable degree, and the uranyl ion may then bind to cellular proteins in the tubular wall, which may then impair tubular function. The overall elimination half-life of uranium in humans at normal intakes has been estimated to be between 180 and 360 days (WHO, 2004).

Radiological toxicity of uranium

6.186 Natural uranium exists in three different forms, termed isotopes (see Table 48). The two most abundant isotopes, uranium-235 and uranium-238, have radioactive half-lives of about 710,000,000 and 4,510,000,000 years, respectively. The radioactive half-life is the time taken for the activity of any amount of a radioactive material to reduce to half its original value. Highly radioactive materials can have half-lives measured in days or less (e.g. radon gas that accumulates within houses has a half-life of just under 4 days). Uranium-235 and uranium-238 were present when the earth was formed. The third isotope, uranium-234, is produced during the radioactive decay of uranium-238. It is more radioactive than uranium-235 and uranium-238 with a half-life of about 247,000 years (The Royal Society, 2001; Health Protection Agency, 2005).

Table 48: Proportion of uranium isotopes in natural uranium and their half-lives

Isotope	Percentage in natural uranium	Half-life
Uranium-234	0.0057%	247,000 years
Uranium-235	0.72%	710,000,000 years
Uranium-238	99.28%	4,510,000,000 years

6.187 The uranium used as a fuel in nuclear power plants is enriched in uranium-235. Most reactors require fuel that is enriched in uranium-235 from its normal level of 0.72% to about 3% (The Royal Society, 2001).

6.188 The main health concern from the radiological toxicity of low level exposure to uranium is cancer. The Royal Society (2001), in an assessment of the health hazards of depleted uranium, reviewed 14 epidemiological studies of mortality, including cancer mortality, in the nuclear industry. It should be noted that workers may have been exposed to enriched uranium as well as natural uranium and may have been exposed by inhalation as well as ingestion. Therefore, the radiation doses may in some cases have been higher than those of members of the general public exposed only to natural uranium. The report concludes: "Overall the findings on 120,000 workers in uranium plants, among whom 33,000 deaths have been reported, do not suggest an excess mortality from either cancer, genito-urinary disease, or all causes combined." However, the report cautions that there are many difficulties in assessing the studies and adds " For the reasons discussed above it would not, however, be justified to conclude on the basis of the available data that there are definitely no long-term hazards associated with occupational exposure to uranium. What can be said is that if there were a relatively small excess of any particular condition, it would probably be undetectable, given the limitations of the existing data. However, comparatively large excesses, for example a true doubling in the risk of any of the relatively common conditions considered here, would probably be evident in the data examined, despite the methodological problems outlined above" (The Royal Society, 2001).

6.189 Because natural uranium is only weakly radioactive, it is classified by the International Atomic Energy Agency in the lowest hazard class for radioactive materials. The chemical toxicity of natural uranium is considered to be more detrimental to health than its radiological toxicity (The Royal Society, 2001) and is the basis of the current WHO Provisional Water Guideline Value. The chemical toxicity of uranium is described below.

Toxicological data

Animal data

6. 90 The reported oral LD_{50} of uranyl ethanoate dihydrate in rats and mice was 204 and 242 mg/kg, respectively (WHO, 2004).

6.191 In a 4-week study in rats, in which uranyl ethanoate dihydrate was administered in drinking-water, changes were reported in blood biochemistry and haematology parameters; the authors considered the NOAEL to be equivalent to 1.1 mg uranium/kg bw/day (Ortega *et al*, 1989). In a study in which rats were

administered uranyl nitrate hexahydrate for 91 days at doses up to 36.7 mg uranium/kg bw/day in males and 53.6 mg uranium/kg bw/day in females, treatment-related histopathological changes were seen in the liver and kidney, with the kidney the most affected tissue (Gilman *et al*, 1998). The most important findings were considered to be capsular sclerosis of glomeruli and reticulin sclerosis of the interstitial membranes in the females; these occurred in all dose groups and were considered to be irreversible. The LOAEL for adverse effects in both male and female rats, based on the frequency of degree of degenerative lesions in the renal proximal convoluted tubule, was considered to be 0.96 mg of uranyl nitrate hexahydrate/l (equivalent to 0.09 mg uranium/kg bw/day in females and 0.06 mg uranium/kg bw/day in males).

6.192 Short-term studies in rabbits, in which uranyl nitrate hexahydrate was administered in drinking-water, also identified the kidney as the most sensitive target organ. The smallest LOAEL identified was 0.05 mg uranium /kg bw/day in a study in male rabbits with a concomitant *Pasteurella* infection. In *Pasteurella*-free rabbits, the LOAELs were considered to be equivalent to 0.5 mg uranium/kg bw/day in female rabbits and "to lie between 24 and 600 mg uranyl nitrate hexahydrate/l" (1.4 and 41 mg uranium/kg bw/day) in males (WHO, 2004).

6.193 In a series of studies in mice, uranyl acetate dihydrate was administered by gavage to investigate the reproductive and developmental toxicity of uranium. In a teratology study, there was a dose-related reduction in maternal weight gain and food consumption; and a dose-related increase in fetotoxicity at doses of 2.8 mg uranium/kg bw/day (the lowest dose administered) and above. Cleft palate, minor bone anomalies and developmental variations were seen at 14 mg uranium/kg bw/day and above (Domingo *et al*, 1989a). When animals were dosed between day 13 of pregnancy and day 21 of lactation, maternal deaths were seen in 5/40 animals at 2.8 mg uranium/kg bw/day and above, but there were no other signs of maternal toxicity. Reduced pup viability during lactation occurred at 28 mg uranium/kg bw/day; a NOEL of 2.8 mg uranium/kg bw/day was identified for developmental effects (Domingo *et al*, 1989b). No treatment-related effects were seen on male or female mating performance nor on fertility when male rats were dosed for 60 days prior to mating and female rats for 14 days prior to mating at doses up to the equivalent of 14 mg uranium/kg bw/day and exposure was continued through mating, gestation, parturition and nursing of litters (Paternain *et al*,1989). Decreased pup viability was seen at doses of 5.6 mg uranium/kg bw/day and above, and both embryolethality and retarded development during lactation were seen at 14 mg uranium/kg bw/day. Minor effects were seen in the testes of male mice exposed to uranyl acetate dihydrate in drinking-water for 64 days at doses from 5.6 to 44.8 mg uranium/kg bw/day prior to mating with untreated females, but there were no effects on testicular function or spermatogenesis (Llobet *et al*, 1991). There was a significant decrease in the pregnancy rate of the females, but this was not dose-related.

6.194 WHO (2004) reports that animal studies do not show carcinogenic effects from ingestion of uranium compounds; no details are provided.

Humans

6.194 Little information is available on the chronic health effects of oral exposure to natural uranium in humans. WHO (2004) describes four studies which investigated effects of uranium in drinking water and kidney function. Some positive correlations were reported with uranium concentration/intake/urinary uranium and excretion of urinary parameters indicative of tubular or glomerular damage. No correlation was reported with overt renal disease. The results of studies on mortality in the nuclear industry are described in paragraph 6.188.

Current recommended upper intake levels

6.196 WHO has set a TDI for uranium of 0.6 µg/kg bw/day, based on the LOAEL of 60 µg/kg bw/day in male rats in the 91-day rat study (Gilman *et al*, 1998) and an uncertainty factor of 100. The COT, in an assessment of uranium levels in water used to reconstitute infant formula, considered that there were a number of limitations in the design and interpretation of this study but that, despite these limitations, the TDI would be expected to be protective of public health (Committee on Toxicity, 2006).

Key Points

1. We have reviewed the data in the scientific literature on the toxicity of the chemical contaminants of concern. Studies carried out in both humans and laboratory animals have been considered. Only studies using routes of exposure relevant to the contamination incident were considered. Where available, we have made use of authoritative reviews by national and international experts. We have considered both the acute toxicity of each contaminant i.e. the effects of a single or short-term high exposure, and the chronic toxicity i.e. effects which might be seen after a longer-term lower level exposure, or which might occur at some time after exposure.

2. Aluminium was the main metallic contaminant in drinking water after the Lowermoor incident. Aluminium compounds occur widely in the environment as they are major components of soil. They are used in the treatment of drinking water, in aluminium-based food additives, and as medicines (antacids) to relieve the symptoms of ulcers and excess acid in the upper gastrointestinal tract. Exposure to aluminium is widespread and the main source for most people is food.

3. Aluminium exists in water in different forms, depending on the acidity of the water, and the form affects its solubility and the amount of aluminium absorbed by the body. Some other compounds, such as citrates, may enhance the absorption of aluminium; other compounds, such as phosphate or silicic acid, may lower its absorption. In general, the absorption of aluminium across the gut or across the skin is low. In healthy young adults, only about 0.2-0.4% of aluminium is absorbed from water, although a 10-fold higher rate of absorption has been recorded in one individual. Even in the presence of citrate, which would have been present in fruit squashes used to improve the palatability of the contaminated water, it is likely that only a small proportion of aluminium would have been absorbed from the contaminated water. Absorbed aluminium is usually excreted rapidly by the kidneys but excretion will be less efficient in individuals with impaired renal function, for example, some older people. Also, in children under the age of 2 years, excretion of aluminium can be relatively inefficient. A small

proportion of aluminium can be transferred to suckling animals via the mother's milk.

4. Aluminium has not been shown to be acutely toxic in humans. In experimental animals, the acute toxicity of aluminium is low and depends on the compound administered: the higher the degree of absorption of the compound, the higher its acute toxicity.

5. When administered in high doses to laboratory animals, aluminium compounds can cause adverse effects on the brain, kidney, bone and the stomach. Reproductive toxicity has been reported following the administration of aluminium nitrate to animals, including effects on the development of the fetus. Long-term, high exposures in man can also cause bone disease.

6. The key effect of concern is neurotoxicity. A reversible dementia - dialysis dementia - was seen in the past in patients with kidney failure undergoing renal dialysis with tap water containing aluminium, or taking aluminium-containing phosphate binders. It was considered in the past that aluminium might be involved in the aetiology of Alzheimer's disease but this now appears to be increasingly unlikely. Aluminium is also neurotoxic in animals. A number of potential mechanisms exist by which it could cause neurotoxicity. For repeated exposure, it is possible to identify a dose of aluminium in laboratory animals which does not cause effects on brain function (a "No Observed Adverse Effect Level" or NOAEL). The NOAEL identified in this report was 30.7 milligrams per kilogram body weight per day. Some studies reported changes at a lower level of aluminium but it is not clear that these changes are adverse or due only to the administered aluminium. Other studies also show effects at lower levels but there are problems with the design and/or reporting of these studies which makes them unreliable to use in determining the NOAEL. It is not possible to identify a NOAEL for single, or very short term, exposures from the scientific studies available.

7. Following the pollution incident, copper was dissolved into the water from copper piping and fittings by the action of the acidic water. Copper in solution can impart an unpleasant, metallic taste, although the concentration at which the taste becomes detectable varies among individuals. Copper is an essential element for man. Acute copper toxicity is rare, but it has been reported in humans who have consumed contaminated beverages or food. Symptoms include salivation, abdominal pain, nausea, vomiting and diarrhoea. The threshold for symptoms varies among individuals and also depends on the concentration and form of exposure. Ingestion of extremely high amounts of copper can be lethal.

8. Copper rarely causes chronic systemic toxicity because the amount in the body is controlled by homeostatic mechanisms. A toxic amount of copper only accumulates in individuals with genetic defects in these mechanisms such as patients with Wilson's disease. Symptoms of gastric irritation, resulting from a chronic local effect on the gastrointestinal tract, have been reported in normal individuals with daily intakes of 2 to 32 mg copper in drinking water.

9. Zinc may also have been dissolved from galvanised pipes and fittings into the water following the pollution incident as a result of the action of the acidic water. Zinc is also an essential element for humans and is considered to be of low toxicity. Acute toxicity can occur following massive ingestion of zinc and is usually characterised by abdominal pain, dizziness, nausea, vomiting and diarrhoea. The chronic effects are largely a consequence of zinc-induced copper deficiency following prolonged high exposure to zinc. However, even where severe effects have resulted from long-term, excessive zinc intake, it has been shown that individuals recover after high zinc consumption stops, with or without copper supplementation.

10. Concentrations of lead in drinking water may have increased after the Lowermoor incident as a result of the acidic water enhancing the dissolution of lead from lead service pipes or old domestic plumbing. Humans are mainly exposed to lead through consuming food or drink contaminated with small amounts. Lead is transported round the body bound to red blood cells. Whole blood lead concentrations are used as a measure of body burden and of the absorbed (internal) dose of lead. In adults, over 90% of the total body burden is found in bone, where it is largely inert. However, the high turnover rate of bone mineral in growing children can release lead and prolong exposure of sensitive target sites to the metal.

11. Lead can cause a range of adverse effects, in particular on the kidney, brain and nervous system, on sperm formation, blood pressure and blood forming tissues. High doses can cause cancer in animals and there is limited evidence that humans with sustained exposure to high levels of inorganic lead compounds also have a higher than usual risk of cancer. However, the key adverse effect of lead at low doses is on the development of intellect and learning ability in children. No exposure or blood concentration of lead have been identified at which it is certain that such effects will not occur. Therefore, policy on lead in the developed world has been for some time to lower exposure wherever possible. As a result, both environmental concentrations and blood lead concentrations in children have fallen substantially in developed countries in the last few decades.

12. The flushing programmes carried out to remove the contaminated water from the distribution system may have disturbed sediments of manganese oxide in the mains, resulting in increased manganese concentrations at the tap. Manganese is an abundant metal which occurs naturally in the environment. It is an essential element for humans. It has been found that chronic occupational exposure to manganese, by breathing elevated levels of manganese dusts or fumes, can cause a neurotoxic condition similar to Parkinson's disease, called 'manganism'.

13. Two epidemiological studies have considered a possible correlation between exposure to manganese in drinking water and neurological effects. One study carried out in Greece found an association between progressive increases in neurotoxicity and drinking water concentrations of manganese; the other, carried out in Germany, did not. Although the data from these studies are not ideal, they can be used to estimate acceptable total manganese intakes for both the general population and for older people, who may may be more susceptible to the neurological effects of manganese.

14. The flushing programmes may also have disturbed sediments of iron oxides in the mains, resulting in raised iron concentrations at the tap. Iron is an essential element for humans and is a common contaminant of tap water in some areas of the UK. Acute iron toxicity usually occurs in children, following accidental ingestion of iron supplements intended for adults, and is characterised by constipation, nausea, diarrhoea and vomiting. High acute doses can be lethal. However, in general, the body regulates the level of iron in the body by controlling the amount absorbed from food and drink according to the amount required. Severe chronic iron toxicity usually occurs only in individuals with certain genetic disorders or hereditary anaemias.

15. It was suggested to us that adverse health effects may have been caused by a combination of two or more of the contaminants. Therefore, a review was conducted of literature data on biological interactions between the above metals. A limited amount of information was found. The review considered only studies which had used oral exposure. Metals were considered in pairwise combinations, with particular reference to aluminium, as this was the main contaminant.

16. A number of studies showed inhibitory interactions between the metals in question, often at the level of uptake in the gut. Several combinations of metals showed inhibitory interactions, and some of the effects were inconsistent between studies. The biological significance of these effects has not always been defined. There were few data which suggested toxic effects due to combinations of increased intakes of two or more metals. Such effects were only seen when high doses of metals were given for periods of several weeks or months.

17. Analysis of a service pipe residue from the Camelford area and of residue in a kettle showed the presence of a low concentration of uranium. This metal is naturally occurring and is found, normally in low amounts, in all drinking water, food and air. Natural uranium is only weakly radioactive and is classified in the lowest hazard class for radioactive materials. Its chemical toxicity is considered to be of more concern than its radioactivity. The key effect of concern from its chemical toxicity is kidney toxicity and the safety limit for uranium in water is set on this basis.

18. High concentrations of sulphate in drinking water render it unpalatable; the taste threshold varies according to the sulphate compound. High concentrations in drinking water can also affect the gastrointestinal tract, causing gastrointestinal irritation and a purgative effect. Large amounts of magnesium or sodium sulphate can thus cause dehydration. Apart from these acute effects, it is considered to be one of the least toxic anions.

19. The aluminium sulphate solution which caused the initial contamination in the Lowermoor incident rendered the water acidic. Acidity is measured by pH, which is a measure of acid or alkaline nature of a solution. A pH of 1 is ten times more acidic than a pH of 2. pH 7 is neutral, acid solutions have a pH less than 7, alkaline more than 7. Exposure to water of low or high pH results in irritation to the eyes, skin and mucous membranes and gastrointestinal irritation may occur.

7 Implications for health of exposure to the contaminants

Introduction

7.1 We have reviewed the data in the scientific literature on the toxicity of those contaminants in the water supply of which the concentrations were increased as a result of the Lowermoor incident. The data are summarised in Chapter 6. The water sampling data are described in Chapter 3. These comprise measured concentrations of the contaminants up to the end of 1989. Calculated and modelled estimates of potential human exposure to each contaminant, based on these measurements, are given in Chapter 4. In this chapter we consider the implications for health of exposures to the contaminants after the incident, in the context of their toxicity.

7.2 There are a large number of uncertainties involved in assessing the implications for health of exposure to the contaminants, many of which have been discussed previously. Those most relevant to this chapter are summarised in Table 49 below.

7.3 Some of these uncertainties arise because our investigation took place many years after the incident occurred and it is not possible to collect the ideal data on water quality or exposure. Others arise from limitations in the scientific database on the contaminants of concern, which is not unusual in toxicological risk assessments of contaminants. It is inevitable that there are some uncertainties in the science, and the evaluation of scientific evidence is to some extent subjective. For this reason, scientists are rarely definitive in their conclusions. Where uncertainty exists, however small, we use terms such as "it is likely that…" and " it is not expected that…" to indicate where the balance of evidence lies. We highlight below any specific uncertainties which arise in the assessment of the implications to exposure of each of the contaminants discussed.

WHO Guideline Values

7.4 In this chapter we refer to the WHO Guideline Value for the contaminants of interest, which take the form of a maximum recommended concentration for a contaminant in drinking water. All Guideline Values are set to ensure protection of public health and, if the concentration of a contaminant in drinking water is below the Guideline Value, it is considered not to be harmful to health.

7.5 In this report, we use the 1984 WHO Guideline Values as these were relevant in 1988 and 1989, when the water samples discussed below were taken. As Table 50 illustrates, only in the case of lead was the Guideline Value based on health considerations. The other Guideline Values are set to protect against effects on plumbing materials or on aesthetic grounds. There were no statutory limits for contaminants in drinking water at the time the contamination incident occurred. Limits were introduced in the Water Supply (Water Quality) Regulations which came fully into force on 1 January 1990.

Table 49: Uncertainties affecting the assessment of the health implications of exposure to the contaminants

Data category	Main areas of uncertainty	Contribution to uncertainty
Water quality data	• exact concentrations of aluminium and sulphate that entered the mains water supply unclear. • concentrations of contaminants in the water supply system in the early stages of the incident unknown. • nature and concentrations of minor contaminants largely unknown.	+++ +++ +
Exposure	• no contemporaneous data on blood concentrations of contaminants in exposed individuals. • exact exposure by any individual to any contaminant unknown. • duration of exposure of any individuals to any contaminant unknown. • ascertainment of exposed and non-exposed populations. • intakes from contaminated food unknown.	++ +++ +++ +++ +
Data on chemical contaminants	• incomplete scientific database on aluminium including: - no studies examining long-term effects of a high, short-term exposure, - limited data on the bioavailability of aluminium in humans and the reasons for the reported interindividual variation in absorption, - extrapolation from studies on salts other than aluminium sulphate, which may have different bioavailabilities, - much human data obtained from small populations. • limited data on the oral toxicity of manganese.	 ++ ++ ++ ++ +
Other	• variation in response between experimental animals and humans • individual variability in response to contaminants	++ ++

7.6 Table 50 lists the 1984 WHO Guideline Values for the contaminants of interest and the basis upon which they were set. For comparison, the current standard for drinking water quality is also given.

Table 50: 1984 WHO Guideline Values (GV) for drinking water quality and current standards

Contaminant	1984 GV[a] (mg/l)	Basis of 1984 GV	Current standard (mg/l)[b]
Aluminium	0.2	To avoid depositions in the distribution system and discolouration of the water	0.2
Sulphate	400	Palatability of drinking water	250
Copper	1	Staining of laundry and sanitary ware	2
Zinc	5	Palatability of drinking water	No standard
Lead [c]	0.05	Protection of health	0.025
Manganese	0.1	Staining of sanitary ware and laundry	0.05
Iron	0.3	Staining of laundry and sanitary ware, and palatability of drinking water	0.2

a: WHO, 1984
b: SI No 3184, 2000
c: The WHO Guideline Values and other water standards for lead have undergone successive reductions as part of policies to lower exposure to a minimum. The current standard will be lowered to 0.01 mg/l after 2013.

7.7 The WHO guidance on the acidity of drinking water at the time of the incident was that the pH should be maintained between 6.5 and 8.5 to avoid excessive corrosion of the pipework. The current standard stipulates that the pH should lie between 6.5 and 9.5.

Overview of contaminant concentrations

Aluminium, copper and lead

7.8 The monitoring data set out in Chapter 3 indicate that the incident led to increased concentrations of aluminium, copper and lead in the water supply for several days in the first week after the contamination incident. Thereafter, the concentrations of all three metals fell substantially. Table 51 shows the percentages of SWWA samples taken after the incident which exceeded the relevant 1984 WHO Guideline Value for these contaminants and compares them with the equivalent percentages in the six months prior to the incident. It should be noted that the sampling data for the period 7 July 1988 to 4 August 1988 were presented to us in a different form from the other data (see Chapter 3). Table 51 shows that, after the immediate post-incident period, the percentages of samples containing copper and lead concentrations in excess of the relevant Guideline Value fell

to below pre-incident levels. For aluminium, this percentage did not fall to the pre-incident level until 1989.

Table 51: Percentage of SWWA samples (total number of samples) exceeding the relevant 1984 WHO Guideline Values for aluminium, copper and lead in drinking water

Contaminant	Percentage of SWWA samples[a] (total number of samples) exceeding the relevant 1984 WHO Guideline Value			
	Pre-incident (6/1/88 – 5/7/88)	Immediate post-incident[b] (7/7/88 – 4/8/88)	5/8/88 – 31/12/88	1989
Aluminium	5 (179)	89 (217)[c]	30 (916)	6 (2729)
Copper	9 (32)	6 (199)[c]	0.5 (957)	1 (2844)
Lead	14 (7)	5 (199)[c]	1 (976)	1 (2864)

a: Note the comments about these data in paragraphs 3.26-3.27 and 3.33.
b: Post-incident monitoring by SWWA for aluminium began on 7 July 1988, and for copper and lead it began on 8 July 1988.
c: Including cold and hot water samples.

Sulphate, zinc, manganese and iron

7.9 SWWA began post-incident sampling for sulphate on 9 July 1988. Two samples taken by private individuals on 6 and 7 July 1988 contained concentrations of 2,200 and 4,500 mg sulphate/l, which exceeds the 1984 Guideline Value for sulphate of 400 mg/l. No subsequent sample exceeded the Guideline Value.

7.10 After the incident, 6 of 3,316 water samples contained more than the 1984 WHO Guideline Value for zinc of 5 mg/l. Three of these were in the first month after the incident (one taken by SWWA and two by private individuals), two were taken later in 1988 and one in 1989. However, in most samples, the zinc concentration was below 1 mg/l.

7.11 Table 52 shows the percentages of SWWA samples taken after the incident which exceeded the 1984 WHO Guideline Values for manganese and iron and compares them with the equivalent percentages in the six months prior to the incident. The percentage of samples exceeding the relevant Guideline Value increased for both contaminants in the immediate post-incident period. For manganese, the percentage then fell below 1%. However, for iron, the percentage in 1989 did not fall to the pre-incident level.

Table 52: Percentage of SWWA samples (total number of samples) exceeding the relevant 1984 WHO Guideline Values for manganese and iron in drinking water

Parameter	Percentage of SWWA samples[a] (total number of samples) exceeding the relevant 1984 WHO Guideline Value			
	Pre-incident (6/1/88 – 5/7/88)	Immediate post-incident (7/7/88 – 4/8/88)	5/8/88 – 31/12/88	1989
Manganese	0 (172)	11 (147)	1 (727)	1 (1966)
Iron	1 (172)	7 (147)	4 (960)	6 (2864)

a: Note the comments about these data in paragraphs 3.26-3.27 and 3.33.

7.12 In summary, the monitoring data indicate that the period of exposure to increased concentrations of contaminants was likely to have been of short duration, with the exception of aluminium, where 30% of samples exceeded the 1984 WHO Guideline Value until the end of 1988, although only three exceeded 2 mg aluminium/l[52] (see Chapter 3, Table 9) and most contained less than 0.5 mg/l. High concentrations of other metals occurred only sporadically and did not show any pattern and we do not know if these are linked in any way to the incident. Therefore, we have not calculated exposures more than one month after the incident for any contaminant other than aluminium. Nevertheless, it is possible that an individual could have been exposed to increased concentrations for longer than indicated above. Contaminated water may have been stored unused in household tanks during a period of absence and used at a later date. As stated in Chapter 4, continued delivery of contaminated water to local properties, albeit diluted to some extent by fresh water, might have occurred because of characteristics of the water network such as the presence of dead ends. Therefore, although most individuals will have experienced short periods of increased exposure to these contaminants, exposure periods may have been longer in some cases, although we are not able to say how long.

Exposures

7.13 The establishment of the degree of exposure of individuals to the contaminants is of critical relevance in assessing any potential health effects. In order to estimate the exposure of individuals to the contaminants in the water we have examined the pattern of exposure indicated by the analyses of water samples taken at the point of supply to the individual and two models of the water supply dealing with the passage of the contaminants through the water distribution network (see Chapters 3 and 4).

7.14 Our assessment of the likely exposures to chemical contaminants is limited by the lack of data on exposure of individuals to the contaminants concerned. There are several important areas of uncertainty. We have had to make assumptions about the extent to which the concentration of contaminants found at monitored points in the water supply network applied to the area as a whole and about the amount of water consumed by individuals. We do not know, for any one individual, both the amount of contaminated water he or she consumed and the concentrations of contaminants in that water. It has

[52] 10 times the Guideline Value

been reported in the past that the most highly contaminated water was undrinkable. One individual who spoke to us described the water coming out of the tap as "dark green sludge". Other individuals reported that they did drink the water on the first night of the incident, even though it had an unpleasant taste, and continued to do so. In the case of bottle-fed infants, consumption of highly contaminated tap water may have been restricted by difficulty in making up baby feed in this water, as individuals frequently told us that it caused milk to curdle.

7.15 The contamination of the water supply peaked in different areas at different times as the bolus of contaminated water travelled through the water distribution system. It may be that individuals who drank the water on the first night of the incident did not live in areas where the level of contamination was highest; equally the opposite may be true. It is not possible to reach a conclusion about this.

7.16 We examined the information from human and animal studies of tissue concentrations of contaminants, but found these of limited help in our evaluation. The studies were, with few exceptions, conducted some months or years after the incident, were limited in design in different ways, and generally involved small numbers of individuals (see paragraphs 5.176 to 5.179). Our recommendations in Chapter 9 include observations on the management of future incidents, including on the strategy for surveillance and monitoring which should be considered.

7.17 In Chapter 4, for adults, we calculated both *average* and *high level* estimates of exposure to contaminants from the polluted water on specific days. This was done by assuming that people drank tap water with the maximum concentrations of a contaminant measured, and that they were either an average or high level consumer[53] of tap water. To assess average and extreme consumptions of tap water we used data from a 1995 survey of water consumption in England and Wales (M.E.L. Research, 1996). In summary:

Average exposure to contaminant	=	highest concentrations of contaminant	x	*average* intake of tap water
High level exposure to contaminant	=	highest concentrations of contaminant	x	*high level* intake of tap water

7.18 We have also calculated estimates of exposure for toddlers and for bottle-fed babies, again on the assumption of consistent consumption of water with the highest measured concentrations of a contaminant. To assess consumption of tap water by toddlers, we used the average intake of tap water per day in England and Wales by children aged 0 to 5 (M.E.L. Research, 1996). No high level intake of water was available for this group. For bottle-fed infants, we used an average intake of 0.9 litres of water per day, which is the fluid requirement of a 6 kg infant at an intake up to 150 ml/kg for a 0 to 6 month old baby (Clinical Pediatrics and Child Health, 2001).

[53] "High level" was taken as the average intake of the top 2.5% of tap water consumers.

7.19 When we took personal evidence, we were told by one family that they always filled the kettle from the hot water tap. Therefore, we have calculated exposures using concentrations of contaminants from both hot and cold water samples, where these are available. We do not know how widespread this practice was.

7.20 Chapter 4 also describes the modelling of exposure estimates carried out for South West Water Ltd in 1991. The modelling used the SWWA water quality data from cold water samples only and estimates of tap water consumption provided by ten adults living in 3 water supply areas within the Lowermoor network. We have included the results for modelled intakes of a contaminant, where these are available.

7.21 We have not included potential exposures of contaminants from use of tap water in cooking, as it is not possible to quantitify exposure from this usage. We have also excluded potential exposure by the dermal route, because we were advised that dermal absorption was likely to have been quantitatively unimportant in comparison with oral exposure (see paragraphs 4.39 to 4.41).

7.22 The estimated exposures in Chapter 4 were made on the basis of the amount of contaminant consumed per person per day. Exposure estimates are presented below on a body weight basis i.e. the potential exposure to a contaminant of each age group is divided by the mean body weight for that age group. The potential exposure for a child is calculated using the mean body weight for toddlers to give a worst case for children (because of the low body weight of toddlers). This process generates an intake figure expressed as milligrams of contaminant per kilogram of body weight per day (mg/kg bw/day) and enables a comparison to be made with the toxicity data discussed in Chapter 6. The mean body weights used are:

- Adults: 60 kg[54]
- Toddlers: 14.5 kg[55]
- Infant: 6 kg[56].

Aluminium

Exposures

7.23 Potential exposures to aluminium from 7 July to 4 August 1988, based on SWWA monitoring data, are given in Table 53 and in Figures 34 and 35. The modelled exposures calculated by Crowther Clayton Associates (1991), and discussed in Chapter 4, are included in the table for comparison. Initial exposures are given on a daily basis (or over 2 days when data are only available on that basis) and later exposures are given at intervals of a few days. It should be remembered that the exposures are based on the maximum concentration measured on each day and represent a worst-case estimate. The range of concentrations recorded each day is given in Chapter 3. Some of these

[54] This figure is routinely used as the mean adult body weight in toxicological assessments.
[55] The mean body weight for a toddler derived by the Food Standards Agency from food consumption surveys.
[56] The body weight of a 3-4 month old infant.

maximum concentrations were recorded at the tap and some from reservoirs; they were recorded at different locations in the area receiving contaminated water. Table 53 also includes the calculated exposures, based on the same assumptions, if the water contained aluminium at the 1984 WHO Guideline Value concentration of 0.2 mg/l.

Table 53: Estimated worst-case exposures to aluminium from drinking water, 7 July to 4 August 1988 (calculated and modelled using water quality data from SWWA)

Date	**Highest aluminium concentration (mg/l)**	**Estimated exposures to aluminium (mg/kg bw/day)**				
		Adults			**Toddlers**	**Bottle-fed infants**
		Calculated		*Modelled*[a]	*Calculated*	*Calculated*
		Average	*High*			
7/7/88	109	2.07	4.36	4.17	3.76	16.35
8/7/88	34.5	0.66	1.38	1.54	1.19	5.18
9/7/88 - 10/7/88	12.0	0.23	0.48	1.14	0.41	1.80
11/7/88	0.7	0.01	0.03	0.33	0.03	0.10
14/7/88	2.0	0.04	0.08	0.12	0.07	0.30
18/7/88	1.0	0.02	0.04	0.10	0.03	0.15
21/7/88	2.2	0.04	0.09	0.09	0.08	0.33
26/7/88	0.72	0.01	0.03	0.07	0.02	0.11
1/8/88	0.37	0.007	0.01	0.05	0.01	0.06
4/8/88	0.29	0.006	0.01	0.04	0.01	0.04
Calculated intakes based on the 1984 WHO Guideline Value of 0.2 mg/l		0.004	0.008	NA	0.007	0.03

a: Maximum modelled intake of those calculated for 10 individuals (Crowther Clayton Associates, 1991).
Intake on mg/kg bw/day basis calculated for a 60 kg individual.
NA: not available

Figure 34: Estimated worst-case exposures to aluminium from drinking water (mg/kg bw/day) calculated and modelled from SWWA water monitoring data, 7 July to 4 August 1988: Adults

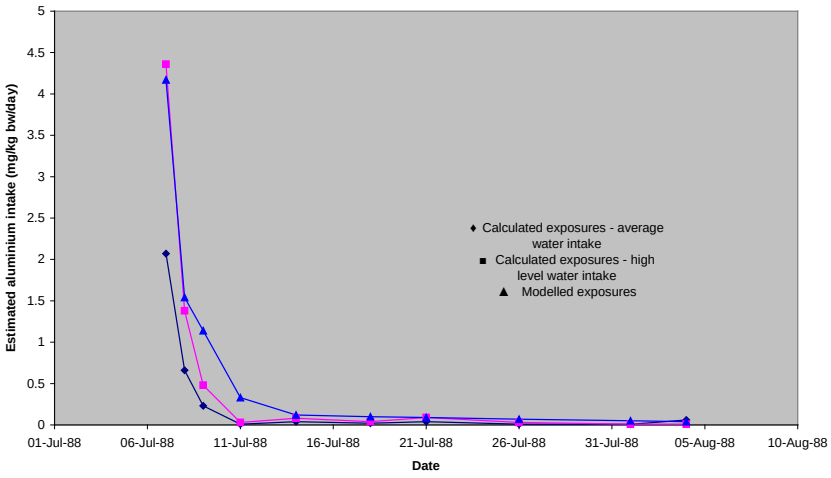
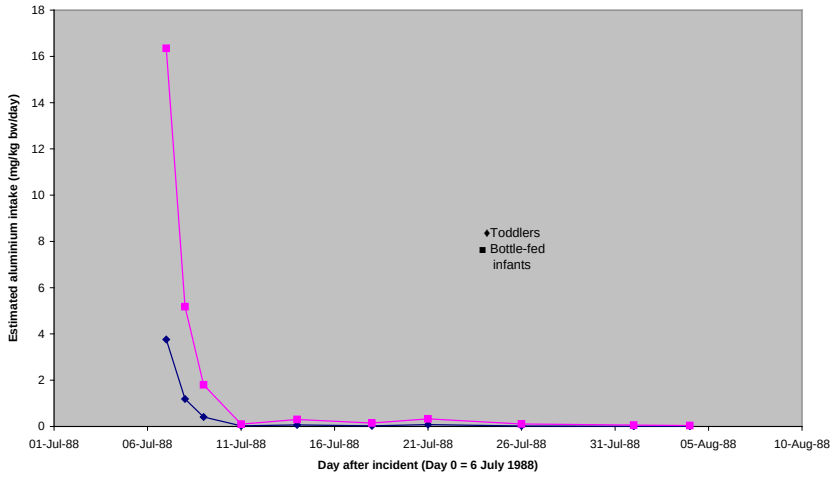


Figure 35: Estimated worst-case exposures to aluminium from drinking water (mg/kg bw/day) calculated from SWWA monitoring data, 7 July to 4 August 1988: Toddlers and bottle-fed infants



7.24 Table 54 gives exposures calculated using concentrations of contaminants in water samples taken by private individuals (non-SWWA sources) and analysed in laboratories other than those used by SWWA (see paragraph 3.66 and Table 13).

Table 54: Estimated exposures to aluminium from drinking water, 6 to 11 July 1988 (calculated using concentrations of aluminium in water samples from non-SWWA sources[a])

Date	Highest aluminium concentration (mg/l)	Estimated exposures to aluminium (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Calculated		*Calculated*	*Calculated*
		Average	*High*		
6/7/88	188-251[b]	3.6-4.8	7.5-10	6.5-8.7	28.2-37.7
7/7/88	460-720[c]	8.7-13.7	18.4-28.8	15.9-24.8	69-108
11/7/88 (Hot water sample)	3.1	0.06	0.12	0.11	0.47

a: Note the comments about these data in paragraphs 3.26-3.27 and 3.334.
b: three separate analyses of this sample recorded concentrations of 188, 190 and 251 mg aluminium/l
c: three separate analyses of this sample recorded concentrations of 460, 620 and 720 mg aluminium/l

7.25 Modelling carried out by Black & Veatch Ltd (B&V), and described in Chapter 3, predicted that the highest concentration of aluminium leaving the treatment works would have been 325 mg/l on 6 July 1988 if there was no sludge in the contact tank at the water treatment works and 472 mg/l if sludge was present. The maximum contaminant concentration at specific sites from 7 to 11 July 1988 was also modelled (see Chapter 3, Table 14). The exposures at these modelled concentrations are shown in Tables 55 and 56.

Table 55: Estimated worst-case exposures to aluminium from drinking water, 6 July to 4 August 1988 (calculated using the results of modelling by Black & Veatch Ltd[a], Appendix 13, and the assumption that no sludge was present in the contact tank)

Date	Highest aluminium concentration (mg/l)	Estimated exposures to aluminium (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Calculated		*Calculated*	*Calculated*
		Average	*High*		
6/7/88	325	6.18	13	11.21	48.75
7/7/88	324	6.16	12.96	11.17	48.6
8/7/88	129	2.45	5.16	4.45	19.35
9/7/88	9	0.17	0.36	0.31	1.35
10/7/88	5	0.10	0.2	0.17	0.75
11/7/88	2	0.04	0.08	0.07	0.3

a: note the comments about the modelling work in paragraph 3.73

Table 56: Estimated worst-case exposures to aluminium from drinking water, 6 July to 4 August 1988 (calculated using the results of modelling by Black & Veatch Ltd[a], Appendix 13, and the assumption that there was a layer of sludge on the base of the contact tank)

Date	Highest aluminium concentration (mg/l)	Estimated exposures to aluminium (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Calculated		*Calculated*	*Calculated*
		Average	*High*		
6/7/88	472	8.97	18.88	16.28	70.8
7/7/88	466	8.85	18.46	16.07	69.9
8/7/88	187	3.55	7.48	6.45	28.05
9/7/88	5	0.10	0.2	0.17	0.75
10/7/88	2	0.04	0.08	0.07	0.3
11/7/88	2	0.04	0.08	0.07	0.3

a: note the comments about the modelling work in paragraph 3.73

7.26 Up to the end of 1988, 30% of SWWA water samples contained concentrations of aluminium in excess of the 1984 WHO Guideline Value. The three highest calculated estimated exposures to aluminium during this time are given in Table 57. It is not known whether these were hot or cold water samples. Most samples contained less than 0.5 mg aluminium/l. In 1989, the percentage of samples exceeding the Guideline Value for aluminium was similar to the pre-incident level (see Table 51).

Table 57: Estimated exposures to aluminium from drinking water from the 3 highest concentrations recorded between 5 August 1988 and 31 December 1988 (SWWA data)

Date	Highest aluminium concentration (mg/l)	Estimated exposures to aluminium (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Average	*High*		
18/8/88	6.9	0.13	0.28	0.24	1.04
29/11/88	7.8	0.15	0.31	0.27	1.17
16/12/88	58.7	1.12	2.35	2.03	8.8

Toxicity

7.27 The toxicity of all the contaminants has been discussed in detail in Chapter 6 and only brief summaries are presented here.

7.28 Studies on aluminium show that, in general, absorption across the gut is low. In healthy young adults, about 0.2-0.4% of aluminium is absorbed from ingested water

although inter-individual variation may occur. The degree of absorption also depends upon which salt of aluminium is administered. Aluminium nitrate and aluminium chloride appear to be more bioavailable than the sulphate or hydroxide. Citrate, present in fruit squashes which were used to improve the palatability of the contaminated water, can increase the absorption of aluminium. However, in most cases it is probable that less than 1% of aluminium would have been absorbed from the contaminated water, even in the presence of citrate[57]. There are limited data on inter-individual variation in absorption of aluminium but one study has indicated that some individuals can show considerably increased absorption compared to normal. Absorbed aluminium is usually excreted rapidly by the kidneys but excretion would be less efficient in individuals with impaired renal function, for example some older people. Also, infants under 1-2 years of age have relatively inefficient excretion of aluminium.

7.29 The critical toxic endpoint for longer-term exposure to aluminium is neurotoxicity. A reversible dementia (dialysis dementia) was seen in patients with kidney failure undergoing dialysis with water containing aluminium, or taking aluminium-based phosphate binders. There is evidence from studies in experimental animals that aluminium is neurotoxic. It was previously considered that aluminium might be involved in the aetiology of Alzheimer's disease. Although the current evidence now suggests that aluminium may not cause Alzheimer's disease, it has not been established whether it may contribute indirectly in some cases.

7.30 Osteomalacia has been reported in humans following intake of several grams per day of aluminium-containing antacids for several months and it is well documented in patients with chronic kidney failure. Short-term exposure to high doses of aluminium in animals has not been reported to cause adverse musculoskeletal effects. Osteomalacia would not be anticipated to occur following exposures of the magnitude and duration which occurred after the Lowermoor incident.

7.31 Reproductive toxicity, including teratogenicity and developmental toxicity, was seen in studies in laboratory animals. In one series of studies, involving repeated dosing by gavage with aluminium nitrate, a salt with relatively high bioavailability, adverse effects were reported on fetal development. Aluminium nitrate is more bioavailable than alumininium sulphate. Also, when given by gavage, aluminium is expected to produce higher peak plasma concentrations than would be achieved if it was consumed in drinking water. Two two-generation studies in which rats were given aluminium sulphate and aluminium ammonium sulphate in drinking water reported retardation of sexual development in the offspring but this is likely to have been caused by significant reductions in drinking water consumption and decreased body weight gain by the parent generation due to the taste of the water, rather than the aluminium salts directly. A reproductive study with aluminium citrate identified a No Observed Adverse Effect Level (NOAEL) of 30 mg aluminium/kg bw/day when given to pregnant rats in drinking water as the citrate. Above this level, renal damage and neuromuscular effects were reported in the offspring. This dose does not include the aluminium intake from the rats' diet, which

[57] We note that data on serum aluminium concentrations in one individual indicate a higher level of absorption (see paragraphs 4.42 – 4.44).

would lead to a higher overall NOAEL. There is no information on the reproductive toxicity of aluminium in humans.

7.32 In Chapter 6 we reviewed the data on neurological responses for aluminium from studies in experimental animals and identified a No Observed Adverse Effect Level (NOAEL) for functional neurotoxic effects of 30.7 mg aluminium/kg bw/day from a study in which aluminium chloride was administered in drinking water to rats for 90 days (see paragraph 6.82). This includes the intake of aluminium from the diet. There are no studies specifically with aluminium sulphate which are considered suitable to be used for derivation of a NOAEL or Lowest Observed Adverse Effect Level (LOAEL) and extrapolation from the results of a study using a different salt adds further uncertainties to the risk assessment. It should also be noted that the studies from which these values are taken do not exactly mimic the exposures which individuals drinking the contaminated water would have experienced. In particular, the high exposures of the experimental animals to aluminium lasted longer than would have been the case after the Lowermoor incident.

7.33 Some toxicological studies reported effects at levels lower than the NOAEL identified above but there are problems with the interpretation of these studies, mainly either because a single dose level of aluminium was administered and, therefore, no information on dose-response is available, or because they report only minor biochemical changes and it is not clear that they would result in adverse health implications.

Discussion

7.34 To put the intakes of aluminium from contaminated water following the incident in context, Table 58 gives an estimate of the usual intakes of aluminium which might be consumed daily by adults, toddlers and infants from the diet and from tap water. Maximum intakes from licensed medicines, another important potential source of aluminium, are also included. However, it should be noted that the bioavailability of chemicals from water and from food and other sources may be different, giving rise to different concentrations within the body.

Table 58: Usual intakes of aluminium from food and water and potential intakes from medicines (mg/kg bw/day)

Source	Intakes of aluminium (mg/kg bw/day)					
	Adults		Toddlers		Bottle-fed infants	
	Mean	*High level*	*Mean*	*High level*	*Normal diet*	*Soya diet*
Food[a]	0.07	0.14	0.19	0.35	0.142	0.242
Tap water[b]	0.004	0.008	0.007	NA	0.03	0.03
Licensed medicines[c]	13.3	13.3	—	—	—	—

a: Adults and toddlers: estimated upper bound mean and high level dietary exposures from the 2006 Total Diet Study (Food Standards Agency, 2010). Infants: from a 2001-2002 survey of metals in infant food (Food Standards Agency, 2003).
b: Calculated intakes based on the 1984 WHO Guideline Value of 0.2 mg/l.
c: Antacids: maximum possible exposures (see paragraph 6.15).
NA: Not available
— Not applicable

7.35 It is possible to calculate a "Margin of Exposure" (MoE) between the LOAEL or NOAEL identified from toxicity studies and the intake of a chemical by humans, as follows:

$$\text{Margin of Exposure (MoE)} = \frac{\text{NOAEL or LOAEL for chemical (mg/kg bw/day)}}{\text{Daily intake of chemical (mg/kg bw/day)}}$$

For example, if the NOAEL of a chemical is 500 mg/kg bw/day and the daily intake is 10 mg/kg bw/day, then the Margin of Exposure would be: $\frac{500}{10} = 50$.

The higher the MoE, the more reassurance there is that the intake of chemical was not high enough to have harmed health. As a general rule, a MoE of 100 is considered adequate for long-term exposure to most chemicals if it is based on a NOAEL. This allows for the fact that humans may be more sensitive to the chemical than the test species, and for the fact that there may be differences in sensitivity among humans (see paragraph 6.5). A smaller MoE may be acceptable in the case of a minor adverse effect (Committee on Toxicity, 2007). A higher MoE is often required if the MoE is based on a LOAEL rather than a NOAEL or in certain other circumstances, e.g. if the chemical has serious, irreversible effects or if a vulnerable group such as young infants is being considered.

7.36 We have calculated the MoE for adults, toddlers and bottle-fed infants before and after the pollution incident, using:

- the worst-case estimated exposures to aluminium in Tables 53 to 56 from consumption of the contaminated water (using the high level intake for adults, to give a worst case),
- the usual mean intakes of aluminium from the diet given in Table 58.

7.37 The total intakes thus derived were compared with the NOAEL of 30.7 mg aluminium/kg bw/day for functional neurotoxic effects. The resulting MoE values are given in Table 59.

Table 59: Summary of estimated Margin of Exposure (MoE) for aluminium after the pollution incident based on worst-case measured or modelled aluminium concentrations in water[a], mean intakes of aluminium from the diet and a NOAEL for functional neurotoxic effects of 30.7 mg aluminium/kg bw/day[b]

Date	Adults	Toddlers	Bottle-fed infants	
			Normal diet	*Soya diet*
6/7/88				
(non-SWWA sample)	3.0-4.1[c]	3.5-4.6[c]	<1-1.1	<1-1.1
(B&V estimate – no sludge[d])	2.3	2.7	<1	<1
(B&V estimate – sludge[e])	1.6	1.9	<1	<1
7/7/88				
(SWWA sample)	6.9	7.8	1.9	1.9
(non-SWWA sample)	1.1-1.7	1.2-1.9	<1	<1
(B&V estimate – no sludge[d])	2.4	2.7	<1	<1
(B&V estimate – sludge[e])	1.7	1.9	<1	<1
11/7/88				
(SWWA sample)	307	140	127	90
(non-SWWA sample)	162	102	50	43
(B&V estimate – no sludge[d])	205	118	69	57
(B&V estimate – sludge[e])	205	118	69	57
14/7/88				
(SWWA sample)	205	118	69	57
4/8/88				
(SWWA sample)	384	154	169	109
Usual MoE for aluminium from diet and tap water	394	156	177	113

a: from Chapters 3 and 4
b: from Mameli *et al* (2006)
c: the estimated Margin of Exposure is provided as a range because the estimated exposures on this date are provided as a range (see Table 54)
d: modelling carried out with assumption that there was no sludge in the contact tank
e: modelling carried out with assumption that there was a layer of sludge on the base of the contact tank

7.38 In the comparison with the NOAEL of 30.7 mg aluminium/kg bw/day for functional neurotoxicological effects (Table 59), in the case of adults, the usual Margin of Exposure for aluminium from food and tap water is 394. Both the monitoring data and the B&V modelling indicate that the MoE for adults in the first 2-3 days after the incident would have been low, no more than 6.9 at most. It rose to 205 at the beginning of the

second week and to 384 by the end of the first month. In view of the caveats given above, and the fact that there was a low MoE for only a short period whereas the NOAEL was derived from a study entailing 90 days exposure to aluminium, on the basis of current evidence, it is unlikely that the period of increased exposure to aluminium would have caused, or would be expected to cause, delayed or persistent harm to health in adults.

7.39 Consumption of the contaminated water by pregnant women may have led to exposure of the developing fetus. Although the period of exposure to increased levels of aluminium was low, in view of the neurodevelopmental effects seen in animals administered aluminium salts *in utero*, we consider that the possibility of delayed or persistent harm to health should be explored further in this group.

7.40 In the case of toddlers, Table 59 shows that the usual Margin of Exposure for aluminium from food (mean consumption) and tap water (average consumption[58]) is 156. Both the monitoring data and the B&V modelling indicate that the MoE for toddlers in the first 2-3 days after the incident would have been low, no more than 7.8 at most. It rose to 118 by the beginning of the second week and 154 by the end of the first month after the incident, which is similar to the usual MoE for intake of aluminium from food and water. In view of the caveats given above, and the fact that there was a low MoE for only a short period whereas the NOAEL was derived from a study entailing 90 days exposure to aluminium, it is unlikely that the period of increased exposure to aluminium would have caused, or would be expected to cause, delayed or persistent harm to health in toddlers.

7.41 In the case of bottle-fed infants, the usual MoE is 177 for infants on a normal diet and 113 for those on a soya-based diet. Both the monitoring data and the B&V modelling on the first two days of the incident indicate that the maximum MoE for infants would have been, at most, 1.9 and, frequently, was below 1 on these days. By the beginning of the second week, it was 69 for infants on a normal diet and 57 for infants on a soya-based diet. By the end of the first month after the incident, it was 169 for infants on a normal diet and 109 for infants on a soya-based diet, which are similar to the usual MoEs for intake of aluminium from food and water. In view of the caveats given above, and the fact that there was no MoE for only a short period whereas the NOAEL was derived from a study entailing 90 days exposure to aluminium, it is unlikely that the period of increased exposure to aluminium would have caused, or would be expected to cause, delayed or persistent harm to health in infants. However, because there was a short period of time in which the Margin of Exposure was very low and infants have been identified as likely to be the most susceptible group, we consider that the possibility of delayed or persistent harm to health should be explored further in this group. We have made recommendations for further work in Chapter 9.

7.42 From 5 August 1988 to the end of 1988, approximately 30% of water samples contained aluminium concentrations above the 1984 Guideline Value (see paragraph 3.60 and Table 7). However, most of these samples contained less than 0.5 mg aluminium/l.

[58] No data are available on high level intakes of tap water by toddlers.

At this concentration of aluminium, the MoE for adults and toddlers when compared with the NOAEL for functional neurotoxic effects of 30.7 mg/kg bw/day would have been 341 and 148, respectively. That for infants on a normal diet would have been 141 and that for infants on a soya-based diet would have been 97. These MoE values are slightly lower than the usual MoE for aluminium derived from the diet and tap water.

Copper

Exposures

7.43 Copper was a secondary contaminant which entered the water supply as a result of the effect of the acidic water on copper pipes and fittings. As stated previously, the concentrations of copper fell considerably after the first few days. Estimated exposures to copper are given in Tables 60 and 61 below. Modelled data are not included because the Crowther Clayton Associates modelling report, which used the results of cold water analyses, starting 2 days after the incident, simply concluded that daily intake of copper for the 10 individuals involved was "always well below the acceptable levels". Tables 60 and 61 show that exposure to copper could have been up to 0.9 mg/kg bw/day in adults, 0.78 mg/kg bw/day in toddlers and 3.38 mg/kg bw/day in bottle-fed infants in the first few days after the incident if drinking water was taken from the hot water tap. Thereafter, concentrations of copper in cold water samples did not exceed the 1984 Guideline Value, and concentrations in hot water samples only exceeded it on one occasion.

Table 60: Estimated worst-case exposures to copper from drinking water, 8 July 1988 to 4 August 1988 (calculated using water quality data from SWWA)

Date	Highest copper concentration (mg/l)	Estimated exposures to copper (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Average	*High*		
8/7/88	1.7	0.03	0.07	0.06	0.25
9/7/88 -10/7/88	8.8	0.17	0.35	0.30	1.32
Hot water sample	20	0.38	0.8	0.69	3
11/7/88	0.05	0.001	0.002	0.002	0.008
Hot water sample	13	0.25	0.52	0.45	1.95
14/7/88-4/8/88	0.8	0.02	0.03	0.03	0.12
Hot water sample	1.1	0.02	0.04	0.04	0.17
Calculated intakes based on the 1984 WHO Guideline Value of 1 mg/l		0.02	0.04	0.03	0.15

Table 61: Estimated exposures to copper from drinking water (calculated using water quality data from non-SWWA sources)

Date	Highest copper concentration (mg/l)	Estimated exposures to copper (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Average	*High*		
6/7/88	6.0	0.11	0.24	0.21	0.9
7/7/88	6.3	0.12	0.25	0.22	0.95
11/7/88 (Hot water sample)	22.5	0.43	0.9	0.78	3.38

Toxicity

7.44 Dissolved copper imparts an unpleasant metallic, bitter taste to tap water but the concentration at which individuals perceive this taste varies. A small volunteer study showed that all 61 subjects ingesting tapwater tasted copper sulphate when it was present at 8 mg copper/l. However, it is likely that the taste threshold rises when the water is drunk in beverages. The presence of copper may have contributed to the abnormal taste of water as reported to us and might have deterred some people from drinking water containing increased concentrations of copper, although it cannot be assumed that everyone would have been deterred. Some individuals told us that they drank the water shortly after the incident despite it having a bitter taste.

7.45 Consumption of water containing high concentrations of copper can cause acute gastrointestinal symptoms. The volunteer study referred to above found that individuals experienced nausea at concentrations of 4 mg copper/l and above. More severe acute effects of copper, such as kidney and liver failure, occur after intakes some 200-300 times higher than those reported in Tables 60 and 61. There are few reports in the scientific literature of chronic copper toxicity because copper is kept under tight homeostatic control in man which prevents the accumulation of excess amounts[59].

Discussion

7.46 For comparison with the estimated intakes given above, Table 62 gives an estimate of the usual intakes of copper which might be consumed daily by adults, toddlers and infants from the diet and from tap water, and potential intakes from licensed medicines and from dietary supplements.

7.47 The increased concentrations of copper in the first week or thereabouts after the incident probably contributed to symptoms such as nausea, vomiting and/or diarrhoea. It is possible that the presence of other contaminants in the water might have enhanced this

[59] Except in those with Wilson's disease.

effect. However, we would not anticipate any delayed or persistent effects of copper from intakes at this time, because of the homeostatic control of copper balance in man.

Table 62: Usual intakes of copper from food and water and potential intakes from medicines and dietary supplements (mg/kg bw/day)

Source	Intakes of copper (mg/kg bw/day)					
	Adults		Toddlers		Bottle-fed infants	
	Mean	*High level*	*Mean*	*High level*	*Normal diet*	*Soya diet*
Food[a]	0.02	0.03	0.05	0.08	0.072	0.098
Water[b]	0.02	0.04	0.03	NA	0.15	0.15
Medicines[c]	0.07	0.07	—	—	—	—
Supplements[c]	0.03	0.03	—	—	—	—

a: Adults and toddlers: estimated dietary exposures from the 2006 Total Diet Study (Rose *et al*, 2010). Infants: from a 2001-2002 survey of metals in infant food (Food Standards Agency, 2003).
b: Calculated intakes based on the 1984 WHO Guideline Value of 1mg/l.
c: Maximum exposures (see paragraph 6.86)
NA: Not available
— Not applicable

Zinc

Exposure

7.48 Zinc was a secondary contaminant which entered the water supply as a result of the effect of the acidic water on galvanised iron service pipes or fittings containing zinc.

7. 49 In the first month after the incident, 3 water samples exceeded the 1984 WHO Guideline Value for zinc of 5 mg/l. The estimated exposures to zinc arising from the concentrations in these samples are shown in Table 63. Modelled data are not included because the Crowther Clayton Associates modelling report concluded that the daily intake of zinc for the 10 individuals involved was "always well below the acceptable levels".

Table 63: Estimated exposures to zinc from drinking water calculated for samples taken between 6 July 1988 and 4 August 1988 which exceeded the 1984 WHO Guideline Value

Date	Zinc concentrations (mg/l)	Estimated exposures to zinc (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Average	*High*		
6/7/88[a]	7.1	0.14	0.28	0.25	1.07
7/7/88[a]	9.0	0.17	0.36	0.31	1.35
19/11/88[b] (Hot water sample)	7.8	0.15	0.31	0.27	1.17
Calculated intakes based on the 1984 WHO Guideline Value of 5 mg/l		0.1	0.2	0.17	0.75

a: non-SWWA sample
b: SWWA sample
c: From equivalent amounts of water containing the 1984 WHO Guideline Value (GV) of 5 mg zinc/l.

Toxicity

7.50 Zinc is generally considered to be non-toxic, although consumption of high concentrations can cause gastrointestinal effects such as abdominal pain, nausea, diarrhoea and/or vomiting. The chronic effects of zinc are largely a result of zinc-induced copper deficiency following prolonged exposure. Long-term intakes of 2.5 to 30 mg zinc/kg bw/day can result in severe haematological effects due to copper deficiency but these are reversible after cessation of zinc.

Discussion

7.51 For comparison with the estimated intakes given above, Table 64 gives an estimate of the usual intakes of zinc which might be consumed daily by adults, toddlers and infants from the diet and from tap water and potential intakes from food supplements.

Table 64: Usual intakes of zinc from food and water and potential intakes from dietary supplements (mg/kg bw/day)

Source	Intakes of zinc (mg/kg bw/day)					
	Adults		Toddlers		Bottle-fed infants	
	Mean	*High level*	*Mean*	*High level*	*Normal diet*	*Soya diet*
Food[a]	0.14	0.27	0.39	0.78	1.26	1.5
Water[b]	0.1	0.2	0.17	NA	0.75	0.75
Supplements[c]	2.5	2.5	—	—	—	—

a: Adults and toddlers: estimated dietary exposures from the 2006 Total Diet Study (Rose *et al*, 2010). Infants: from a 2001-2002 survey of metals in infant food (Food Standards Agency, 2003).
b: Calculated intakes based on the 1984 WHO Guideline Value of 5 mg/l
c: Maximum exposures (see paragraph 6.105)
NA: Not available
—: Not applicable

7.52 The occasional high concentrations of zinc in Table 63 would have led, at most, to a 30% increase in daily exposures compared to exposures based on the 1984 WHO Guideline Value. These concentrations may have contributed to acute, adverse gastrointestinal symptoms. However, on the basis of the current evidence, it could be concluded that exposures to zinc were not high enough nor prolonged enough to cause, or be expected to cause, delayed or persistent harm to health.

Lead

Exposure

7.53 Lead was a secondary contaminant which entered the water supply as a result of the effect of the acidic water on plumbing and service pipes, where these were made of lead. As stated previously, the concentrations of lead fell considerably after the first few days. Estimated exposures to lead are given in Tables 65 and 66 below. These show that exposures to lead could have been high for 3 to 4 days after the incident, after which time they decreased. Modelled data are not included. The Crowther Clayton Associates modelling report, which used the results of cold water analyses, starting 2 days after the incident, concluded that the daily intake of lead was almost certainly well below the levels considered acceptable, although there were four days in July/August 1988 when lead concentrations exceeded 0.05 mg/l and several days when it was recorded as less than 0.08 mg/l (the level of detection). Exposures of the 10 adults concerned on these days were estimated not to exceed 0.44 mg lead/day (equivalent to 0.007 mg/kg bw/day for a 60 kg adult).

Table 65: Estimated worst-case exposures to lead from drinking water, 8 July 1988 to 4 August 1988 (calculated using water quality data from SWWA)

Date	Highest lead concentration (mg/l)	Estimated exposures to lead (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Average	*High*		
8/7/88	0.12	0.002	0.005	0.004	0.018
9/7/88 -10/7/88	0.22	0.004	0.009	0.008	0.033
Hot water sample	0.46	0.009	0.018	0.016	0.068
11/7/88	<0.05	<0.001	<0.002	<0.002	<0.008
14/7/88-4/8/88	0.009	0.0002	0.0004	0.0003	0.0013
Hot water sample	0.02	0.0003	0.0008	0.0007	0.0033
Calculated intakes based on the 1984 WHO Guideline Value of 0.05 mg/l		0.001	0.002	0.002	0.008

Table 66: Estimated exposures to lead from drinking water (calculated using water quality data from non-SWWA sources)

Date[a]	Highest lead concentration (mg/l)	Estimated exposures to lead (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Calculated		*Calculated*	*Calculated*
		Average	*High*		
6/7/88	0.025	0.0005	0.001	0.0009	0.0038
7/7/88	4 [b]	0.076	0.16	0.14	0.6
	0.025 [b]	0.0005	0.001	0.001	0.004

a: the sample taken on 11/7/88 was not analysed for lead

b: this sample was analysed twice. One analysis reported that it contained 4 mg lead/l and the second analysis by a different laboratory reported a lead concentration of 0.025 mg/l, which is below the 1984 WHO Guideline Value

Toxicity

7.54 The key health concern with environmental exposures to lead relates to adverse effects on intellectual and cognitive development in children. No threshold has been demonstrated for this effect i.e. it is not possible to identify an exposure without any risk. Transfer of lead to the human fetus occurs throughout pregnancy. An evaluation of the carcinogenicity of lead by the International Agency for Research on Cancer (IARC) classified inorganic lead compounds as “probably carcinogenic in humans”, based on limited evidence of cancer in occupational studies, sufficient evidence in animal studies and the fact that lead can damage genetic material in ways which would contribute to a carcinogenic response if exposure is sustained. A recent assessment by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) withdrew the previous Provisional Tolerable Weekly Intake (PTWI) and concluded that, because the available

data do not indicate that there is a threshold for lead neurotoxicity and cardiovascular toxicity, a new PTWI could not be established. Environmental guidelines for lead are set to minimise exposure and hence to minimise risk.

Discussion

7.55 For comparison with the estimated intakes given above, Table 67 gives an estimate of the usual intakes of lead which might be consumed daily by adults, toddlers and infants from the diet, from tap water and from air and dust. There are other potential important sources of lead, such as smoking tobacco, and, for young children, chewing flakes of lead paint. Intakes from these sources can be significant, but are not readily quantifiable.

7.56 It should be noted that the intake of lead from the diet has decreased considerably in recent years as the amount of lead in the environment has fallen. The average dietary intake of adults fell from 0.036-0.069 mg/day in 1982 to 0.015-0.028 mg/day in 1991 (MAFF, 1998), and the mean intake in the 2006 Total Diet Study was 0.007 mg lead/day. We have used data from the 2006 Total Diet Study for consistency, and because, unlike the 1982 and 1991 studies, it provides data on intake by toddlers. However, the intakes of lead from food in 1988, when the pollution incident occurred, would have been higher than those given in Table 68 and, therefore, the impact of the contaminated water on total intakes would have been less than described below.

Table 67: Usual intakes of lead (mg/kg bw/day)

Source	Intakes of lead (mg/kg bw/day)					
	Adults		Toddlers		Bottle-fed infants	
	Mean	*High level*	*Mean*	*High level*	*Normal diet*	*Soya diet*
Food[a]	0.0001	0.0002	0.0003	0.0004	0.0004	0.0006
Water[b]	0.001	0.002	0.002	NA	0.008	0.008
Air and dust[c]	0.0017	0.0003	0.004	0.007	NA	NA

a: Adults and toddlers: estimated dietary exposures from the 2006 Total Diet Study (Rose *et al*, 2010). Infants: from a 2001-2002 survey of metals in infant food (Food Standards Agency, 2003).
b: Calculated intakes based on the 1984 WHO Guideline Value of 0.05 mg/l.
c: From IPCS, 1996. Figures are not available from babies.
NA: Not available.

7.57 The data in Tables 65 to 66 indicate that intakes of lead may have increased for 3 to 4 days following the incident. The data indicate that intakes by bottle-fed infants (the most highly exposed group on a body weight basis) from drinking water on 8 to 10 July 1988 may have been up to 8 times higher than the usual levels. There is uncertainty about the water sample taken by a private individual on 7 July 1988 (Table 67). This was analysed by two different laboratories: one reported a concentration below the 1984 Guideline Value and the other reported a concentration of 4 mg lead/l, which is 80 times higher than the Guideline Value. This concentration of lead, if consumed by bottle-fed babies, could have resulted in intakes up to 72 times higher on that day that if the lead concentration was at the 1984 WHO Guideline Value.

7.58 Unlike most other substances, the parameter used to assess the impact of lead on health is not exposure but the blood lead concentration. A number of models exist which estimate the blood lead concentration likely to arise from a given exposure level but these consider the impact of long-term exposures, not of a short-term increased exposure as may have occurred after the Lowermoor incident. No information is available on blood lead concentrations after the incident. This is an additional area of uncertainty in assessing the health implications of the period of potentially increased exposure to lead.

7.59 No acute lead poisoning was reported after the incident. However, any increased exposure of young children or the fetus to lead is undesirable. The highest potential exposures would have been in bottle-fed babies and we have made recommendations in Chapter 9 for monitoring of the cognitive, behavioural and educational development of this age group. We recommend that those who were *in utero* at the time of the incident are included in this monitoring.

7.60 There is limited evidence that individuals exposed to high levels of lead over a long period have a higher risk of cancer than usual but any increased risk of cancer at the small additional exposures to lead which occurred following the incident is likely to be negligible. The cancer incidence and mortality rates for the area which received contaminated water are discussed in Chapter 8 and our recommendations for continued monitoring of the population are discussed in Chapter 9.

Manganese

Exposure

7.61 Manganese oxide deposits form commonly in water mains from oxidation of manganese derived from natural sources or human activity. Flushing of the water mains, which took place after the incident, could have caused the disturbance of these deposits, giving higher than usual concentrations at the tap. The deposits would have been visible as small, black particles.

7.62 The water quality data for manganese for the first month after the incident are limited. Only SWWA water quality data are available as the non-SWWA samples were not analysed for manganese. In this month, 16 of 147 samples (11%) exceeded the 1984 WHO Guideline Value of 0.1 mg manganese/l, compared to 0 of 172 before the incident from 6 January to 5 July 1988. The range of concentrations above the Guideline Value was 0.11 to 1.3 mg/l. Exposures to the highest concentration recorded is compared to the exposure if manganese was present at the Guideline Value in Table 68.

Table 68: Estimated worst-case exposures to manganese from drinking water, 6 July to 4 August 1988 (calculated from SWWA data)

Date	Manganese concentrations (mg/l)	Estimated exposures to manganese (mg/kg bw/day)			
		Adults		Toddlers	Bottle-fed infants
		Calculated		*Calculated*	*Calculated*
		Average	*High*		
9/7/88	1.3	0.03	0.05	0.04	0.20
Calculated intakes based on the 1984 WHO Guideline Value of 0.1 mg/l		0.002	0.004	0.003	0.015

Toxicity

7.63 The EVM, which reviewed manganese in 2003, noted that there was a suggestion of neurotoxic effects from consuming drinking water containing higher concentrations of manganese. The effects reported include muscle pain, fatigue, tremor, memory problems and impaired reflexes. An epidemiological study from Greece showed an increasing effect in cohorts of elderly people with estimated exposures for more than 10 years to up to 0.08 mg/kg bw/day manganese from drinking water (Kondakis *et al*, 1989). However, a study in Germany showed no effect in younger people with estimated exposures for 10-40 years to up to 0.07 mg/kg bw/day manganese from drinking water (Vieregge *et al*, 1995*)*. The EVM commented that these studies had limitations, in that neither provided data on water consumption or manganese intake from the diet. It also noted that the effect level in Kondakis *et al* (1989) is apparently lower than occupational exposure levels not associated with adverse effects. The authors considered that this may be due to the increased sensitivity of the ageing brain to manganese. The EVM estimated that the acceptable total manganese intakes were 12.2 mg/day for the general population (0.20 mg/kg bw/day), based on the NOAEL in a study by Vieregge et al (1995) and a dietary intake of 8.2 mg/day, and 8.7 mg/day for older people (0.15 mg/kg bw/day), based on the NOAEL in the Kondakis *et al* (1989) study and the same dietary intake. It should be noted that most of the manganese in drinking water after flushing the system would have been in the form of insoluble particles of manganese dioxide, and absorption of manganese from these particles would be low (Roels *et al*, 1997).

Discussion

7.64 For comparison with the estimated intakes given above, Table 69 gives an estimate of the usual intakes of manganese which might be consumed daily by adults, toddlers and infants from the diet and from tap water and potential intakes from dietary supplements.

Table 69: Usual intakes of manganese from food and water and potential intakes from dietary supplements (mg/kg bw/day)

Source	Intakes of manganese (mg/kg bw/day)					
	Adults		Toddlers		Bottle-fed infants	
	Mean	*High level*	*Mean*	*High level*	*Milk-based infant formula*	*Soy-based infant formula*
Food[a]	0.07	0.12	0.17	0.31	0.18	NA
Water[b]	0.002	0.004	0.003	NA	0.015	0.015
Supplements[c]	0.17	0.17	—	—	—	—

a: Adults and toddlers: estimated dietary exposures from the 2006 Total Diet Study (Rose *et al*, 2010).
Infants: mean intake by 24 U.S. babies at 3 months (Stastny *et al*, 1984).
b: Calculated intakes based on the 1984 WHO Guideline Value of 0.1mg/l.
c: Maximum exposures (see paragraph 6.131)
NA: Not available
—: Not applicable

7.65 From the figures in Tables 68 and Table 69, consumption of water with the highest concentration of manganese could have resulted in a daily intake on a body weight basis of up to 55% higher in adults, 28% higher in toddlers and 90% higher in bottle-fed infants receiving a milk-based formula than if they were consuming water containing the 1984 WHO Guideline Value for manganese.

7.66 For adults, total estimated exposures to manganese on 9 July 1988 (when the highest concentrations were recorded in drinking water) would not have exceeded the EVM's estimated acceptable total intake for the general population of 0.2 mg manganese/kg bw/day. On the basis of current evidence, it is not anticipated that the period of increased exposure to manganese would have caused, or would be expected to cause, delayed or persistent harm to health in adults.

7.67 For toddlers, high level consumers of food would have exceeded the EVM's estimated acceptable total intake both before and after the incident. However, on the basis of current evidence, it is not anticipated that the sporadic high concentrations of manganese in the water after the incident would not have caused, or would be expected to cause, increased delayed or persistent harm to health in toddlers.

7.68 For bottle-fed infants receiving a milk-based formula, the EVM's estimated acceptable total intake for the general population would have been exceeded on those occasions when the concentration of manganese in water exceeded 0.13 mg/l. Thirteen samples exceeded this concentration. On the basis of current evidence, it is not anticipated that these sporadic high concentrations of manganese would have caused, or would be expected to cause, delayed or persistent harm to health in infants, but we have made recommendations in Chapter 9 for the monitoring of the cognitive, intellectual and educational development of this age group.

Iron

Exposure

7.69 Iron oxide deposits often form in water mains. Flushing of the water mains, as occurred after the incident, could have caused the disturbance of these deposits, resulting in higher than usual concentrations at the tap.

7.70 The water quality data for iron for the first month after the incident are limited. Only SWWA water quality data are available as the samples from other sources were not analysed for iron. In the first month after the incident, 10 of 147 samples (7%) exceeded the 1984 WHO Guideline Value of 0.3 mg iron/l, compared with 2 out of 172 (1%) before the incident. The highest concentration recorded was 9.5 mg/l on 9 July 1988. Table 70 compares the estimated exposures at this concentration to those estimated if iron was present at the Guideline Value.

Table 70: Worst-case estimated exposures to iron from drinking water, 6 July to 4 August 1988 (calculated from SWWA data)

Date	**Iron concentrations (mg/l)**	**Estimated exposures to iron (mg/kg bw/day)**			
		Adults		**Toddlers**	**Bottle-fed infants**
		Calculated		*Calculated*	*Calculated*
		Average	*High*		
9/7/88	9.5	0.18	0.38	0.33	1.43
Calculated intakes based on the 1984 WHO Guideline Value of 0.3 mg/l		0.006	0.012	0.01	0.045

Toxicity

7.71 In general, the body regulates the level of iron by controlling the amount absorbed from food and drink according to iron status. Severe chronic iron toxicity usually occurs only in individuals with certain genetic disorders or hereditary anaemias. Acute iron toxicity can occur, causing nausea, diarrhoea and vomiting, but usually at a dose some 20 times higher than the maximum calculated daily exposures in Table 70.

Discussion

7.72 For comparison with the estimated intakes given above, Table 71 gives an estimate of the usual intakes of iron which might be consumed daily by adults, toddlers and infants from the diet and from tap water and potential exposures from dietary supplements.

Table 71: Usual intakes of iron from food and water and potential intakes from dietary supplements (mg/kg bw/day)

Source	Intakes of iron (mg/kg bw/day)					
	Adults		Toddlers		Bottle-fed infants	
	Mean	*High level*	*Mean*	*High level*	*Milk-based infant formula*	*Soy-based infant formula*
Food	0.21[a] 0.17[b]	NA NA	0.43[c]	NA	0.31[d]	NA
Water[e]	0.006	0.012	0.01	NA	0.045	0.045
Supplements[f]	1.0	1.0	—	—	—	—

a: Adult men: estimated dietary exposures from the 2008/9 National Diet and Nutrition Survey (Food Standards Agency, 2010).
b: Adult women, as above.
c: Toddlers, as above.
d: From Richmond *et al*, 1993.
e: Calculated intakes based on the 1984 WHO Guideline Value of 0.1 mg/l.
f: Maximum exposures e.g. during pregnancy (EVM, 2003)
NA: Not available
—: Not applicable

7.73 From the figures in Tables 70 and Table 71, consumption of water with the highest concentrations of iron could have resulted in a daily intake on a body weight basis up to 159% higher in men, 202% higher in women, 97% higher in toddlers and 390% higher in bottle-fed infants receiving a milk-based infant formula than if they were consuming water containing the 1984 Guideline Value for iron. However, because of the homeostatic control of iron by the body, we do not consider that the sporadic increases in the concentration of iron in drinking water after the Lowermoor incident will have had any adverse health consequences.

Sulphate

7.74 None of the drinking water samples taken by SWWA or by South West Water Ltd. contained sulphate concentrations in excess of the pre-1989 WHO Guideline Value of 400 mg/l. Although SWWA did not start analysing for sulphate until 2 days after the incident, it can be calculated that the concentration of sulphate would exceed 400 mg/l only when the concentration of the aluminium exceeded 75 mg/l. The SWWA data show that this happened on one occasion; on 7 July 1988 when a concentration of 109 mg aluminium/l was measured at Boscastle Service Reservoir. The equivalent concentration of sulphate would have been 581 mg/l.

7.75 Two samples taken by private individuals on 6 and 7 July 1988 contained 2,200 and 4,500 mg sulphate/l, respectively. Water containing these concentrations of sulphate is likely to have had a noticable taste. Water containing these concentrations of sulphate can cause abdominal pain, diarrhoea and secondary dehydration. However, we have found no evidence in the literature of delayed or persistent harm to health.

Acidity

7.76 pH values recorded in water during the first four weeks after the contamination incident frequently lay outside the guideline range of 6.5 to 8.5 recommended by WHO in 1984. In the few days after the incident, the water samples were often acid, with a minimum value of 3.9. Later, the pH frequently exceeded 8.5, with a maximum value of 10.2.

7.77 Water of very low (acid) or high (alkaline) pH can cause irritation to the eyes, skin and mucous membranes, and gastrointestinal irritation. Cases of skin irritation and sore throat were reported to us as symptoms experienced by individuals soon after the incident. However, such effects are usually reported to occur at a pH below 4 whereas the pH of contaminated water after the incident was rarely this low. Figure 36 compares the acidity of a number of commonly consumed drinks and foods with that of the most acidic sample of water reported (which had a pH value of approximately 3.5). This indicates that many common foods are more acidic but are not reported to cause skin irritation or sore throat.

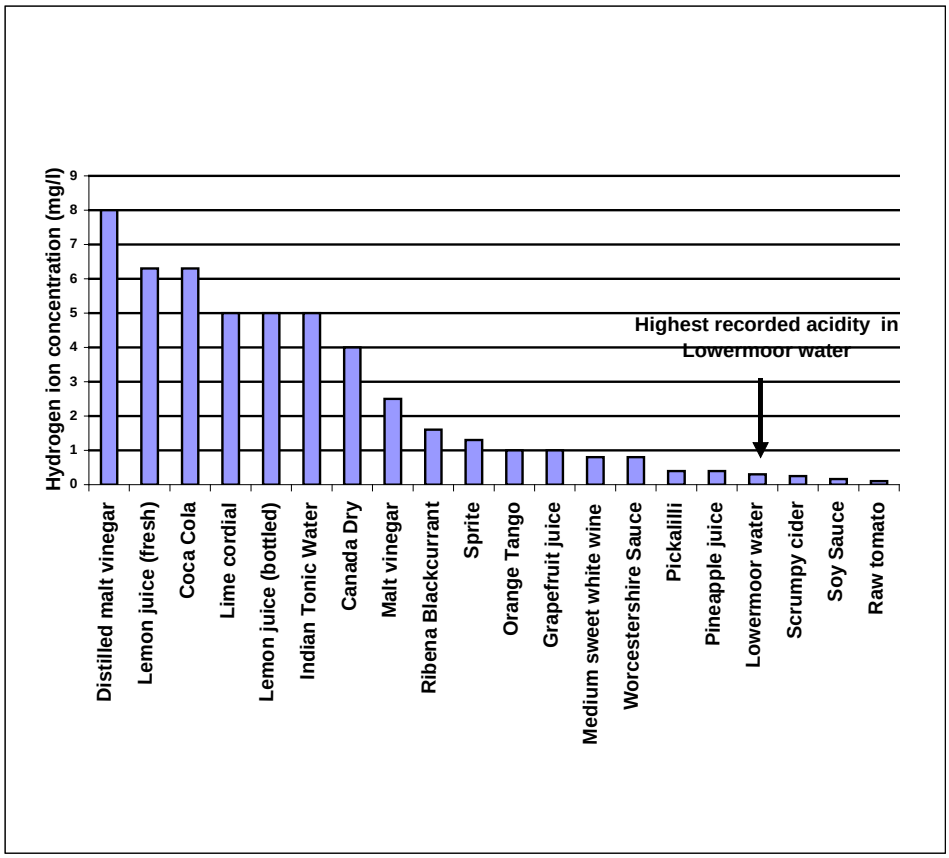


Figure 36: Acidity of some common consumables and of the most acidic sample of Lowermoor water (this shows acidity as concentration of hydrogen ion present and not as pH of the liquid) (Cross, 2004)

Uranium

7.78 In the absence of water quality data on uranium after the incident, we are unable to assess whether concentrations in drinking water were higher than before the incident or to estimate likely exposures. Thus we cannot make a risk assessment based on chemical toxicity.

7.79 In 1996, the independent advisory committee, the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Enviroment was asked for advice on the specific issue of a connection between uranium in sludge and the 3 leukaemia cases in Camelford. The Committee sought a view from the then National Radiological Protection Board (NRPB) with respect to the potential radiological hazards associated with drinking water which might have transiently contained increased amounts of uranium. The NRPB noted that it was not possible to estimate the likely levels of uranium in drinking water from the published data on levels of uranium residue in a steel pipe. Radiation levels in water from the Lowermoor reservoir measured routinely between 1989 and 1995 consistently fell below half the values at which further analysis is recommended by the World Health Organization. From the information available, the NRPB concluded that levels of uranium in water from the Lowermoor reservoir were most unlikely to present a significant radiation dose or subsequent risk to health (Committee on Carcinogenicity, 1998).

Additive or synergistic effects of contaminants

7.80 We have considered the possibility that the combination of metals to which individuals who drank contaminated water were exposed after the incident may have had additive or synergistic effects. We consider that there may have been an additive effect of those contaminants with the potential to cause adverse gastrointestinal effects. This may have led to an unpleasant, acute gastrointestinal response among those who drank the water, even when the concentration of individual contaminants alone was not high enough to cause such a response.

7.81 We evaluated data from *in vivo* scientific studies which examined toxic and other biological interactions of these metals when ingested to investigate the possibility that combinations of the metal contaminants discussed above may have had additive or synergistic chronic effects (see Chapter 6). Metals were considered in pairwise combinations, focussing on aluminium, as this was the main contaminant. Studies which investigated all potential interactions were included. Some studies had evaluated the consequences of high exposures for short periods of time, whilst others had investigated exposure to high or lower exposures for longer periods of time. There were few studies investigating combinations of more than two metals.

7.82 A number of studies showed interactions between the metals. The mechanisms for this are not always clear. It may be due to competition for uptake from the gut or for binding sites on transport proteins. In the studies reviewed, several combinations of

metals showed inhibitory interactions but these findings were not always consistent. The biological significance of these effects had not always been demonstrated. Few data were identified which suggested toxic effects due to combinations of increased exposures to two or more of the metals of concern. Those studies which did show effects had administered high doses of metals, which substantially exceeded the maximum estimated exposures given above, for periods of several weeks or months.

7.83 In Chapter 5 we reviewed studies from Ward (1989 and 2002) and Howard (1993) which reported raised aluminium and copper concentrations, and lowered zinc and iron concentrations in hair, nail and body fluid samples from Camelford residents and holidaymakers who reported drinking the contaminated water (see paragraphs 5.166 to 5.172). The concentrations and duration of exposure in this incident to aluminium and copper after the contamination incident would not have been sufficient to cause low body iron and zinc content (see Chapter 6, paragraphs 6.168-6.169 and 6.172).

7.84 On the basis of the available data, we have not found any evidence which would indicate delayed or persistent harm to health from the combination of metals which occurred as a result of the Lowermoor incident.

Key Points

1. This chapter discusses the implications for health of the estimated exposures to the contaminants after the incident, in the context of the toxicity data in the scientific literature. There are a large number of uncertainties involved in this assessment, including less than ideal data on water quality and exposure and limitations in the scientific database on the contaminants. Theoretical worst-case exposures have been calculated for adults, toddlers and bottle-fed infants. These are **worst-case estimates** of exposure to the contaminants and do not take account of the fact that the poor palatability of the most highly contaminated water may have deterred individuals from consuming it. Estimated worst-case exposures are given on a body weight basis i.e. the potential exposure for each age group is divided by the mean body weight for that age group, to enable a comparison with the toxicity data on the contaminants. Exposures to contaminants have been estimated using both water quality data from SWWA and data on concentrations of contaminants in the samples taken by private individuals. Modelled concentrations and exposures have also been used.

2. To put the estimated intakes of the metals from the contaminated water in context, estimates are also provided of the usual intake of each metal from food and tap water and potential intakes from other sources such as food supplements or licensed medicines.

3. For **aluminium**, the No Observed Adverse Effect Level (NOAEL) for functional neurotoxic effects on the brain identified in Chapter 6 was used to calculate Margins of Exposure for the three age groups before and after the incident. It should be borne in mind, when interpreting this information, that some individuals may experience increased sensitivity, for example, because of higher than usual absorption of aluminium and impaired kidney function. The Margins of Exposure were calculated by dividing the

NOAEL by the daily total intake calculated for each age group. Immediately after the incident, the estimated Margins of Exposure are very low, whether exposure estimates are based on water quality data from SWWA, on water quality data for samples taken by private individuals, or on the modelled data. The exposure estimates rise to the usual level within one month of the incident. Taking into account the fact that there was a low Margin of Exposure for a short period only whereas the NOAEL was derived from studies entailing 90 days exposure to aluminium, on the basis of current evidence, it is unlikely for adults and toddlers that the period of increased exposure to aluminium would have caused, or would be expected to cause, delayed or persistent harm to health. For infants, it is unlikely that the period of increased exposure to aluminium would have caused, or be expected to cause, delayed or persistent harm to health. However, because there was a short period of time in which the MoE appeared to be very low and infants have been identified as likely to be the most susceptible group, we consider that the possibility of delayed or persistent harm to health should be explored further in this group. Consumption of the contaminated water by pregnant women may have led to exposure of the developing fetus. Although the period of exposure to increased levels of aluminium was low, we consider that the possibility of delayed or persistent harm to health should be explored further in this group also.

4. In the case of **coppe**r, we conclude that the increased concentrations of copper in the first week or thereabouts after the incident probably contributed to symptoms such as nausea, vomiting and/or diarrhoea. However, we would not anticipate any delayed or persistent effects of copper from intakes at this time because of the homeostatic control of copper balance in man.

5. In the case of **zinc**, we conclude that the occasional high concentrations of zinc which occurred after the incident may have contributed to acute, adverse gastrointestinal symptoms. However, it can be concluded from the current evidence that exposures to zinc were not high enough nor sustained enough to cause, or be expected to cause, delayed or persistent harm to health.

6. The intake of **lead** may have increased for 3 to 4 days following the incident, although the upper magnitude of the increase is not known because of uncertainty about the concentration of lead in one of the water samples taken by a private individual. Moreover, it is difficult to assess the impact on health of a short-term increased exposure to lead in the absence of information on blood lead concentrations. No acute lead poisoning was reported after the incident. However, any additional exposure of young children to lead is undesirable and we again consider that the possibility of delayed or persistent harm to health should be explored further in those who were bottle-fed infants at the time of the incident, as these were potentially the most highly exposed group. We recommend that those who were *in utero* at the time of the incident are included in this monitoring.

7. Inorganic lead compounds have been classified by the International Agency for Research on Cancer (IARC) as “probably carcinogenic in humans”. However, the evidence for carcinogenicity comes from situations with high, sustained exposure to lead

and any increased risk of cancer at small additional exposures to lead, such as may have occurred after this incident, is likely to be negligible. Our recommendations in relation to continued monitoring of the population are given in Chapter 9.

8. In the case of **manganese**, we note that most of the manganese in drinking water after flushing of the system would have been in the form of insoluble particles of manganese dioxide and absorption of manganese from these particles would be low. For adults, the estimates indicate that the total exposure to manganese after the incident would not have exceeded the EVM's recommended acceptable total intake for the general population of 0.2 mg manganese/kg bw/day. On the basis of current evidence, it could be concluded that the sporadic high concentrations of manganese which occurred after the incident would not have caused, or be expected to cause, delayed or persistent harm to health in adults. For toddlers, high level consumers of food would have exceeded the EVM's recommended acceptable total intake both before and after the incident. On the basis of current evidence, it could be concluded that these sporadic high concentrations of manganese would not have caused, or be expected to cause, increased delayed or persistent harm to health in this age group.

9. Bottle-fed babies receiving a milk-based infant formula could have exceeded the EVM's recommended acceptable total intake for manganese on sporadic occasions after the incident. On the basis of current evidence, it could be concluded that these sporadic high concentrations of manganese would not have caused, or be expected to cause, delayed or persistent harm to health in infants, but we have made recommendations in Chapter 9 for the monitoring of the cognitive, intellectual and educational development of this age group.

10. We conclude that, because of the homeostatic control of **iron** by the body, the sporadic increases in the concentrations of this metal in drinking water after the Lowermoor incident would not have caused, or be expected to cause, any adverse health consequences.

11. We note that the sporadic high concentrations of **sulphate** recorded could have caused acute gastrointestinal effects. However, we have found no evidence in the literature of delayed or persistent harm to health from this contaminant.

12. We note that irritation of the skin and mucous membranes, and gastrointestinal irritation can be caused by acid water (water of low pH) and that cases of sore throat and of skin irritation were reported to us as symptoms experienced by individuals soon after the incident. Such effects are usually reported to occur at a pH lower than that recorded after the Lowermoor incident. Moreover, many common foods have a pH lower than that recorded after the incident but are not reported to cause skin irritation or sore throat. This implies that the cases of skin irritation and sore throat reported to us cannot be attributed simply to the acidity of the water.

13. We have considered the possibility that the combination of metals in the contaminated water may have had additive or more than additive (synergistic) effects.

We conclude that there may have been an additive effect of those contaminants with the potential to cause adverse gastrointestinal effects and that this may have led to an unpleasant, acute gastrointestinal response among those who drank the water, even when the concentration of individual contaminants alone was not high enough to cause such a response. However, on the basis of the available data in the scientific literature, we have not found any evidence which would indicate delayed or persistent harm to health from the combination of metals which occurred as a result of the Lowermoor incident.

14. There are no water quality data on uranium following the incident and so it is not possible to comment on whether concentrations in drinking water were higher than before the incident, to estimate exposures or to advise on the risk to health from its chemical toxicity. In 1996, the then National Radiological Protection Board (NRPB) was asked for advice on the potential radiological hazards associated with drinking water which might have transiently contained increased amounts of uranium. The NRPB noted that it was not possible to estimate the likely levels of uranium in drinking water from the published data on levels of uranium residue in a steel pipe but, from the information available, it concluded that levels of uranium in water from the Lowermoor reservoir were most unlikely to present a significant risk to health.

Chapter 8 Evaluation of the health effects reported by individuals following the Lowermoor pollution incident

Introduction

8.1 The terms of reference of our investigation are:

> ***"To advise on whether the exposure to chemicals resulting from the 1988 Lowermoor water pollution incident has caused, or is expected to cause, delayed or persistent harm to human health; and***
>
> ***"To advise whether the existing programme of monitoring and research into the human health effects of the incident should be augmented and, if so, to make recommendations."***

8.2 In this chapter we continue to address the first of these terms of reference, and consider both the immediate and the long-term and persistent health effects of the incident. We have examined, carefully and systematically, all the evidence made available to us in order to advise whether the Lowermoor pollution incident "has caused, or is expected to cause, delayed or persistent harm to health". We believe that this report contains the most comprehensive account of the information relating to the Lowermoor pollution incident that is currently available.

8.3 Earlier chapters in this report have explored in detail this information in the context of both the symptoms reported by individuals (or reported in studies of or surveys of the local population) and the current scientific and medical database relating to the chemicals which contaminated the water. In this chapter we consider these different types and categories of evidence together in an evaluation of the implications for human health.

8.4 In the course of our investigation we have discovered a great deal of new information which was not available at the time of the previous investigations (LIHAG, 1989 and 1991). We have pursued each and every new avenue of enquiry exhaustively, whether arising from new submissions to the subgroup or from a need for additional information to complement existing evidence. We have visited Camelford and met individuals from the local population, local health professionals and those concerned with the Lowermoor Water Treatment Works. We have heard, often at first hand, the views of the local population and their health professionals. We have reexamined previous evidence, reviewed new evidence, and commissioned additional work and expert opinion to inform our deliberations. All of these approaches have been invaluable in giving us a perspective from which to assess the incident and its effects and we are grateful to all those who have given time to assist us with this investigation.

8.5 Nevertheless, the data available to us in formulating our recommendations are often sparse, and limited in quality. In addition, the fact that our investigation has been

carried out up to 24 years after the pollution incident occurred has presented problems in several ways: with the location and availability of information, in the construction of models of the delivery of contaminants in the water supply as it was at the time of the incident, and in the different interpretations of events by the local population after the passage of time.

8.6 The establishment of a link between exposure to contaminants and the occurrence of health effects, whether immediate or long-term, requires accurate and representative information about:

- The **exposure** of individuals: how much, when and where, and for how long,
- **Scientific and toxicological data** relating to the known effects of the contaminants to which individuals were exposed.
- Any **symptoms** experienced by individuals at the time, or months or years after the event,
- The **health status** of the population prior to exposure,
- The pattern of **health outcomes** in the population as a whole.

Symptoms experienced at the time and/or some time after the event

8.7 All the reported symptoms and health effects are considered in the context of the evidence relating to potential exposures to the contaminants and their known toxic effects.

8.8 We have identified the symptoms reported as health effects of the incident from five sources:

- Reports to us from individuals in interviews or in writing (paragraphs 5.15 to 5.19, Tables 31 and 32).
- Reports to us from local health professionals of symptoms or potential health effects in patients (paragraphs 5.32 to 5.50).
- The survey of self-reported symptoms by Rowland *et al*, 1990 (paragraphs 5.55 to 5.56).[60]
- Other questionnaire surveys (paragraphs 5.125 to 5.130).
- The report of the North Cornwall Homeopathic Project (Smith, 1992) (paragraph 5.131 to 5.135).
- Neuropsychological studies of individuals from the area receiving contaminated water (paragraphs 5.78 to 5.124).

8.9 The information elicited from advertisement and interview has been most valuable in providing lines of enquiry and we noted that there was a recognisable pattern of symptoms and diagnoses among the individuals who provided personal evidence. However, the information is not sufficient to provide conclusive evidence that the frequency of the symptoms and illnesses reported to us is higher in individuals exposed to

[60] The symptom survey by Rowland *et al* (1990) was carried out shortly after the pollution incident and, therefore, provided information on acute symptoms, not delayed or persistent symptoms

the contaminated water than in those who were not. The reasons for this concerns the way in which data must be collected to provide evidence of a causal link between symptoms and exposure to a contaminant or contaminants. The process of seeking information by advertisement and interview does not constitute the rigorous survey required to provide scientific evidence that exposure to chemicals has resulted in adverse health effects. Such a survey would require a comparison of symptoms in a randomly selected group of people from the population who drank contaminated water following the pollution incident with those in a similar, comparison group from a non-exposed population (controls).

8.10 There are also problems with the neuropsychological studies, as discussed in paragraphs 5.99 to 5.100, 5.112 to 5.115 and 5.123 to 5.124. These include the non random selection of test subjects, lack of appropriate control groups, lack of exposure data and, in some cases, small group sizes.

Health outcomes in the population and scientific data

8.11 We have made an assessment of the likelihood that each of the symptoms, or symptom groups, commonly reported in the sources listed in paragraph 8.8 are related to the chemicals in the contaminated water. To do this, we have used the following scientific data:

- Our assessment in Chapter 7 of data in the scientific literature on the chemicals of concern and estimated calculated or modelled exposures to these chemicals.
- Formal epidemiological studies which compared health outcomes in the population supplied with contaminated water with comparison populations not receiving contaminated water. These studies have investigated:
    1. Pregnancy outcomes (Golding *et al*, 1991) (paragraph 5.57 to 5.58).
    2. The growth of children (Hawkins *et al*, undated) paragraphs 5.59 to 5.60).
    3. Hospital discharge rates (Owen and Miles, 1995) (paragraphs 5.61 to 5.62).
    4. Mortality rates (Owen *et al*, 2002) (paragraphs 5.63 to 5.66).
    5. Cancer incidence and mortality (Owen *et al*, undated) (paragraphs 5.67 to 5.71).
    6. Studies relevant to the Camelford leukaemia cluster (Foster *et al*, 1997 and Alexander, 2002) (paragraphs 5.72 to 5.77).

8.12 As discussed in paragraphs 5.5 and 5.53, exposure assessment was also a problem in interpretation of the results of the epidemiological studies. Most of these have used place of residence as a proxy measure of exposure and they are likely to have suffered to some degree from exposure misclassification. Moreover, these studies are limited by the lack of information about individual exposures, and about contaminant concentrations in individual properties, as discussed above. Other problems with the epidemiological studies are discussed in paragraphs 5.53 to 5.54 and in Appendix 18. These include the fact that they did not include non-residents e.g. holiday-makers; that individuals who had moved out since the pollution incident may have been excluded; and that, in some cases, the design did not adequately adjust for confounding factors.

Health effects

8.13 Our conclusions are presented below and should be considered in the light of the limited evidence available to us and its quality. In some cases we do not find a link between potential exposure and symptoms; in some cases we find insufficient information available to enable a firm conclusion and recommend further investigation and monitoring; and in other cases we find unexplained symptoms with no link to the available evidence on exposure or known effect of the contaminants.

Acute Effects

8.14 We define **acute** adverse health effects arising from a chemical exposure as those health effects which occur up to 14 days after the exposure. These effects may be short-lived, resolving soon after exposure is discontinued, or may develop into chronic symptoms which persist for a period of months or years. We discuss acute effects which occurred shortly after the incident as these show that exposures were sufficient to produce adverse health effects and thus may be important in determining the likelihood of chronic effects.

8.15 The types of acute effects reported by individuals were similar in all the information sources listed in paragraph 8.8. The main types were:

- Nausea, vomiting, diarrhoea and/or abdominal pain (acute gastrointestinal symptoms).
- Mouth, tongue and/or throat ulceration and/or soreness.
- Skin rash and/or irritation.

8.16 As discussed in Chapter 7, three of the chemical contaminants involved in this incident (copper, zinc and sulphate) can cause an acute gastrointestinal response when ingested at high concentrations. The published toxicology data on zinc and sulphate indicate that concentrations after the contamination incident would only rarely have been as high as those reported to cause such an effect. It may be that consumption of a mixture of several such contaminants together resulted in an effect at lower concentrations.

8.17 The monitoring data reported in Chapter 3 indicate that the acidity of the contaminated water, while higher than usual for tap water, was rarely high enough to cause irritation to the mucous membranes and skin. Nevertheless, such effects were reported both by local individuals and by GPs who saw individuals after the incident. We are not able to say what accounted for the cases of skin irritation and sore throat reported to us.

Chronic Effects

8.18 **Chronic** health effects resulting from chemical exposure include *persistent* effects, which occur shortly after the exposure but persist for a period of months or years, and *delayed* effects, which result from the exposure but do not occur immediately (e.g. cancer). The types of chronic symptoms and diseases reported to us most frequently fall into the following categories:

- Neuropsychological effects
- Joint pains and/or swelling
- Effects on nails
- Cancer
- Thyroid disease.

Each of these symptoms or diseases is discussed below. Although acute gastrointestinal symptoms were common after the incident, chronic gastrointestinal symptoms were reported infrequently. Therefore, these are not discussed further.

8.19 Many of the symptoms listed above were also reported in the North Cornwall Homeopathic Project, published in 1992. This report also cited "sensitisation" to tap water as a common finding after the incident and so we discuss this also. Some parents also expressed concern about the subsequent behaviour of children who consumed the contaminated water and that the children's academic performance had suffered as a result of the incident. We discuss this also below.

Neuropsychological effects

8.20 The neuropsychological effects reported to us were: deterioration in memory, depression, word-finding difficulty, personality change, concentration difficulties and coordination problems. Individuals also reported tiredness and/or lethargy. Chronic fatigue, which is a common symptom, reported in more than 20% of people seen in primary care, can be due to neuropsychological causes as well as other illnesses (Chaudhuri and Behan, 2004). Some local health professionals reported seeing individuals complaining of memory problems and tiredness/malaise some months or years after the incident.

8.21 Concern about possible neuropsychological effects also arises because three of the metals to which exposures may have been increased after the incident are potentially neurotoxic i.e. aluminium, lead and manganese. In Chapter 7, we considered the exposures to aluminium, lead and manganese after the incident. For each, after considering both the magnitude and length of likely exposures, we concluded that it is unlikely, on the basis of current evidence, that the increased exposures after the incident by adults and children would have caused, or would be expected to cause, delayed or persistent harm to health. However, we concluded that babies who were bottle-fed at the time of the incident could have been exposed to high concentrations of one or more metals for a short period after the incident and that cognitive, intellectual and educational development should be monitored in this cohort of individuals, now in late adolescence or early adult life. We also consider that, as a precautionary measure, cognitive, intellectual and educational development should be monitored in those who were *in utero* at the time of exposure and in whom potential effects on cognitive and behavioural

development have not previously been investigated. We make recommendations in Chapter 9.

8.22 Among the available epidemiological data, only the study of hospital discharges between 1987 and 1993 (Owen and Miles, 1995) provides relevant information. This study did not report increases in hospital discharge rates for neurological or psychological diseases in the area supplied with contaminated water when compared with the rest of Cornwall.

8.23 Specific studies to test for neuropsychological effects were undertaken on some subjects who received contaminated water, as described in Chapter 5. We sought expert advice on these studies, and on the interpretation of the results, from Professor MR Rugg of the University of California, Irvine, USA. One study indicated that the subjects tested showed an impairment of memory and abnormalities of information processing (McMillan *et al*, 1990, 1993). It reported that there was no correlation between poor test results and ratings of anxiety or depression. In a series of tests at St Lawrence's Hospital, Bodmin, Wilson (1990) reported that 75% of a group of individuals from the area supplied with the contaminated water had significant memory deficit of some kind. A control group showed no significant deficit below the norm for the test. Altmann *et al* (1999) administered a battery of neuropsychological tests to 55 individuals who claimed to have suffered cerebral damage following the pollution incident. We were advised by Professor Rugg that the overall pattern of results reported in this study indicated subtle neuropsychological effects in the individuals tested which were unlikely to be due to a psychological factor such as depression or to intentional bias.

8.24 Unfortunately, it is impossible to determine whether the neurological findings in these studies are due to ingesting contaminated water because of the deficiencies in the design of the studies, as outlined in paragraph 8.10. Nevertheless, Professor Rugg advised us that the results of the study by Altmann *et al* (1999) indicate the need for further work. We have made recommendations for such work in Chapter 9.

Joint pains and/or swelling

8.25 Joint pains and/or swelling were reported frequently to us by members of the public. Some local health professionals who saw patients from the area some months to years after the incident told us that joint and muscle problems were commonly reported symptoms. The study of hospital discharge rates in the 4 years following the incident (Owen and Miles, 1995) found that the rate of discharges for arthropathies and related disorders increased after the incident in men, but not in women, in the area served by the Lowermoor Water Treatment Works compared to the rest of Cornwall.

8.26 Osteomalacia, which has the symptoms of bone softening, bone pain and an increased incidence of spontaneous fractures, has been reported in individuals who consume very large amounts of aluminium (several grams every day) in antacids for several months. However, the doses of aluminium and duration of exposure required to produce osteomalacia are far in excess of the worst-case estimated exposures after the

pollution incident and we do not anticipate that long-term bone disease would occur as a result of consumption of aluminium in the contaminated water. There is no other indication from toxicological data that the contaminants concerned can cause effects on muscles or joints.

8.27 Joint problems are common in the community. More than 7 million adults in the UK (15% of the population) have long-term health problems due to arthritis and related conditions and almost 9 million (19% of the population) visited their GP in the past year with these conditions (Arthritis and Rheumatism Council, December 2004). We conclude that, on the basis of current evidence, the increased exposures to the chemicals resulting from the pollution incident are unlikely to have caused the joint problems reported. Nevertheless, we recognise that many individuals who spoke to us were concerned about joint problems. We have made recommendations for further work in Chapter 9.

Effects on nails

8.28 Of the 54 individuals we interviewed, 11 individuals reported effects on fingernails and toenails e.g. they changed appearance or fell off (known by the medical term "onycholysis"). Such effects were also reported at the time of the incident and 3 patients suffering from onycholysis were examined two years after the incident by a consultant dermatologist (see paragraph 5.30). The consultant reported that onycholysis is not a rare condition and that he would expect to find several cases of mild onycholysis of no known cause and several cases of nail changes due to psoriasis, eczema or trauma in any single GP practice. He did not consider that any further metabolic investigation of the patients' nails was required.

8.29 None of the epidemiological studies provide information on onycholysis and the toxicological data are limited with regard to this endpoint, in that effects on nails are not routinely investigated in animal studies. We have nothing to add to the opinion of the consultant dermatologist referred to above.

Cancer

8.30 A few individuals told us that they, their friends or their relatives had developed cancer since the incident. In addition, in 1995/6, there were three cases of acute leukaemia in children aged between 13 and 14 who attended the same tutor group in Sir James Smith's School in Camelford and who were resident in the area in 1988.

8.31 The toxicological data indicate that lead is the only metal among the contaminants considered to be a potential chemical carcinogen in humans. The data in Chapter 7 indicate that exposures to lead could have been higher than usual approximately 5 days after the incident i.e. for a short period only. Concern has also been expressed about the presence of uranium in residues in a pipe after the incident and whether this could be associated with the cases of leukaemia described above.

8.32 A study of the cancer incidence rates from 1988-1998 in the Lowermoor area (Owen *et al*, undated) found that both the overall cancer incidence rate, and the incidence of leukaemia, in the population who received polluted water was lower in this period than in Cornwall as a whole, in South West England as a whole, and in a comparison population supplied by a different water treatment works (see paragraphs 5.67 to 5.69 and 5.77). Although we have noted limitations in this study, it provides no evidence of an increased overall cancer risk arising from the incident.

8.33 A study was conducted to investigate whether infection could have contributed to the occurrence of a cluster of leukaemia cases in Sir James Smith's School (Alexander, 2002), because infections have been implicated in the aetiology of leukaemia. The author found that the results were consistent with the hypothesis that the incidence of leukaemia could be affected by prior exposure to infectious agents, but that the pollution incident did not cause an increased incidence of infection. Deficiencies have been identified in this study with respect to exposure assessment, potential incompleteness and inaccuracies in the health data and response rate (see Appendix 18).

8.34 The data from the study of cancer incidence and mortality are reassuring and provide no evidence of an increased cancer risk from the incident. We are informed that data on cancer incidence and mortality are available for these cohorts from 1998 to the present day and, therefore, further analyses could be carried out.

Thyroid disease

8.35 Five individuals reported that they had developed thyroid disease since the incident. Both underactive and overactive thyroid conditions (hypothyroidism and hyperthyroidism, respectively) were reported. The nurse who spoke to us also noted in 1992 that a high proportion (7/31) of her patients had thyroid problems (see paragraphs 5.47 to 5.50).

8.36 There is one reference from 2004 which reports that aluminium can lower the concentrations of the thyroid hormone thyroxine (see paragraph 6.75). None of the other contaminants concerned in the Lowermoor incident is reported to have effects on thyroid function. There was no increase in hospital discharges for thyroid disease following the incident (Rowland *et al*, 1995). Thyroid disease is common in the population: in Caucasians, hypothyroidism occurs in 2% of females and in 0.2% of males, and thyrotoxicosis occurs in 2-3% of females and 0.2-0.3% of males (Oxford Textbook of Medicine, 2003). However, we recognise that many individuals remain concerned about a possible link between thyroid disease and the incident. We have made recommendations for further work in Chapter 9.

Sensitivity to tapwater

8.37 In Chapter 5, paragraphs 5.132 to 5.135, we describe the reports of sensitivity to tapwater in the report of the North Cornwall Homeopathic Project. Several individuals who spoke to us also reported that, since the contamination incident, they had become

sensitised to tap water and felt unwell after drinking it. We have noted that this reaction does not seem to be the immune-mediated condition termed "sensitisation" and it has been proposed that it may be a manifestation of the non-immune condition termed "chemical sensitivity". We conclude that it is difficult to assess the potential significance of this process in the context of the Lowermoor incident in view of the lack of firm mechanistic evidence and of robust means of diagnosis. Therefore, at this stage, it is not possible to draw conclusions or make recommendations in relation to these symptoms.

Further testing of individuals

8.38 In a response to the consultation exercise, a physician proposed that certain procedures could be carried out on individuals who had been exposed to the contaminated water and who were suffering from ill health which "should prove efficacious in diagnosing and developing a treatment protocol in the damaged patient." Many of these procedures were carried out in the physician's practice. We are grateful to the correspondent for the response, and for a later letter providing clarification. However, although we sympathise with individuals who are suffering health complaints, it is not our remit to develop a diagnostic or treatment protocol; neither are we required, or have the expertise, to advise on whether any of the procedures recommended by the correspondent would be appropriate within the future research and surveillance programmes we recommend in Chapter 9. To make such recommendations would constrain the specialists who design such programmes. The correspondence is included in the compendium of consultation responses in Appendix 5 of this report and can be consulted as required by these specialists.

Behaviour and academic performance of children

8.39 Some parents told us that the incident had an adverse effect on the behaviour and, in some cases, the academic performance of their children. With regard to academic performance, during our investigation we were also informed that there was a higher proportion of children with a statement of Special Educational Needs (SEN) in North Cornwall than in the rest of Cornwall and that individuals were concerned that this might be related to the pollution incident (see paragraphs 5.146 to 5.155). We obtained the statistics on SEN rates in Cornwall for 1997 to 2001 for Sir James Smith's School, the secondary school likely to have the highest proportion of children from the area with the contaminated water supply, and for other schools in Cornwall. We found that there was no consistent difference in the percentages of children with statements between Sir James Smith's School and other schools in North Cornwall or in Cornwall as a whole. Moreover, advice received from two expert educational psychologists indicated that the determination of children with SEN is influenced by many different factors and no conclusions could be drawn from SEN rates about the long-term impact of the incident on health. We received no information on the behaviour of children after the incident which could be analysed.

Case of severe congophilic angiopathy in a resident of Camelford

8.40 In paragraphs 5.137 to 5.149 we report on a case of severe cerebral amyloid angiopathy in an individual who was resident in Camelford at the time of the contamination incident. The case was the subject of an inquiry by the West Somerset coroner. Analysis of sections of brain from the individual had shown higher than normal concentrations of aluminium, although there was marked variability in the concentrations in the different sections. Samples from the brain of an individual with similar neuropathology, but of unknown aluminium exposure, also showed higher than normal concentrations. The inquiry concluded in March 2012 and the coroner found that "As the deceased was exposed to an excessive amount of aluminium in July 1988 and in the absence of any evidence of any other incident or occasion when she might have ingested an excessive amount of aluminium, the aluminium discharged as a result of the problems at Lowermoor Treatment Works at the beginning of July 1988 give rise to the very real possibility that such aluminium may be a factor in her death." He also found that "However as this would be the first such reported case of severe CAA without associated Alzheimer's pathology in the United Kingdom in someone of this age, the suggestion that aluminium was a causative factor must remain only a slight possibility." We agree that this case is clearly an important observation but there are a number of uncertainties which make it impossible to conclude whether it is causally associated with the contamination incident or not. Nevertheless, we consider that further work is required to follow up this observation and we make recommendations in Chapter 9.

9. Recommendations

Future monitoring and research on health

9.1 Our recommendations for future monitoring and research on health are given below and are set in the context of the uncertainties described in Chapter 7, paras 7.2 to 7.3 and in Table 49. It should be noted that it is not within our terms of reference to carry out this further research. Any research could be commissioned by the Government or other research funding bodies and placed with a research group which has the necessary specialist expertise to carry out that particular study.

Futher studies on the population potentially exposed to the contaminated water

Neuropsychological, developmental and neuropathological investigations

9.2 In Chapter 7 we concluded, on the basis of the scientific literature, that it was unlikely that the short period of increased exposure to aluminium after the incident would have caused delayed or persistent effects in adults or toddlers. However, after receiving expert advice on the results of the neuropsychological studies conducted to date, we consider that further work is indicated. We recommend that further studies are carried out to determine whether consumption of the contaminated water is associated with an increased risk of abnormal neuropsychological status or any different pattern of neuropathology. We do not underestimate the difficulties inherent in these types of study and we recognise that it will be difficult to link any outcomes of the neuropsychological and developmental studies to exposure to the contaminated water so long after the event.

9.3 In Chapter 5 we reported on the case of severe cerebral amyloid angiopathy in an individual who was resident in Camelford at the time of the contamination incident and who was found to have high concentrations of aluminium in the brain *post mortem*. We consider that the observation merits further research. Proposals which were made by our parent committee when they discussed our draft report in December 2004 were for studies:

- to examine whether there is a higher than expected incidence of degenerative brain disease in North Cornwall and, if so, whether there is an association with exposure to the contaminated water,
- to compare the aluminium content of brains and other tissues from a random sample of individuals in North Cornwall with those of individuals showing the same pattern of pathology from elsewhere in the UK.

9.4 In Chapter 7 we concluded it was unlikely that infants who were bottle-fed with formula made up in tap water after the incident would be suffering delayed or persistent harm to health. Nevertheless, because infants as a whole are a vulnerable group and the Margin of Exposure for aluminium for this group was zero/low in the first week or so after the incident, we recommend that investigations be carried out into the cognitive, behavioural and educational development of all children who were under 1 year of age at this time of the incident and of children who were *in utero* at the time of the incident to determine whether exposure to the contaminated water may have adversely affected development.

9.5 We sought expert advice on the design and conduct of suitable studies to address the above research recommendations. In March 2009, representatives of the Subgroup met Professor Carol Brayne from the University of Cambridge, Professor Margaret Esiri of Oxford University and Oxford Radcliffe NHS Trust, and Professor Chris Exley, University of Keele, to discuss suitable designs for studies to address the recommendations for neuropathological investigations outlined above. Recommendations were made for either (1) a long-term study which would compare both the neuropathological status and aluminium concentration in donated brains from individuals in all age groups from different regions of Cornwall or (2) a shorter-term study which would draw up a register of early-onset dementia cases and compare prevalence in the area receiving the contaminated water with that in other parts of Cornwall, possibly supported by investigations of donated brain samples as above. In April 2009, representatives of the Subgroup discussed the design of the neurological study in adults and the developmental study in children with Dr Brian Stollery from the Department of Experimental Psychology at the University of Bristol. It was recommended that the study in adults should compare neurological status in a group of adults who drank the contaminated water with that in a matched reference group. The subjects would undergo an appropriate assessment of pre-morbid IQ and a battery of neuropsychological tests. In the developmental study, a group of individuals *in utero* at the time of the incident, whose mothers drank the water, would undergo a number of tests and their performance would be compared with that of a matched referent group whose mothers did not drink the water. A similar design would be used to assess the development of individuals who were children under one year of age at the time of the incident. The research recommendations arising from these discussions are given in full in Appendix 30.

Analysis of health statistics (cancer including leukaemia; thyroid disease)

9.6 We are informed that data are available from 1998 to the present day for those cohorts which have undergone assessment of cancer incidence and mortality and, therefore, further analyses could be carried out. We consider that the burden of this work should be removed from the local primary care trust and that it should, in future, be carried out by an academic department familiar with the analysis of routine health statistics. If possible, the assessment of the exposed population should be refined to take account of the fact that some areas experienced a higher level of contamination than others. If such a refinement is possible, it could also be applied retrospectively.

Joint pains and/or swelling

9.7 In Chapter 8 we concluded that, on the basis of current evidence, the increased exposures to the chemicals resulting from the pollution incident would not have caused the joint problems reported. However, we recognised that many individuals who spoke to us were concerned about such problems. Routine health statistics cannot be used to monitor the prevalence of these problems. There is a high prevalence of joint pains and/or swelling in the population but we recommend that a study should be carried out to assess whether the prevalence in the population who received contaminated water is higher than normal.

Toxicological studies

9.8 The toxicological data on aluminium, although extensive, are insufficient on which to base a definitive hazard assessment. We note that there is a need for further work on the toxicity of aluminium to assist in the risk assessment of exposure of humans to different aluminium salts, including:

- studies to identify No Observed Adverse Effect Levels for aluminium salts to which humans may be exposed, using both acute and chronic exposure and a range of salts of different bioavailabilities. Specific endpoints to be investigated include neurotoxicity, reproductive toxicity and developmental toxicity.
- mechanistic data on the neurotoxicity of aluminium and of its potential role in neurological disease, including abnormalities of neurodevelopment, and other disorders.
- further investigations of the bioavailability of aluminium in humans, including the extent of and reasons for the reported interindividual variation.
- studies which mimic the exposure conditions experienced by individuals who drank the contaminated water i.e. a short, high initial exposure to aluminium, with a long period of follow-up.

Future management of similar incidents

9.9 Our terms of reference do not require us to make recommendations about the handling of future incidents. There have been a large number of changes since the Lowermoor pollution incident in the contingency arrangements for and the management of any future chemical incidents. These are described in Appendix 31. We welcome these improvements but we have identified a few areas arising from our investigation which we consider may require particular consideration in the management of a future incident. These are as follows:

- it is vital to identify populations which may need to be monitored in any later epidemiological studies as early as possible after the incident. If identification of these populations is delayed, exposed individuals may move out of the area and be lost to follow-up.
- if the exposed population includes a large number of transient residents e.g. holiday makers who are in the area temporarily at the time of the incident, consideration must be given to how to identify this population for inclusion in any future monitoring programme.
- the need for rapid, widespread dissemination of clear and accurate advice should not be underestimated. Individuals should be informed about what has happened, the likely consequences and any action they may need to take as promptly as possible. An information point, such as an enquiry line or drop-in centre, should be set up and should continue to operate for some time after the incident so that individuals can seek advice on new concerns if and when they arise. This could also act as a gathering point for information.
- there needs to be consideration of the effect of contamination upon the intake of chemical species from food when there are either direct or indirect routes for the contamination of food.

References

Note: these references are those referred to in the main body of the report above. Further references can be found in Appendices 21-29.

Aaseth J and Norseth T (1986). In: Handbook of the Toxicology of Metals II. Eds Friberg L, Nordberg GF and Vouk VB. Oxford, Elsevier.

Acheson D (1998). Independent inquiry into inequalities in health, November 26 1998. The Stationery Office, London.

Ackrill P and Day JP (1985). Desferrioxamine in the treatment of aluminum overload. Clinical Nephrology **24**:s94-s97.

Akyol A, Boyvat A and Kundakçi N (2004). Contact sensitivity to aluminum. International Journal of Dermatology **43(12)**: 942.

Alexander F (2002). Childhood health events in relation to the Lowermoor water incident and the Camelford leukaemia cluster. Unpublished report to the Department of Health, dated May 2002.

Alfrey AC, Mishell JM, Burks J, Contiguglia SR, Rudolph H, Lewin E and Holmes JH (1972). Syndrome of dyspraxia and multifocal seizures associated with chronic hemodialysis. Trans Am Soc Artif Intern Organs **18**: 257-261.

Alfrey AC (1980). Aluminium metabolism in uremia. Neurotoxicology **1**: 43-53.

Allen WM (1988). The possible consequences of the Lowermoor Incident on the health and welfare of livestock in the Camelford area. South West Water Authority, Exeter.

Al-Saleh I, Nester M, DeVol E, Shinwari N, Munchari L and Al-Shahria S (2001). Relationships between blood lead concentrations, intelligence, and academic achievement of Saudi Arabia schoolgirls. Int J Hyg Environ Health **204**: 165-174.

Altmann P, Dhanesha U, Hamon C, Cunningham, J, Blair J and Marsh F (1989). Disturbance of cerebral function by aluminium in haemodialysis patients without overt aluminium toxicity. Lancet **2**: 7-12.

Altmann P. The toxic effects of aluminium in haemodialysis patients. London: The University of London, 1991 (MD thesis).

Altmann P, Cunningham, J, Dhanesha U, Ballard M, Thompson J and Marsh F (1999). Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident. British Medical Journal **319**: 807-811 and Data Supplement www.bmj.com/cgi/content/full/319/7213/807/DC1

Alzheimer's Society (2002). Facts about dementia. Aluminium and Alzheimer's disease. http://www.alzheimers.org.uk/Facts_about_dementia/Risk_factors/info_aluminium.htm

Anane R, Bonini M, Grafeille JM and Creppy EE (1995). Bioaccumulation of water soluble aluminium chloride in the hippocampus after transdermal uptake in mice. Archives of Toxicology **69**(8): 568-571.

Anane R, Bonini M and Creppy EE (1997). Transplacental passage of aluminium from pregnant mice to fetus organs after maternal transcutaneous exposure. Human and Experimental Toxicology **16**: 501-504.

Andrasi E, Farkas E, Scheibler H, Reffy A and Bezur L (1995). Al, Zn, Cu, Mn and Fe levels in brain in Alzheimers disease. Archives of Gerontology and Geriatrics **21**(1): 89-97.

Andrasi E, Pali N, Molnar Z and Kosel S (2005). Brain aluminum, magnesium and phosphorus contents of control and Alzheimer-diseased patients. J of Alzheimer's Disease **7:** 273-284.

Andreoli SP, Bergstein JM and Sherrard DJ (1984). Aluminum intoxication from aluminum-containing phosphate binders in children with azotemia not undergoing dialysis. N Engl J Med **310**: 1079-84.

Anghileri LJ, Maincent P and Thouvenot P (1994). Long-term oral administration of aluminum in mice. Aluminum distribution in tissues and effects on calcium metabolism. Annals of Clinical & Laboratory Science **24**(1): 22-6.

Araya M, Chen B, Klevay LM, Strain JJ, Johnson L, Robson P, Shi W, Nielsen F, Zhu H, Olivares M, Pizarro F and Haber L (2003). Confirmation of an acute no-observed-adverse-effect and low-observed-adverse-effect level for copper in bottled drinking water in a multi-site international study. Regulatory Toxicology and Pharmacology **38**: 389-399.

Arnich N, Cunat L, Lanhers M-C and Burnel D (2004). Comparative *in situ* study of the intestinal absorption of aluminum, manganese, nickel and lead in rats. Biol Trace Element Research **99**: 157-171.

Arthritis and Rheumatism Council. Factfile – arthritis at a glance. www.arc.org.uk/about_arthritis/astats.htm.

Aslam, Davis K, Pejović-Milić A and Chettle DR (2009). Noninvasive aluminium in human bone: Preliminary human study and improved system performance. J Inorg Biochem **103**: 1585-1590.

ATSDR (Agency for Toxic Substances and Disease Registry) (2001). Hair analysis panel discussion: exploring the state of the science. Summary report. Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry) (2000). Toxicological Profile for Manganese. Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry) (2008). Toxicological profile for aluminium (updated). Atlanta, GA

Audit Commission (2002). Statutory assessment and statements of SEN: in need of review? Audit Commission, London.

Banks WA and Kastin AJ (1985). Aluminum alters the permeability of the blood-brain barrier to some non-peptides. Neuropharmacology **24**: 407-412.

Barker J, Templar J, King SJ, Day JP, Bradbury MWB, Radunovic A, Ueda F, Raja K, Lilley JS and Drumm PV (1997). AMS measurements to study uptake and distribution of Al-26 in mice and the role of the transferrin receptor in aluminium absorption mechanisms. Nuclear Instruments and Methods in Physics Research. Section B. Beam Interactions with Materials and Atoms **123**(1-4): 275-278.

Bataineh H, Al-Hamood MH and Elbetieha AM (1998). Assessment of aggression, sexual behavior and fertility in adult male rat following long-term ingestion of four industrial metals salts. Human and Experimental Toxicology **17**: 570-576.

Bayer TA, Schafer S, Simons A, Kemmling A, Kamer T, Tepest R, Eckert A, Schussel K, Eikenberg O, Sturchler-Pierrat C, Abramowski D, Staufenbiel M and Multhaup G (2003). Dietary Cu stabilizes brain superoxide dismutase 1 activity and reduces amyloid A^{β} production in APP23 transgenic mice. Proc Nat Ac Sciences **100**: 14187-14192.

Becaria A, Lahiri DK, Bondy SC, Chen D, Hamadeh A, Li H, Taylor R and Campbell A (2006). Aluminum and copper in drinking water enhance inflammatory or oxidative events specifically in the brain. J Neuroimmunol. **176**(1-2):16-23.

Belles M, Sanchez DJ, Gomez M, Corbiella J and Domingo JL (1998). Silicon reduces aluminum accumulation in rats: Relevance to the aluminum hypothesis of Alzheimer disease. Alzheimer Disease and Associated Disorders **12**(2): 83-87.

Bernuzzi V, Desor D and Lehr PR (1989). Effects of postnatal aluminium lactate exposure on neuromotor maturation in the rat. Bull Environ Contam Toxicol **42**:451-455.

Bernuzzi V, Desor D and Lehr PR (1989a). Developmental alterations in offspring of female rats orally intoxicated by aluminium chloride or lactate during gestation. Teratology **40**:21-27.

Beveridge SJ, Boettcher B, Walker WR and Whitehouse MW (1984). Biodistribution of ^{64}Cu in rats after topical application of two lipophilic anti-inflammatory Cu (II) formulations. Agents Actions **14**:291-295.

Bezwoda W, Charlton R, Bothwell T and Mayet F (1978). The importance of gastric hydrochloric acid in the absorption of nonheme food iron. Journal of Laboratory and Clinical Medicine **92**: 108-116.

Bielby G (1988). The Lowermoor Environmental Report, November 1988. National Rivers Authority.

Bjertness E, Candy JM, Torvik A, Ince P, McArthur F, Taylor GA, Johansen SW, Alexander J, Gronnesby JK, Bakketeig LS and Edwardson JA(1996). Content of brain aluminum is not elevated in Alzheimer disease. Alzheimer Disease and Associated Disorders **10**(3): 171-174.

Black & Veatch Ltd (2004). Lowermoor water quality modelling report. Unpublished report for the Department of Health Committee of Toxicity Subgroup to consider the health effects of the Lowermoor water pollution incident (LSG).

Black & Veatch Ltd (2006). Lowermoor water quality modelling report (Phase 2). Unpublished report for the Department of Health Committee of Toxicity Subgroup to consider the health effects of the Lowermoor water pollution incident (LSG).

Blennow K, de Leon MJ and Zetterberg H (2006). Alzheimer's disease. Lancet **368**: 387-403.

Bondy SC and Truong A (1999). Potentiation of beta-folding of beta-amyloid peptide 25-35 by aluminum salts. Neuroscience Letters **267**(1): 25-28.

Brandt M. Personal communication to Ms F Pollitt, 29 April 2004.

Borak J and Wise JP Snr (1998). Does aluminum exposure of pregnant animals lead to accumulation in mothers or their offspring? Teratology **57**: 127-139.

Border EA, Cantrell AC and Kilroe-Smith TA (1976). The *in vitro* effect of zinc on the inhibition of human delta-aminolevulinic acid dehydratase by lead. Br J Ind Med **33**: 85-87.

Bowdler NC, Beasley DS, Fritze EC, Goulette AM, Hatto JD, Hession J, Ostman DL, Rugg DL and Schmittdiel CJ (1979). Behavioral effects of aluminum ingestion on animal and human subjects. Pharmacology, Biochemistry & Behavior **10**(4): 505-12.

Brenner SR and KW Yoon (1994). Aluminum toxicity in rat hippocampal neurons. Neuroscience Letters **178**(2): 260-262.

Bridges JW (1989). Establishment of public nuisance arising from the Lowermoor incident. Unpublished report from the Robens Institute, Surrey.

British National Formulary (2003) Number 22. British Medical Association and the Pharmaceutical Press, London.

Brock C, Curry H, Hanna C, Knipfer M and Taylor L (1985). Adverse effects of iron supplementation: a comparative trial of a wax matrix iron preparation and conventional ferrous sulphate tablets. Clinical Therapeutics **7**(5):568-573.

BSDA (2003) British Soft Drinks Association website, accessed August 2003. www.britishsoftdrinks.com/htm/qa/AdditivesIngredients/acids/acids.htm

Buckingham C. Personal communication to G Kowalczyk, 17 May 2002.

Buckingham C. Personal communication to the Lowermoor Subgroup, 16 July 2002.

Buckingham C. Personal communication to Ms F Pollitt, June 2003.

Buckingham C. Personal communication to Ms F Pollitt, 2 July 2003.

Buckingham C. Personal communication to Ms F Pollitt, July 2003.

Buckingham C. Personal communication to Ms F Pollitt, 27 January 2004.

Buckingham C. Personal communication to Ms F Pollitt, 17 September 2004.

Buckingham C. Personal communication to Ms F Pollitt, 20 May 2005.

Buckingham C. Personal communication to Ms F Pollitt, 5 October 2005.

Bulaj ZJ, Griffen LM, Jorde LB, Edwards CQ and Kushner JP (1996). Clinical and biochemical abnormalities in people heterozygous for hemochromatosis. New England Journal of Medicine **335**:1799-1805.

Campbell A, Prasad KN and Bondy SC (1999). Aluminum-induced oxidative events in cell lines: Glioma are more responsive than neuroblastoma. Free Radical Biology & Medicine **26**(9-10): 1166-1171.

Campbell A, Smith MA, Sayre LM, Bondy SC and Perry G (2001). Mechanisms by which metals promote events connected to neurodegenerative diseases. Brain Research Bulletin **55**(2): 125-132.

Canavan MM, Cobb S, Srinker C (1934). Chronic manganese poisoning. Archives of Neurology and Psychiatry **32**:501-12.

Candy JM, McArthur FK, Oakley AE, Taylor GA, Chen C, Mountfort SA, Thompson JE, Chalker PR, Bishop HE, Beyreuther K, Perry G, Ward MK, Martyn CK and Edwardson JA (1992). Aluminum Accumulation in Relation to Senile Plaque and Neurofibrillary Tangle Formation in the Brains of Patients with Renal Failure. Journal of the Neurological Sciences **107**(2): 210-218.

Canfield RL, Henderson CRJ, Cory-Slechta DA, Cox C, Jusko TA and Lamphear BP (2003). Intellectual impairment in children with blood lead concentrations below 10ug per decilitre. New Engl J Med **348**: 1517-1526.

Cannata JB and Diaz Lopez JB (1991a). Insights into the complex aluminium and iron relationship. Nephrol Dial Transplant **6**: 605-607.

Cannata JB, Fernandez-Soto I, Fernandez-Menendez MJ, Fernandez-Martin JL, McGregor SJ, Brock JH and Halls D (1991b). Role of iron metabolism in absorption and cellular uptake of aluminum. Kidney Int **39**: 799-803.

Chaudhuri A and Behan PO (2004). Fatigue in neurological disorders. Lancet **363**: 978-988.

Cherroret G, Bernuzzi V, Desor D, Hutin MF, Burnel D and Lehr PR (1992). Effects of postnatal aluminum exposure on choline acetyltransferase activity and learning abilities in the rat. Neurotoxicology & Teratology **14**(4): 259-64.

Christen Y (2000). Oxidative stress and Alzheimer disease. American Journal of Clinical Nutrition **71**(2): 621S-629S.

Clayton RM, Sedowofia SKA, Rankin JM and Manning A (1992). Long-term effects of aluminium on the fetal mouse brain. Life Sci **51**: 1921-1928.

Clinical Pediatrics and Child Health. Eds. D Candy, G Davies, E Ross, p. 368. W Saunders, Edinburgh 2001.

Coburn JW, Mischel MG, Goodman WG and Salusky IB (1991). Calcium citrate markedly enhances aluminium absorption from aluminium hydroxide. Am J Kidney Dis **17**(6): 708-711.

Cochran M, Coates J and Beoh S (1984). The competitive equilibrium between aluminium and ferric ions for the binding sites of transferrin. FEBS Lett. **176**: 129-132.

Colvill S. Personal communication to Mr G Kowalczyk, 19 March 2002

Colvill S. Personal communication to Mr G Kowalczyk, 7 May 2002.

Committee on Carcinogenicity (1997). Annual Report of the Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Department of Health, London.

Committee on Toxicity (2000). Committees on: Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Annual Report 1999. Department of Health, London

Committee on Toxicity (2001). Committees on: Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Annual Report 2000. Department of Health/ Food Standards Agency, London

Committee on Toxicity (2006). COT statement on uranium levels in water used to constitute infant formula. http://www.foodstandards.gov.uk/multimedia/pdfs/cotstatementuranium06.pdf

Committee on Toxicity (2007). Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency. http://www.food.gov.uk/multimedia/pdfs/vutreportmarch2007.pdf

Committee on Toxicity (2008). COT Statement on the 2006 UK Total Diet Study of Metals and Other Elements. http://cot.food.gov.uk/pdfs/cotstatementtds200808.pdf Accessed 24 September 2012.

Committee on Toxicity (2008). Statement on Idiopathic Environmental Intolerance (IEI). http://cot.food.gov.uk/pdfs/cotstatementiei201103.pdf Accessed 24 September 2012.

Committee on Toxicity (2011). Statement on Idiopathic Environmental Intolerance (IEI). COT Statement 2011/03. http://cot.food.gov.uk/pdfs/cotstatementiei201103.pdf Accessed 19 November 2012.

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (1999). Organophosphates. Department of Health, London.

Connor DJ, Jope RS and Harrell LE (1988). Chronic, oral aluminum administration to rats: cognition and cholinergic parameters. Pharmacology, Biochemistry and Behavior **31**(2): 467-74.

Constable N. Personal communication to Professor F Woods, 20 February 2002.

Cook DG, Fahn S, Brait KA (1974). Chronic manganese intoxication. Archives of Neurology **30**:59-64.

Coplin, M., Schuette, S, Leichtmann, G and Lashner, B (1991). Tolerability of iron: A comparison of bisglycino iron II and ferrous sulphate. Clinical Therapeutics **13**:606-612.

Coutts I. The Bodmin water clinics. Published in: Proceedings of the Conference held on 3rd February 1990 at the Postgraduate Centre, Royal Cornwall Hospital (Treliske), Truro.

Crapper McLachlan DR, Dam TV, Farnell BJ and Lewis PN (1983). Aluminum inhibition of ADP-ribosylation *in vivo* and *in vitro*. Neurobehav Toxicol Teratol **5**: 645-647.

Cross D. The history of some private sector samples taken during the week of the Lowermoor Incident. Unpublished report dated 29 December 1988, submitted to the Lowermoor Subgroup.

Cross D (1990a). Letter to Mr F Gilbert dated 23 December 1990, submitted to the Lowermoor Subgroup in May 2004.

Cross D (1990b). The politics of poisoning - The Camelford aluminium sulphate scandal. The Ecologist 20(6):228-233.

Cross D. Copper contamination in the public water of North Cornwall following the 1988 Lowermoor incident. Unpublished report dated 11 April 2002, submitted to the Lowermoor Subgroup.

Cross D. Personal communication to the Lowermoor Subgroup, May 2002.

Cross D. Personal communication to the Lowermoor Subgroup, 9 February 2004.

Cross D. Personal communication to the Lowermoor Subgroup, 10 March 2004

Cross D. Personal communication to Ms F Pollitt, 22 November 2004.

Cross D. Personal communication to the Lowermoor Subgroup, 4 May 2007.

Crowther Clayton Associates. Report on the estimated consumption of aluminium, sulphate, copper, zinc, lead and pH following the contamination incident on 6th July 1988. Unpublished report no. 91/2737 for South West Water Ltd.

Crowther Clayton Associates. A description of the Lowermoor water treatement works and part of the distribution system. Unpublished report dated 1st December 1993.

Crowther Clayton Associates. Report to the Lowermoor Subgroup on concentrations of contaminants in the Lowermoor water distribution system. Unpublished report dated 12 June 2003.

Crowther Clayton Associates. Personal communication to Ms F Pollitt, 21 November 2003.

Davies-Jones A. Personal communication to Ms F Pollitt, 10 January 2006.

Davis CD, Wolf TL and Greger JL (1992). Varying levels of manganese and iron affect absorption and gut endogenous losses of manganese by rats. J Nutrition **122**:1300-1308.

Davis K, Aslam, Pejović-Milić A and Chettle DR (2008). *In vivo* measurement of bone aluminium in population living in southern Ontario, Canada. Med Phys **35**(11): 5115-5123.

Deloncle R and Guillard O (1990). Mechanism of Alzheimer's disease: arguments for a neurotransmitter-aluminium complex implication. Neurochem. Res. **15**: 1239-1245.

Deng ZY, Coudray C, Gouzoux L, Mazur A, Rayssiguier Y and Pepin D (2000). Effects of acute and chronic coingestion of $AlCl_3$ with citrate or polyphenolic acids on tissue retention and distribution of aluminum in rats. Biological Trace Element Research **76**(3): 245-256.

Dent CE and Winter CS (1974). Osteomalacia due to phosphate depletion from excessive aluminum hydroxide ingestion. BMJ **1**: 551.

Department of Environment, Food and Rural Affairs (Defra) News Release 99/01, 14 August 2001.

Department of Health (1991). Iron. In: Dietary reference values for food, energy and nutrients for the United Kingdom: Report of the panel on dietary reference values of the committee on medical aspects of food policy. HMSO, London, pp. 161-166.

Derogatis LR (1977). Symptom checklist-90-R: administration, scoring and procedure manual. Baltimore Clinical Psychometrics Research.

Deugnier Y, Turlin B and Loreal O (1998). Iron and neoplasia. Journal of Hepatology **28** (Suppl.1), 21-25.

DFE (1994). Code of Practice on the identification and assessment of special educational needs. Department for Education. Central Office for Information.

DHSS Cicular HRC(74)13. Local Authority Circular 10/74. Reorganisation of local government, Reorganisation of the National Health Service: Transitional arrangements and organisation and development of services: Environmental health. London, 1974.

Domingo JL, Llobet JM, Gomez M, Tomas JM and Corbella J. (1987a) Nutritional and toxicological effects of short term ingestion of aluminium by the rat. Res Commun Chem Pathol Pharmacol **56**: 409-419.

Domingo JL, Paternain JL, Llobet JM and Corbella J (1987b) The effects of aluminium ingestion on reproduction and postnatal survival in rats. Life Sci **4**1: 1127-1131.

Domingo JL, Paternain JL, Llobet JM and Corbella J (1987c) Effects of oral aluminium administration on perinatal and postnatal development in rats. Res Commun Chem Pathol Pharmacol 57: 129-132.

Domingo JL, Paternain JL, Llobet JM and Corbella J (1989a). The developmental toxicity of uranium in mice. Toxicology **55(1-2)**: 143-152.

Domingo JL, Ortega A , Paternain JL, and Corbella J (1989b). Evaluation of the perinatal and postnatal effects of uranium in mice upon oral administration. Archives of Environmental Health **44(6)**: 395-398.

Domingo JL, Gomez M, Bosque MA and Corbella J (1989c). Lack of teratogenicity of aluminium hydroxide in mice. Life Sci **45(3)**: 243-247.

Domingo JL, Gomez M, Llobet JM, and Richart C (1991). Effect of ascorbic acid on gastrointestinal aluminium absorption. Lancet **338**: 1467.

Domingo JL, Llorens J, Sanchez DJ, Gomez M, Llobet JM and Corbella J (1996). Age-related effects of aluminum ingestion on brain aluminum accumulation and behavior in rats. Life Sciences **58**(17): 1387-1395.

Donald JM, Golub MS, Gershwin ME, Keen CL (1989). Neurobehavioral effects in offspring of mice given excess aluminium in diet during gestation and lactation. Neurotox and Teratol **11**: 345-351.

Drinking Water Inspectorate. Personal communication to Ms A Gowers, July 2003.

Drinking Water Inspectorate. Personal communication to Ms F Pollitt, September 2003.

Drinking Water Inspectorate. Personal communication to Ms F Pollitt, 16 March 2005.

Drueke TB, Jouhanneau P, Bande H, Lacour B, Yiou F and Raisbeck G (1997). Effects of silicon, citrate and the fasting state on the intestinal absorption of aluminium in rats. Clinical Science **92**(1): 63-67.

Dutkiewicz B, Dutkiewicz T and Milkowska G (1979). The effect of mixed exposure to lead and zinc on ALA level in urine. Int Arch Occup Environ Health **42**: 341-348.

Dyer SH. Personal communication to Ms F Pollitt, April 2008.

Eastwood JB, Levin GE, Pazianaz M, Taylor AP, Denton J and Freemont AJ (1990). Aluminium deposition in bone after contamination of drinking water supply. Lancet **336:** 462-464.

EC (1998) Council Directive 98/83/EC of 3 November 1998 on the Quality of Water Intended for Human Consumption. Official Journal of the European Communities, L 330/32 EN, 5.12.98

Ecelbarger CA and Greger JL (1991). Dietary citrate and kidney function affect aluminum, zinc and iron utilization in rats. J Nutrition **121**: 1755-1762.

Edwardson JA, Candy JM, Ince PG, McArthur FK, Morris CM, Oakley AE, Taylor GA and Bjertness E (1992). Aluminium accumulation, beta-amyloid deposition and neurofibrillary changes in the central nervous system. Ciba Foundation Symposium **169**: 165-79.

El-Demerdash FM (2004). Antioxidant effect of vitamin E and selenium on lipid peroxidation, enzyme activities and biochemical parameters in rats exposed to aluminium. Journal of Trace Elements in Medicine and Biology **18**: 113-121.

Ellis HA, McCarthy JH and Herrinton J (1979). Bone aluminium in haemodialysed patients and in rats injected with aluminium chloride: relationship to impaired bone mineralisation. J Clin Pathol **32**: 832-844.

El-Rahman SSA (2003). Neuropathology of aluminum toxicity in rats (glutamate and GABA impairment). Pharmacological Research **47**: 189-194.

Eriksson F, Johansson SV, Mellstedt H, Stranberg O and Wester PO (1974). Iron intoxication in two adult patients. Acta Medica Scandinavica 196(3): 231-6.

European Food Safety Authority (2011). On the evaluation of a new study related to the bioavailability of aluminium in food. EFSA Journal 9(5): 2157. www.efsa.europa.eu/efsajournal.

Exley C (1999). A molecular mechanism of aluminium-induced Alzheimer's disease? J Inorg Biochem **76**(2): 133-140.

Exley C and Esiri MM (2006). Severe cerebral congophilic angiopathy coincident with increased brain aluminium in a resident of Camelford, Cornwall, UK. J Neurol Neurosurg Psychiatry **77**(7): 877-9.

Exley C, House E, Polwart A and Esiri MM (2012). Brain burdens of aluminum, iron and copper and their relationships with amyloid-β pathology in 60 human brains. Journal of Alzheimer's Disease. **31**:1-6.

Expert Group on Vitamins and Minerals (2002). Review of iron – revised version. http://www.food.gov.uk/multimedia/pdfs/evm-01-12r.pdf

Expert Group on Vitamins and Minerals. Safe Upper Levels for Vitamins and Minerals. Food Standards Agency, London, May 2003.

Fairlie DP and Whitehouse MW (1991). Transdermal delivery of inorganic complexes as metal drugs or nutritional supplements. Drug Des Discov **8**:83-102.

Farina M, Rotta LN, Soares FA, Jardim F, Jacques R, Souza DO and Rocha JB (2005). Hematological changes in rats chronically exposed to oral aluminum. Toxicology, **209**(1):29-37.

Fasman GD, Perczel A and Moore CD (1995). Solubilization of beta-amyloid-(1-42)-peptide: reversing the beta-sheet conformation induced by aluminum with silicates. Proceedings of the National Academy of Sciences of the United States of America **92**(2): 369-71.

Fattoretti P, Bertoni-Freddari C, Balietti M, Mocchegiani E, Scancar J, Zambenedetti P and Zatta P (2003). The effect of chronic aluminum(III) administration on the nervous system of aged rats: Clues to understand its suggested role in Alzheimer's disease. Journal of Alzheimer's Disease **5**(6):437-44.

FDA 2003. Antiperspirant drug products for over-the counter human use; final monograph. US Department of Health and Human Services. Food and Drug Administration. Federal Register **68**(110): 34273 -34293. June 9, 2003.

Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A, Dormishian F, Domingo R Jr, Ellis MC, Fullan A, Hinton LM, Jones NL, Kimmel BE, Kronmal GS, Lauer P, Lee VK, Loeb DB, Mapa FA, McClelland E, Meyer NC, Mintier GA, Moeller N, Moore T, Morikang E, Wolff RK *et al*. (1996). A novel MHC class I-gene is mutated in patients with hereditary hemochromatosis. Nature Genetics **13**:399-408.

Fisch RO, Deinar, AS, Disch LJ and Krivit W (1975). Potential toxicity of iron overload in successive generations of rats. American Journal of Clinical Nutrition **8**:136-139.

Flarend R, Bin T, Elmore D and Hem SL (2001). A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminium-26. Food and Chemical Toxicology **39**(2): 163-168.

Flaten TP, Glattre E, Vista A and Søreide O (1991). Mortality from dementia among gastro-duodenal ulcer patients. J Epidemiol Community Health **45**: 203-206.

Flendrig JA, Kruis H and Das HA (1976). Aluminium and dialysis dementia. Lancet **1**: 1235.

Florence AL, Gauthier A, Ward RJ and Crichton RR (1995). Influence of hydroxypyridones and desferrioxamine on the mobilization of aluminium from tissues of aluminium-loaded rats. Neurodegeneration **4**(4): 449-455.

Food and Agriculture Organisation. Requirements of Vitamin A, iron, folate and B12. Report of a joint FAO/WHO consultation (Food and Nutrition Series No. 23). Rome: FAO, 1988.

Food Standards Agency (2004). FSIS Information Sheet 48/4. www.foodstandards.gov.uk/multimedia.pdfs/fsismetals.pdf

Food Standards Agency (2004a). FSIS Information Sheet 56/04. http://www.food.gov.uk/science/surveillance/fsis2004branch/fsis5604

Food Standards Agency (2010). National Diet Nutrition Survey: Headlines from year 1 (2008/9). Tables. http://tna.europarchive.org/20110116113217/tna.europarchive.org/20110116113217/http://www.food.gov.uk/science/dietarysurveys/ndnsdocuments/ndns0809year1. Accessed 14 September 2012.

Forster DP, Newens AJ, Kay DWK and Edwardson JA (1995). Risk factors in clinically diagnosed presenile dementia of the alzheimer type - a case-control study in northern England. Journal of Epidemiology & Community Health **49**(3): 253-258.

Foster AM. Personal communication to Ms A Gowers, 6 February 2004.

Frederickson N. Personal communication to G Kowalczyk, 28 August 2002.

Freemont AJ (1990). Published in: Proceedings of the Conference held on 3rd February 1990 at the Postgraduate Centre, Royal Cornwall Hospital (Treliske), Truro.

Fullerton A, Andersen JR, Hoelgaard A and Menne T (1986). Permeation of nickel salts through human skin *in vitro*. Contact Dermatitis **15**(3): 173-177.

Freeland-Graves JH, Friedman BJ, Han W-H, Shorey R and Young R (1980). Alterations in zinc absorption and salivary sediment after a lacto-ovo-vegetarian diet. Am J Clin Nutr **33**: 1757-1766.

Gajdusek DC and Salazar AM (1982). Amyotrophic lateral sclerosis and parkinsonian syndromes in high incidence among the Auyu and Jakai people of West New Guinea. Neurology **32**: 107-126.

Gandolfi L, Stella MP, Zambenedetti P and Zatta P (1998). Aluminum alters intracellular calcium homeostasis *in vitro*. Biochimica et Biophysica Acta Molecular Basis of Disease **28**(3): 315-320.

Ganrot PO (1986). Metabolism and possible health effects of aluminum. Environ Health Perspect **65**:363-441.

Garruto RM, Fukatsu R, Yanagihara R, Gajdusek DC, Hook G and Fiori CE (1984). Imaging of calcium and aluminum in neurofibrillary tangle-bearing neurons in parkinsonism-dementia of Guam. Proc Natl Acad Sci USA **81**: 1875-1879.

Gersh I. Personal communication to G Kowalczyk, 30 August 2002.

Gherardi RK, Coquet M, Cherin P, Belec L, Moretto P, Dreyfus PA, Pellissier JF, Chariot P and Authier FJ (2001). Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle. Brain **124** (Pt 9): 1821-31.

Gilman AP, Villeneuve DC, Secours VE, Yagminas AP, Tracy BL, Quinn JM, Valli VE, Willes RJ and Moss MA (1998). Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. Toxicological Sciences **41**: 117-128.

Gitelman HJ (1995). Aluminum exposure and excretion. Science of the Total Environment **163**(1-3): 129-35.

Glynn AW, Sparen A, Danielsson LG, Sundstrom B and Jorhem L (1999). Concentration-dependent absorption of aluminum in rats exposed to labile aluminum in drinking water. Journal of Toxicology and Environmental Health **56**(7): 501-512.

Goering PL and Fowler BA (1987). Metal constitution of metallothionein influences inhibition of delta-aminolaevulinic acid deydratase (porphobilinogen synthase) by lead. Biochem J **245**: 339-345.

Golding J, Rowland A, Greenwood R and Lunt P (1991). Aluminium sulphate in water in north Cornwall and outcome of pregnancy. British Medical Journal **302**: 1175-1175

Golub MS and Germann SL (2001). Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior of Swiss Webster mice. Neurotoxicology & Teratology **23**(4): 365-372.

Gomez M, Sanchez DJ, Llobet JM, Corbella J and Domingo JL (1997). Concentrations of some essential elements in the brain of aluminum-exposed rats in relation to the age of exposure. Archives of Gerontology and Geriatrics **24**(3): 287-294.

Gomez M, Esparza JL , Domingo JL, Singh PK and Jones MM (1999). Chelation therapy in aluminum-loaded rats: influence of age. Toxicology **137**(3): 161-168.

Gonda Z and Lehotzky K (1996). Effect of prenatal aluminium lactate exposure on conditioned taste aversion and passive avoidance task in the rat. Journal of Applied Toxicology **16**(6): 529-32.

Gorsky JE, Dietz AA, Spencer H and Osis D (1979). Metabolic balance of

aluminum studied in six men. Clinical Chemistry **25**(10): 1739-43.

Gould D. Personal communication to the Lowermoor Subgroup, 12 November 2003.

Grasbeck R, Kuovonen I, Lundberg M and Tenhunen R (1979). An intestinal receptor for heme. Scandinavian Journal of Haematology **23:** 5-9.

Graske A, Thuvander A, Johannisson A, Gadhasson I, Schutz A, Festin R and Wicklund Glynn A (2000). Influence of aluminium on the immune system – an experimental study on volunteers. BioMetals **13**: 123-133.

Graveling RA, Pilkington A, George JPK, Butler MP and Tannahill SN (1999). A review of multiple chemical sensitivity. Occup Environ Med **56**: 73-85.

Greger JL and Radzanowski (1995). Tissue aluminium distribution in growing, mature and ageing rats: relationship to changes in gut, kidney and bone metabolism. Food Chemical Toxicology **33(10)**: 867-875.

Greger JL (1999). Nutrition versus toxicology of manganese in humans: Evaluation of potential biomarkers. Neurotoxicology **20**: 205-212.

Greger JL and Baier MJ (1983). Effect of dietary aluminum on mineral metabolism of adult males. Am J Clin Nutr **38**: 411-419.

Greger JL and Sutherland JE (1997). Aluminum exposure and metabolism. Critical Reviews in Clinical Laboratory Sciences **34**(5): 439-474.

Hammond CR. 'The Elements' in Handbook of Chemistry and Physics, 78th edition, 1997-1998. Ed. David R Lide. CRC Press.

Harkness JE and Wagner JE (1989). The Biology and Medicine of Rabbits and Rodents, 3rd Edition. Lea and Febiger, Philadelphia.

Harrington CR, Wischik CM, McArthur FK, Taylor GA, Edwardson JA and Candy JM(1994). Alzheimers-disease-like changes in tan protein processing – association with aluminium accumulation in brains of renal dialysis patients. Lancet **343**(8904): 993-997.

Haugen AA, Becher G and Bjørseth A (1983). Biological monitoring of occupational exposure to polycyclic aromatic hydrocarbons (PAHs) in an aluminium plant (Abstract). Eur J Cancer Clin Oncol **19**: 1287.

Hawke C. Personal communication to Ms S Fisher, December 2005.

Hawkins N, Greenwood R, Golding J and Harris J (undated). Excess aluminium sulphate in drinking water in North Cornwall and growth of children. Unpublished report submitted to the Department of Health, 1999.

Health Protection Agency (2005). What is uranium? http://www.hpa.org.uk/radiation/faq/du/du1.htm

Hebert CD, Elwell MR, Travlos GS, Fitz CJ and Bucher JR (1993). Subchronic toxicity of cupric sulphate administered in drinking water and feed to rats and mice. Fund Appl Toxicol **21**: 461-475.

Henderson LM, Brewer GJ, Dressman JB, Swidan Sahar Z, DuRoss DJ, Adair CH, Barnett JL, Berardi RR (1995). Effect of intragastric pH on the absorption of oral zinc acetate and zinc oxide in young healthy volunteers. J Parent Ent Nutr **19**: 393-397.

Henderson LM, Brewer GJ, Dressman JB, Swidan Sahar Z, DuRoss DJ, Adair CH, Barnett JL, Berardi RR (1996). Use of zinc tolerance test and 24-hour urinary zinc content to assess oral zinc absorption. J Am Coll Nutr **15**: 79-83.

Hicks JS, Hackett DS and Sprague GL (1987). Toxicity and aluminium concentration in bone following dietary administration of two sodium aluminium phosphate formulations in rats. Food Chem Toxicol **25**(7): 533-538.

Hirata-Koizumi M, Fujii S, Ono A, Hirose A, Imai T, Ogawa K, Ema M and Nishikawa A (2011a). Two-generation reproductive toxicity study of aluminium sulfate in rats. Reprod Toxicol **31:** 219–230.

Hirata-Koizumi M et al. (2011b). Evaluation of the reproductive and developmental toxicity of aluminium ammonium sulfate in a two-generation study in rats. Food Chem Toxicol **49**(9): 1948–1959.

House E, Esiri M, Forster G, Ince PG and Exley C (2012). Aluminium, iron and copper in human brain tissues donated to the Medical Research Councils's Cognitive Function and Aging Study. Metallomics **4**(1): 56-65.

Howard P (1993). The possible effects of aluminium pollution of a water supply on health. MSc thesis. University of Reading. August 1993.

Huang Y, Herman MM, Liu J, Katsetos CD, Wills MR and Savory J (1997). Neurofibrillary lesions in experimental aluminum-induced encephalopathy and alzheimers-disease share immunoreactivity for amyloid precursor protein, a-beta, alpha(1)-antichymotrypsin and ubiquitin-protein conjugates. Brain Research **771**(2): 213-220.

Huebers HA, Brittenham GM, Csiba E and Finch CA (1986). Absorption of carbonyl iron. Journal of Laboratory and Clinical Medicine **108**: 473-478

Hurley LS, Keen CL (1987). Manganese. In: Mertz W, ed. Trace Elements in Human and Animal Nutrition, Vol. 1. 5th ed. New York, NY, Academic Press, pp. 185-223.

Hutton CW. Personal communication to Dr K John, 4 September 1990. Submitted to the Subgroup by Mr D Cross.

IARC (2004). Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 87: Inorganic and organic lead compounds. 10–17 February 2004. International Agency for Research on Cancer, Lyon, France.

Institute for Environment and Health. Recent developments in low-level lead exposure and intellectual impairment in children. Unpublished report for Department of Environment, Food and Rural Affairs, October 2003.

IOM (2001) Institute of Medicine. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. A report of the Panel on Micronutrients, Subcommittees on Upper Reference levels of Nutrients and of Interpretation and use of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board, Institute of Medicine. Washington, DC: National Academy Press.

IPCS (International Programme on Chemical Safety). Environmental Health Criteria no.165. Inorganic lead. WHO, Geneva, 1995.

IPCS (International Programme on Chemical Safety). Environmental Health Criteria no.194. Aluminium. WHO, Geneva, 1997.

IPCS (International Programme on Chemical Safety). Environmental Health Criteria no.200. Copper. WHO, Geneva, 1998.

IPCS (International Programme on Chemical Safety). Environmental Health Criteria no.221. Zinc. WHO, Geneva, 2001.

Ittel TH, Kinzel S, Ortmanns A and Sieberth HG (1996). Effect of iron status on the intestinal absorption of aluminum: a reappraisal. Kidney International **50**: 1879-1888.

Jansson E (2001). Aluminum exposure and Alzheimer's disease. Journal of Alzheimer's Disease **3**: 541-549.

Jellinger KA and Mitter-Ferstl E (2003). The impact of cerebrovascular lesions in Alzheimer disease--a comparative autopsy study. J Neurol.**250(9)**:1050-5.

JECFA (2007). Safety Evaluation of certain food additives and contaminants. WHO Food Additives Series 58. WHO, Geneva.
http://jecfa.ilsi.org/evaluation.cfm?chemical=ALUMINIUM&keyword=ALUMINIUM

JECFA (2012). Safety Evaluation of certain food additives and contaminants. WHO Food Additives Series 65. WHO, Geneva. http://whqlibdoc.who.int/publications/2012/9789241660655_eng.pdf

Jouhanneau P, Raisbeck GM, Yiou F, Lacour B, Banide H and Drueke TB (1997). Gastrointestinal absorption, tissue retention, and urinary excretion of dietary aluminum in rats determined by using Al-26. Clinical Chemistry **43**: 1023-1028.

Karlberg AT, Boman A and Wahlberg JE (1983). Copper - a rare sensitiser. Contact Dermatitis **9**(2): 134-139.

Kasa P, Szerdahelyi P and Wisniewski HM (1995). Lack of topographical relationship between sites of aluminum deposition and senile plaques in the Alzheimers disease brain. Acta Neuropathologica **90**(5): 526-531.

Katz AC, Frank DW, Sauerhoff MW, Zwicker GM and Freudenthal RI (1984). A 6-month dietary toxicity study of acidic sodium aluminium phosphate in beagle dogs. Food Chem Toxicol **22**: 7-9.

Kaur A and Gill KD (2005). Disruption of neuronal calcium homeostasis after chronic aluminium toxicity in rats. Basic and Clinical Pharmacology and Toxicology **96**: 118-122.

Kaur A, Joshi K, Minz RW and Gill KD (2006). Neurofilament phosphorylation and disruption: A possible mechanism of chronic aluminium toxicity in Wistar rats. Toxicology **219**: 1-10.

Keen CL, Bell JG, Lönnerdal B (1986). The effect of age on manganese uptake and retention from milk and infant formulas in rats. Journal of Nutrition **116**:395-402.

Khan A, Ashcroft AE, Higenell V, Korchazhkina OV and Exley C (2005). Metals accelerate the formation and direct the structure of amyloid fibrils of NAC. J Inorg Biochem **99(9)**: 1920-1927.

Kohila T, Parkkonen E and Tähti H (2004). Evaluation of the effects of aluminium, ethanol and their combination on rat brain synaptosomal integral proteins *in vitro* and after 90-day oral exposure. Arch Toxicol **78**: 276-282.

Komura, J and Sakamoto, M. (1992). Effects of manganese forms on biogenic amines in the brain and behavioural alterations in the mouse: long term administration of several manganese compounds. Environmental Research **57:** 34-44.

KondakisXG, Makris N, Leotsinidis M, Prinou M, Papapetropoulos T (1989). Possible health effects of high manganese concentration in drinking water. Archives of Environmental Health **44**: 175-178.

Kontur PJ, Fechter LD (1988). Brain regional manganese levels and monoamine metabolism in manganese-treated neonatal rats. Neurotoxicology and Teratology **10**: 295-303.

Krasovskii GN, Vasukovich LY and Chariev OG (1979). Experimental study of biological effects of lead and aluminum following oral administration. Environ. Health Perspectives **30**: 47-51.

Kumar S (1998). Biphasic effect of aluminium on cholinergic enzyme of rat brain. Neuroscience Letters **248**:121-123.

Kutcha, B (1982). Experiments and ultrastructural investigations on the mouse embryo during early teratogen-sensitive stages. Acta Anatomica **113**: 218-225.

Laskey JW, Rehnberg GL, Hein JF and Carter SD (1982). Effects of chronic manganese (Mn_2O_4) exposure on selected reproductive parameters in rats. Journal of Toxicology and Environmental Health **9**: 677-687.

Lawrence J. Report of an Inquiry into an incident at Lowermoor water treatment works of South West Water Authority. Unpublished report dated 12 August 1988.

Lecyk M (1980). Toxicity of $CuSO_4$ in mice embryonic development. Zool Pol **28**:101-105.

Li X, Hu C, Zhu Y, Sun H, Li Y, Zhang Z. Effects of Aluminum Exposure on Bone Mineral Density, Mineral, and Trace Elements in Rats. Biol Trace Elem Res. 2010 epub, ahead of print

Litov RE, Sickles VS, Chan GM, Springer MA and Cordana A (1989). Plasma aluminum measurements in term infants fed human milk or a soy-based infant formula. Pediatrics **84**(6):1105 – 1107.

Litovitz, TL, Clark LR and Soloway RA (1994). 1993 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. American Journal of Emergency Medicine **12**:546-584

Liu JY and Stemmer KL (1990a). Interaction of aluminum with zinc and copper and its effects on the pituitary-testicular axis: a histological study. Biomedical and Environmental Sciences **3**:1-10.

Liu JY and Stemmer KL (1990b). Interaction between aluminum and zinc or copper and its effects on the pituitary-testicular axis. II Testicular enzyme and serum gonadotropin assay. Biomedical & Environmental Sciences **3**: 11-19.

Liu J, Nordberg GF and Frech W (1996). Aluminium accumulation in some tissues

of rats with compromised kidney function induced by cadmium-metallothionein. Pharmacology and Toxicology **78**(5): 289-295.

Lowermoor Incident Health Advisory Group. Water pollution at Lowermoor, North Cornwall. July, 1989.

Lowermoor Incident Health Advisory Group. Water pollution at Lowermoor, North Cornwall. Second report. November, 1991: HMSO.

Lund EK, Wharf SG, Fairweather-Tait SJ and Johnson IT (1998). Increases in the concentrations of available iron in response to dietary iron supplementation are associated with changes in crypt cell proliferation in rat large intestine. Journal of Nutrition **128**(2):175-179.

Luo Y, Nie J, Gong QH, Lu YF, Wu Q, Shi JS (2007). Protective effects of icariin against learning and memory deficits induced by aluminium in rats. Clin Exp Pharmacol Physiol **34**(8): 792-5.

Mameli O, Caria MA, Melis P, Zambenedetti P, Ramila M and Zatta P (2006). Effect of aluminium consumption on the vestibulo-ocular reflex. Metab Brain Dis **21**: 89-107.

Manna GK and Das RK (1972). Chromosome aberration in mice induced by aluminum chloride. Nucleus **15**: 180-186.

Marlowe M, Stellern J, Errera J and Moon C (1985). Main and interaction effects of metal pollutants on visual-motor performance. Arch Environ Health **40**: 221-225.

Martyn CN, Barker DJ, Osmond C, Harris EC, Edwardson JA and Lacey RF (1989). Geographical relation between Alzheimer's disease and aluminum in drinking water. Lancet **1**(8629): 59-62.

Martyn CN, Coggon DN, Inskip H, Lacey RF and Young WF (1997). Aluminum concentrations in drinking water and risk of Alzheimer's disease. Epidemiology **8**(3): 281-6.

Mattson MP (2004). Pathways towards and away from Alzheimer’s disease. Nature **450**: 631-639.

Matyja E. (2000). Aluminum enhances glutamate-mediated neurotoxicity in organotypic cultures of rat hippocampus. Folia Neuropathologica **38**(2): 47-53.

McArdle J. Personal communication to Dr D Miles, 3 March 2005.

McDermott JR, Smith A, Ward MK, Parkinson IS and Kerr DNS (1978). Brain-aluminium concentration in dialysis encephalopathy. Lancet **1**: 901-904.

McLachlan DRC, Dalton AJ, Kruck TPA, Bell MY, Smith WL, Kalow W and Andrews DF (1991). Intramuscular Desferrioxamine in Patients with Alzheimers-Disease. Lancet **337**(8753): 1304-1308.

McLachlan DRC, Bergeron MD, Smith JE, Boomer D and Rifat SL (1996). Risk for neuropathologically confirmed alzheimers disease and residual aluminum in municipal drinking water employing weighted residential histories. Neurology **46**(2): 401-405.

McMillan TM. Preliminary neuropsychological findings from a self selected sample following water pollution in Camelford and Environs in the Lowermoor Area of North Cornwall in July 1988. Published in: Proceedings of the Conference held on 3rd February 1990 at the Postgraduate Centre, Royal Cornwall Hospital (Treliske), Truro.

McMillan TM, Dunn G and Colwill SJ (1993). Psychological testing on schoolchildren before and after pollution of drinking water in North Cornwall. J Child Psychol Psychiatry **34**: 1449-1459.

McMillan TM, Freemont AJ, Herzheimer A, Denton J, Taylor AP, Pazianas M, Cummin ARC and Eastwood JB (1993). Camelford water poisoning accident: serial neuropsychological assessments and further observations on bone aluminium. Human & Experimental Toxicology **12**: 37-42.

M.E.L. Research. Tap water consumption in England and Wales: findings from the 1995 national survey. M.E.L. Research Report 9448/01, 1996.

Merryweather-Clarke AT, Pointon JJ, Shearman JD and Robson KJ (1997). Global prevalence of putative haemochromatosis mutations. Journal of Medical Genetics **34**:275-278.

Mikolaenko I, Pletnikova O, Kawas CH, O'Brien R, Resnick SM, Crain B and Troncoso JC (2005). Alpha-synuclein lesions in normal aging, Parkinson disease, and Alzheimer disease: evidence from the Baltimore Longitudinal Study of Aging (BLSA). J Neuropathol Exp Neurol. **64(2)**:156-62..

Miles D. Personal communication to Ms F Pollitt, 29 October 2003.

Miles D. Personal communication to Ms F Pollitt, 14 March 2005.

Ministry of Agriculture, Fisheries and Food. Aluminium in food. Food Surveillance Paper No. 39. 1993: HMSO.

Ministry of Agriculture, Fisheries and Food. Lead, arsenic and other metals in food. Food Surveillance Paper No. 52. 1998a: HMSO.

Ministry of Agriculture, Fisheries and Food. Cadmium, mercury and other metals in food. Food Surveillance Paper No. 53. 1998b: HMSO.

Moore PB, Day JP, Taylor GA, Ferrier IN, Fifield LK and Edwardson JA (2000). Absorption of aluminium-26 in Alzheimer's disease, measured using accelerator mass spectrometry. Dementia & Geriatric Cognitive Disorders **11**(2): 66-69.

Morris A and English J (1998). Copper is unlikely to cause contact allergy. BMJ **316**: 1902-1903.

Moselhy WA, Helmy NA, Abdel-Halim BR, Nabil TM and Abdel-Hamid MI (2012). Role of ginger against the reproductive toxicity of aluminium chloride in albino male rats. Reprod Domest Anim **47**(2): 335-43.

Muller G, Bernuzzi V, Desor D, Hutin MF, Burnel D and Lehr PR (1990). Developmental alterations in offspring of female rats orally intoxicated by aluminum lactate at different gestation periods. Teratology **42**(3):253-61.

Munoz DG and Feldman H (2000). Causes of Alzheimer's disease. Canadian Medical Association Journal **162** (1): 65-72.

Nagy E and Jobst K (1994). The kinetics of aluminium-containing antacid absorption in man. European Journal of Clinical Chemistry & Clinical Biochemistry **32**(3): 119-121.

Neri LC and Hewitt D (1991). Aluminium, Alzheimer' disease, and drinking water. Lancet **338**: 390.

Newman R. Letter to Mr and Mrs Sigmund, transmitted by facsimile, 20 July 2002.

NTP (1993) National Toxicology Program Technical Report no.428. Toxicology and Carginogenesis Studies of Manganese (II) Sulfate Monohydrate in F344/N Rats and B6C3F1 Mice.

Nutrition Reviews (1984). Conditioned copper deficiency due to antacids. Nutr Rev **42**: 319-321.

Office of National Statistics. Special Educational Needs in England, January 2001. ONS Bulletin, Issue No 12/01: November, 2001. The Stationery Office, Norwich.

Ohman LO and Martin RB (1994). Citrate as the main small molecule binding Al^{3+} in serum. Clinical Chemistry **40**(4): 598-601.

Olivares M, Araya M, Pizarro F and Uauy R (2001). Nausea threshold in apparently healthy individuals who drink fluids containing graded concentrations of copper. Regulatory Toxicol and Pharmacol **33**: 271-275.

Ortega A, Domingo JL, Llobet JM, Tomas JM and Paternain JL (1989). Evaluation of the oral toxicity of uranium in a 4-week drinking-water study in rats. Bulletin of Environmental Contamination and Toxicology **42**: 935-941.
Oxford Textbook of Medicine, 4th edition, ed. Warrel *et al*. Chapter 12.4 The thyroid gland and disorders of thyroid function. OUP, 2003.

Owen PJ and Miles DPB (1995). A review of hospital discharge rates in a population around Camelford in North Cornwall up to the fifth anniversary of an episode of aluminium sulphate absorption. J Pub Health Med **17**(2): 200-204.

Owen PJ, Miles DPB, Draper GJ and Vincent IJ (2002). Retrospective study of mortality after a water pollution incident at Lowermoor in North Cornwall. British Medical Journal **324**: 1189.

Owen PJ, Miles DPB, Draper GJ, Vincent TJ and Harling C (undated). A study of cancer incidence and mortality in two cohorts in North Cornwall affected by the Lowermoor pollution incident. Unpublished report submitted to the Lowermoor Subgroup, July 2003.

Owen PJ, personal communication to Ms F Pollitt, 23 March 2005.

Paik SR, Lee JH, Kim DH, Chang CS and Kim J (1997). Aluminum-induced structural alterations of the precursor of the non-A beta component of Alzheimer's disease amyloid. Arch Biochem Biophys **344**: 325-334.

Paternain JL, Domingo JL, Llobet JM and Corbella J (1988). Embryotoxic and teratogenic effects of aluminum nitrate in rats upon oral administration. Teratology **38**: 253-257.

Paternain JL, Domingo JL, Ortega A and Llobet JM (1989). The effects of uranium on reproduction, gestation, and postnatal survival in mice. Ecotoxicology and Environmental Safety **17**: 291-296.

Pejović-Milić A, Byun SH, Comsa DC, McNeill FE, Prestwich WV and Chettle DR (2005). *In vivo* measurement of bone aluminium: recent developments. J Inorg Biochem **99**(9):1899-903.

Perl DP, Gajdusek DC, Garruto RM, Yanagihara RT and Gibbs CJ (1982). Intraneuronal aluminum accumulation in amyotrophic lateral sclerosis and parkinsonism-dementia of Guam. Science **217**: 1053-1055.

Perl DP (2006). Exposure to aluminium and the subsequent development of a disorder with features of Alzheimer's disease. J Neurol Neurosurg Psychiatry **77**(7): 811.

Pettersen JC, Hackett DS and Zwicker GM (1990). Twenty-six week toxicity study with kasal (basic sodium aluminum phosphate) in beagle dogs. Environ Geochem Health **12**: 121-123.

Pevny I and Binzenhofer A (1984). [Contact allergies of the oral mucosa]. Z Hautkr **59(**4): 245-251.

Phinney AL, Drisaldi B, Schmidt SD, Lugowski S, Cronado V, Liang Y, Horne P, Yang J, Sekoulidis J, Coomaraswamy J, Azhnar Chishti M, Cox DW, Mathews PM, Nixon RA, Carlson GA, St George-Hyslop P and Westaway D (2003). *In vivo* reduction of amyloid-$^{\beta}$ by a mutant copper transporter. Proc Nat Ac Sciences **100**: 14193-14198.

Pigeon C, Turlin B, Iancu TC, Leroyer P, Le Lan J, Deugnier Y, Brissot P and Loreal O (1999). Carbonyl-iron supplementation induces hepatic nuclear changes in BALB/CJ male mice. Journal of Hepatology **30**:926-934.

Pineau A, Guillanrd O, Huguet F, Speich M, Gelot S and Boiteau HL (1993). An evaluation of the biological significance of aluminium in plasma and hair of patients on long-term hemodialysis. Eur J Pharmacol **228**(5-6): 263-268.

Pippard MJ (1994). Secondary iron overload. In Brick JH, Halliday JW, Pippard MJ, Powell LW, eds. Iron Metabolism in Health and Disease. Philidelphia: WB Saunders, pp. 271-309.

Pizarro F, Olivares M, Uauy R, Contreras P, Rebelo A and Gidi V (1999). Acute gastrointestinal effects of graded levels of copper in drinking water. Environ Health Perspect **107**: 117-121.

Plato CC, Galasko D, Garruto RM, Plato M, Gamst A, Craig UK, Torres JM and Wiederholt W (2002). ALS and PDC of Guam: forty-year follow-up. Neurology **58**: 765-773.

Platt B, Fiddler G, Riedel G and Henderson Z (2001). Aluminium toxicity in the rat brain: Histochemical and immunocytochemical evidence. Brain Research Bulletin 55(2): 257-267.

Pollitt F. Personal communication to Mr MR Rose, 14 December 2007.

Poirier J, Semple H, Davies J, Lapointe R, DziwenkaM, Hiltz M and Mujibi D (2011). Double-blind, vehicle-controlled randomized twelve-month neurodevelopmental toxicity study of common aluminum salts in the rat. Neuroscience **193**, 338-362.

Ponka P (1999). Cellular iron metabolism. Kidney International **55** (Suppl. 69), S2-S11.

Poon WT, Ling SC, Chan AY and Mak TWL (2004). Use of hair analysis in the diagnosis of heavy metal poisoning: report of three cases. Hong Kong Med J **10**(3): 197-200.

Powell JJ and Thompson RPH (1993). The chemistry of aluminium in the intestinal lumen and its uptake and absorption. Proc Nutrit Soc **52**: 241-253.

Powell JJ, Ainley CC, Evans R and Thompson RPH (1994). Intestinal perfusion of dietary levels of aluminium: association with the mucosa. Gut **35**: 1053-1057.

Powell JJ, Greenfield SM, Thompson RPH, Cargnello JA, Kendall MD, Landsberg JP, Watt F, Delves HT and House I (1995). Assessment of toxic metal exposure following the Camelford water pollution incident: evidence of acute mobilisation of lead into drinking water. Analyst **120**: 793-808.

Pratico D, Uryu K, Sung S, Tang S, Trojanwoski JQ, and Lee VM (2002). Aluminum modulates brain amyloidsis through oxidative stress in APP transgenic mice. FASEB J. **16**: 1138-1140.

Priest ND, Newton D and Talbot RJ (1991). Metabolism of aluminum-26 and gallium-67 in a volunteer following their injection as citrates. AEA Technology Report, AEA-EE-0206.

Priest ND, Newton D, Day JP, Talbot RJ and Warner A J (1995a). Human metabolism of aluminium-26 and gallium-67 injected as citrates. Human and Experimental Toxicology **14**(3): 287-293.

Priest ND, Talbot RJ and Austin JG (1995b). The bioavailability in young adults of aluminium ingested in drinking water. United Kingdom Atomic Energy Authority report, AEA Technology, AEA-TDP-269.

Priest ND, Talbot RJ, Austin JG, Day JP, King SJ, Fifield K and Cresswell RG (1996). The bioavailability of Al-26-labelled aluminium citrate and aluminium hydroxide in volunteers. Biometals **9**(3): 221-228.

Priest ND, Newton D, Talbot R, McAughey J, Day JP and Fifield K (1998). Industry-sponsored studies on the biokinetics and bioavailability of aluminium in man. In: Health in the Aluminium Industry, ed. Priest ND and O'Donnell TV, Middlesex University Press: London.

Priest ND (2004). The biological behaviour and bioavailability of aluminium in man, with special reference to studies employing ^{26}Al as a tracer. J Environ Monitoring **6**(5): 375-403.

Priest N (2010). The bioavailability of ingested Al-26 labelled aluminium and aluminium compounds in the rat. Mississauga, Ontario, Canada, Atomic Energy of Canada Ltd (unpublished General Nuclear Product Report GNP-121100-REPT-001).

Ray D. Personal communiction to Ms F Pollitt, 23 March 2004.

Rea WJ (1995). Chemical Sensitivity: Clinical Manifestations of Pollutant Overload, Volume III. Lewis Publishers, Inc.

Reiber S, Kukull W and Standishlee P(1995). Drinking water aluminum and bioavailability. Journal American Water Works Association **87**(5): 86-100.

Reusche E, Koch V, Friedrich HJ, Nunninghoff D, Stein P and Rob PM (1996). Correlation of drug-related aluminum intake and dialysis treatment with deposition of argyrophilic aluminum-containing inclusions in CNS and in organ systems of patients with dialysis-associated encephalopathy. Clinical Neuropathology **15**(6): 342-347.

Roels H, Meiers G, Dlos M, Ortega I, Lauwerys R, Buchet JP, Lison D (1997). Influence of the route of administration and the chemical form ($MnCl_2$, MnO_2) on the absorption and cerebral distribution of manganese in rats. Arch Toxicol **71**: 223-230.

Roels HA, Ortega Eslava MI, Ceulemans E, Robert A, Lison D (1999). Prospective study on the reversibility of neurobehavioural effects in workers exposed to manganese dioxide. NeuroToxicology **20**: 255-271.

Rogers MAM and Simon DG (1999). A preliminary study of dietary aluminium intake and risk of Alzheimer's disease. Age and Ageing **28**: 205-209.

Roman E, Simpson J, Ansell P, Kinsey S, Mitchell CD, McKinney PA, Birch JM, Greaves M,and Eden T on behalf of the United Kingdom Childhood Cancer Study Investigators (2007). Childhood Acute Lymphoblastic Leukemia and Infections in the First Year of Life: A Report from the United Kingdom Childhood Cancer Study. American J of Epidemiology **165**: 496–504.

Rondeau V, Iron A, Letenneur L, Commenges D, Duchene F, Arveiler B and J-F Dartigues (2006). Analysis of the effect of aluminium in drinking water and transferrin C2 allele on Alzheimer's disease. Eur J of Neurology **13**: 1022-1025.

Rose M, Baxter M, Brereton N and Baskaran C (2006). Dietary exposure to metals and other elements in the 2006 UK Total Diet Study and some trends over the last 30 years. Food Addit Contam **27**(10): 1380-1404.

Rose MR. Personal communication to Miss F Pollitt, 16 January 2008.

Roy AK, Talukder G and Sharma A (1991a). Similar effects *in vivo* of two aluminium salts on the liver, kidney, bone, and brain of Rattus norvegicus. Bull Environ Contam Toxicol **47**: 288-295.

Roy AK, Sharma A and Talukder G (1991b). Effects of aluminum salts on bone marrow chromosomes in rats *in vivo*. Cytobios **66**: 105-112.

Salim S, Farquharson J, Ameil GC, Cockburn F, Forbes GI, Logan RW, Sherlock JC and Wilson TS (1986). Dietary copper intake in artificially fed infants. Arch Dis Child **61**: 1068-1075.

Sarin S, Julka D and Gill KD (1997a). Regional alterations in calcium homeostasis in the primate brain following chronic aluminium exposure. Molecular & Cellular Biochemistry **168**(1-2): 95-100.

Sarin S, Gupta V and Gill KD (1997b). Alterations in lipid composition and neuronal injury in primates following chronic aluminium exposure. Biological Trace Element Research **59**(1-3 Special Issue SI): 133-143.

Savory J, Herman MM, Erasmus RT, Boyd JC and Wills RC (1994). Partial reversal of aluminium-induced neurofibrillary degeneration by desferrioxamine in adult male rabbits. Neuropathology and Applied Neurobiology **20**(1): 31-37.

Savory J, Exley C, Forbes WF, Huang Y, Joshi JG, Kruck T, McLachlan DR and Wakayama I (1996). Can the controversy of the role of aluminum in Alzheimer's disease be resolved? What are the suggested approaches to this controversy and methodological issues to be considered? Journal of Toxicology and Environmental Health **48**(6): 615-35.

Savory J, Herman MM and Ghribi O (2003). Intracellular mechanisms underlying aluminum-induced apoptosis in rabbit brain. J Inorg Biochem 97 (1), 151-154.

Schonholzer KW, Sutton RAL, Walker VR, Sossi V, Schulzer M, Orvig C, Venczel E, Johnson RR, Vetterli D, Dittrichhannen B, Kubik P and Suter M (1997). Intestinal absorption of trace amounts of aluminium in rats studied with (26)aluminium and accelerator mass spectrometry. Clinical Science **92**(4): 379-383.

Schumann K, Elsenhans B and Maurer A (1998). Iron supplementation. Journal of Trace Elements in Medicine and Biology **12**: 129-140.

Sedman AB, Klein GL, Merritt RJ, Miller NL, Weber KO, Gill WL, Anand H and Alfrey AC (1985). Evidence of aluminium loading in infants receiving intravenous therapy. N Eng J Med **312**(21): 1337-1343.

Shakoor A, Gupta PK and Kataria M. (2003). Influence of aluminium on neurotoxicity of lead in adult male albino rats. Indian J Exp Biol. **41**(6): 587-91.

Shea TB, Wheeler E and Jung C (1997). Aluminum inhibits neurofilament assembly, cytoskeletal incorporation, and axonal transport. Dynamic nature of aluminum-induced perikaryal neurofilament accumulations as revealed by subunit turnover. Molecular and Chemical Neuropathology **32**(1-3): 17-39.

SI No 3184, 2000. Water, England and Wales. The Water Supply (Water Quality) Regulations 2000.

Sjögren B, Lidums V, Hakansson M and Hedstrom L (1985). Exposure and urinary excretion of aluminum during welding. Scand J Work Environ Health **11**: 39-43.

Skalsky HL and Carchman RA (1983). Aluminum homeostasis in man. J Am Coll Toxicol **2**: 405-423.

Skikne B, Baynes RD (1994). Iron absorption. In: Iron Metabolism in Health and Disease. Philadelphia. Eds. Brock JH, Halliday JW, Pippard MJ, Powell LW. WB Saunders, pp. 151-187.

Smans KA, D'Haese PC, Van Landeghem GF, Andries LJ, Lamberts LV, Hendy GN and De Broe ME (2000). Transferrin-mediated uptake of aluminium by human parathyroid cells results in reduced parathyroid hormone secretion. Nephrology Dialysis Transplantation **15**(9): 1328-36.

Smith P, Skudder D and Coleman M. The Lowermoor water pollution incident. Report and discussion document to explore suspected brain damage, endocrinal dysfunction, essential mineral imbalances and resultant homoeostatic disequilibium in the residents of the Lowermoor water supply area, Cornwall. Unpublished report prepared for the North Cornwall Homeopathic Project, 28 April 1992.

Somova LI, Missankov A and Khan MS (1997). Chronic aluminum intoxication in rats: dose-dependent morphological changes. Meth Find Exp Clin Pharmacol **19**(9): 599-604.

South West Water Ltd. Personal communication from South West Water to Lowermoor Subgroup on 3 April 2002.

Sparks DL and Schreurs BG (2003). Trace amounts of copper in water induce β-amyloid plaques and learning deficits in a rabbit model of Alzeimer's disease. PNAS **100**: 11065-11069.

Spencer H and Lender M (1979). Adverse effects of alumunium-containing antacids on mineral metabolism. Gastroenterology **76**(3): 603-606.

Stauber JL, TM Florence, CM Davies, MS Adams and SJ Buchanan (1999). Bioavailability of Al in alum-treated drinking water. Journal American Water Works Association **91**(11): 84-93.

Strong MJ, Garruto RM, Joshi JG, Mundy WR and Shafer TJ (1996). Can the mechanisms of aluminum neurotoxicity be integrated into a unified scheme. Journal of Toxicology & Environmental Health **48**(6): 599-613.

Strozyk D, Launer LJ, Adlard PA, Cherny RA, Tsatsanis A, Volitakis I, Blennow K, Petrovitch H, White LR and Bush AI (2009). Zinc and copper modulate Alzheimer Abeta levels in human cerebrospinal fluid. Neurobiol Aging, **30**(7): 1069-77.

Struys-Ponsar C, Guillard O and van den Bosch de Aguilar P (2000). Effects of aluminum exposure on glutamate metabolism: a possible explanation for its toxicity. Experimental Neurology **163**(1): 157-64.

Sugawara C, Sugawara N, Okawa H, Okazaki T, Otaki J, Taguchi K, Yokokawa K and Miyake H (1987). Effects of ingested 4000ppm aluminum on the essential metals, especially zinc, in intact and ethanol treated mice. Drug Chem Toxicol **10**: 195-207.

Sumino K, Hayakawa K, Shibata T, Kitamura S (1975). Heavy metals in normal Japanese tissues. Amounts of 15 heavy metals in 30 subjects. Archives of Environmental Health **30**:487-494.

Swain C and Chainy GBN (1998). Effects of aluminum sulphate and citric acid ingestion on lipid peroxidation and on activities of superoxide dismutase and catalase in cerebral hemisphere and liver of developing young chicks. Molecular & Cellular Biochemistry **187**(1-2): 163-172.

Swegert CV, Kunjan RD, Katyare SS (1999). Effect of aluminium-induced Alzheimer like condition on oxidative energy metabolism in rat liver, brain and heart mitochondria. Mechanisms of Ageing and Development **112**: 27-42.

Taheri M, Zahedi-Asl S and Ahangarpoor A (2004). Anti-thyroid effect of high aluminum intake in rats. Int J Endocrinol Metab **2**:41-46.

Talbot RJ, Newton D, Priest ND, Austin JG and Day JP (1995). Inter-subject variability in the metabolism of aluminium following intravenous injection as citrate. Human Exp Toxicol **14**: 595-599.

Tanojo H, Hostynek JJ, Mountford HS and Maibach HI (2001). *In vitro* permeation of nickel salts through human stratum corneum. Acta Derm Venereol (Suppl) **212**: 19-23.

Taylor A (1990). Concentrations of aluminium in specimens of serum collected from individuals who were in the Camelford area, 6-7th July 1988. Published in: Proceedings of the Conference held on 3rd February 1990 at the Postgraduate Centre, Royal Cornwall Hospital (Treliske), Truro.

Taylor GA, Ferrier IN, McLoughlin IJ, Fairbairn AF, McKeith IG, Lett D and

Edwardson JA (1992). Gastrointestinal absorption of aluminium in Alzheimer's disease: response to aluminium citrate. Age and Ageing **21**(2): 81-90.

Taylor GA, Moore PB, Ferrier IN, Tyrer SP and Edwardson JA (1998). Gastrointestinal absorption of aluminium and citrate in man. J Inorg Biochem **69**: 165-169.

Tephly TR, Wagner G, Sedman R and Piper W (1978). Effects of metals on heme biosynthesis and metabolism. Fed Proc **37**: 35-39.

Testolin G, Erba D, Ciappellano S and Bermano G (1996). Influence of organic acids on aluminium absorption and storage in rat tissues. Food Additives and Contaminants **13**(1): 21-27.

The Royal Society. The health hazards of depleted uranium munitions. Part I. May 2001. http://www.royalsoc.ac.uk/document.asp?id=1431

The Royal Society. The health hazards of depleted uranium munitions. Part II. March 2002. http://www.royalsoc.ac.uk/document.asp?id=1401

Thorne BM, Donohoe T, Lin KN, Lyon S, Medeiros DM and Weaver ML (1986). Aluminum ingestion and behavior in the Long-Evans rat. Physiology and Behavior **36**(1): 63-7.

Tipton IH, Cook MJ (1963). Trace elements in human tissue. Part II. Adult subjects from the United States. Health Physics **9**:103-145.

Tomljenovic L (2011). Aluminium and Alzheimer's Disease: After a century of controversy, is there a plausible link? Journal of Alzheimer's Disease **23**: 567-598.

Tomonaga (1981). Cerebral amyloid angiopathy in the elderly. J. American Geriatric. Soc. **29**: 151-157

Trapp GA (1983). Plasma aluminum is bound to transferrin. Life Sci **33**: 311-316.

Tsunoda M and Sharma RP (1999). Modulation of tumor necrosis factor alpha expression in mouse brain after exposure to aluminum in drinking water. Archives of Toxicology **73**(8-9): 419-426.

Turgut G, Kaptanoğlu B, Turgut S, Enli Y and Genç O (2004). Effects of chronic aluminum administration on blood and liver iron-related parameters in mice. Yonsei Med J, **45**(1): 135-9.

Türkez H, Yousef MI, Geyikoglu F (2010). Propolis prevents aluminium-induced genetic and hepatic damages in rat liver. Food Chem Toxicol **48**(10): 2741-6.

US Environmental Protection Agency (1987). Summary review of the health effects associated with copper. Environmental Protection Agency, Cincinnati Ohio. EPA 600/8-87/001.

US Environmental Protection Agency (1994) Drinking Water Criteria Document for Manganese. U.S. Environmental Protection Agency, Office of Water, Washington, DC. September, 1993. Updated: March, 1994.

US Environmental Protection Agency (2002) Health Effects Support Document for Manganese. U.S. Environmental Protection Agency, Office of Water, Washington, DC.

US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (1997). Draft Toxicological Profile for Manganese Update.

Uversky VN, Li J and Fink AL (2001). Metal-triggered structural transformations, aggregation and fibrillation of human α-synuclein. J Biol Chemistry 276(47): 44284-44296.

Van der Voet GB and de Wolff FA (1984). A method of studying the intestinal absorption of aluminium in the rat. Arch Toxicol **55**: 168-172.

Van der Voet GB and de Wolff FA (1998). Intestinal absorption of aluminium: effect of sodium and calcium. Arch Toxicol **72**: 110-114.

Vieregge P, Heinzow B, Korf G, Teichert H-M, Schleifenbaum P, Moseinger H-U (1995).Long term exposure to manganese in rural well water has no neurological effects. Canadian Journal of Neurological Science **22**: 286-289.

Vinters HV (1987). A critical review. Stroke **18**: 311-324.

Walton J, Tuniz C, Fink D, Jacobsen G and Wilcox D (1995). Uptake of trace amounts of aluminum into the brain from drinking water. Neurotoxicology **16**(1): 187-190.

Wapnir RA (1998). Copper absorption and bioavailability. Am J Clin Nutr **67**(suppl): 1054S-60S.

Ward NI (1989). Environmental contamination of aluminium and other elements in North Cornwall as a result of the Lowermoor water treatment works incident. In Heavy metals in the Environment, Volume 1, ed Vernet J-P. Geneva.

Ward NI (1991). Multi-element tissue status of sows exposed to aluminium in North Cornwall as a result of the Lowermoor Treatment Works incident. In: "Seventh International Symposium on Trace Elements in Man and Animals" (TEMA-7) Vol. 1, pp 23-1 -- 23-2. Momciloviv B(ed). Zagreb, 1991.

Ward NI. Personal communication to the Lowermoor Subgroup, 30 September 2002.

Welsh Water Authority. Personal communication to D Cross, 1998.

Wenk GL and Stemmer KL (1982). Activity of the enzymes dopamine-beta-hydroxylase and phenylethanolamine-N-methyltransferase in discrete brain regions of the copper-zinc deficient rat following aluminum ingestion. Neurotoxicology 3: 93-99.

Wenk GL and Stemmer KL (1983). Suboptimal dietary zinc intake increases aluminum accumulation into the rat brain. Brain Res **288**: 393-395.

Wettstein A, Aeppli J, Gautschi K and Peter M (1991). Failure to find a relationship between mnestic skills of octogenarians and aluminium in drinking water. Int Arch Occup Environ Health **63**: 97-103.

WHO (1982). Evaluation of certain food additives and contaminants. Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 683. World Health Organization, Geneva.

WHO (1983). Evaluation of certain food additives and contaminants. Twenty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 696. World Health Organization, Geneva.

WHO (1984). Guidelines for Drinking Water Quality. Volume 1: Recommendations. World Health Organization, Geneva.

WHO (1984). Guidelines for Drinking Water Quality. Volume 2: Health Criteria and other supporting information. World Health Organization, Geneva.

WHO (1989). WHO Food Additive Series 24. Aluminium. 05-18-04, http://www.inchem.org/documents/jecfa/jecmono/v024je07.htm

WHO (1993). Guidelines for Drinking Water Quality. Second Edition. Volume 1: Recommendations. World Health Organization, Geneva.

WHO (1993a). Evaluation of Certain Food Additives and Contaminants. Forty-First Report of the Joint FAO/WHO Expert Committee on Food Additives, Technical Report Series No 837, WHO, Geneva.

WHO (1996) Guidelines for Drinking Water Quality. Second Edition. Volume 2: Health Criteria and other supporting information. World Health Organization, Geneva.

WHO (1996). Trace elements in human nutrition and health. World Health Organization, Geneva.

WHO (1998). Guidelines for Drinking Water Quality. Second Edition. Addendum to Volume 1: Recommendations. World Health Organization, Geneva.

WHO (2000). Safety Evaluation of Certain Food Additives and Contaminants. Fifty-Third Meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series 44, WHO, Geneva.

WHO (2004). Guidelines for Drinking Water Quality. Third Edition. World Health Organization, Geneva.
http://www.who.int/water_sanitation_health/dwq/gdwq0506_12.pdf

WHO (2004). Uranium in Drinking-Water. Background document for development of WHO Guidelines for Drinking-water Quality. World Health Organization, Geneva.

WHO (2011). Guidelines for Drinking Water Quality. Fourth Edition. World Health Organisation, Geneva.
http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/

WHO (2012). Safety Evaluation of Certain Food Additives and Contaminants. Prepared by the seventy-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series 65, WHO, Geneva.

Wilhelm M, Passlick J, Busch T, Szydlik M and Ohnesorge FK (1989). Scalp hair as an indicator of aluminium exposure: comparison to bone and plasma. Human Toxicology **8**(1): 5-9.

Wilhelm M and Idel H (1996). Hair analysis in environmental medicine. Zentralbl Hyg Umweltmed **198**(6): 485-501.

Wilhelm M, Pesch A, Rostek U, Begerow J, Schmitz N, Idel H and Ranft U (2002). Concentrations of lead in blood, hair and saliva of German children living in three different areas of traffic density. Sci Total Environ **297**(1-3): 109-118.

Wilson A. Comparison of results of psychometric assessment of clients with their self-reports following Lowermoor water incident July 1988. Published in: Proceedings of the Conference held on 3rd February 1990 at the Postgraduate Centre, Royal Cornwall Hospital (Treliske), Truro.

Wisniewski HM (1994). Aluminium, tau protein, and alzheimers disease. Lancet **344**(8916): 204-205.

Woolridge M, Hay A and Renfrew M (2004). SUREmilk study - Surveillance of Residues in human milk: Pilot studies to explore alternative methods for the recruitment, collection, storage and management of an archive of breast milk samples. Unpublished report for the Food Standards Agency, Department of Health, Defra and HSE.

Worl S, Hemmer W, Focke M, Gotz M and Jarisch R (2001). Copper allergy revisited. J Am Acad Dermatol **45**(6): 863-870.

Wu YH, Zhou ZM, Xiong YL, Wang YL, Sun JH, Liao HB and Luo XD (1998). Effects of aluminum potassium sulfate on learning, memory, and cholinergic system in mice. Chung Kuo Yao Li Hsueh Pao Acta Pharmacologica Sinica **19**(6): 509-12.

Xie CX, St Pyrek J, Porter WH and Yokel RA (1995). Hydroxyl radical generation in rat brain is initiated by iron but not aluminum, as determined by microdialysis with salicylate trapping and GC-MS analysis. Neurotoxicology **16**(3): 489-96.

Xie CX, Mattson MP, Lovell MA and Yokel RA (1996). Intraneuronal aluminum potentiates iron-induced oxidative stress in cultured rat hippocampal neurons. Brain Research **743**(1-2): 271-277.

Xie CX and Yokel RA (1996). Auminum facilitation of iron-mediated lipid peroxidation is dependent on substrate, pH, and aluminum and iron concentrations. Archives of Biochemistry and Biophysics **327**(2): 222-226.

Yale School of Medicine (1999). Yale Animal Resources Center. Veterinary Clinical Services. Normative data: mouse. http://www.med.yale.edu/yarc/vcs/normativ.htm. Accessed 2 December 2008.

Yip R and Dallman PR (1996). Iron. In: Ziegler, E.E. & Filer, L.J. (eds). Present knowledge in nutrition (7th Ed), ILSI Press, Washington DC, pp. 278-292

Yokel RA and O'Callaghan JP (1998). An aluminum-induced increase in gfap is attenuated by some chelators. Neurotoxicology and Teratology **20**(1): 55-60.

Yokel RA, Rhineheimer SS, Brauer RD, Sharma P, Elmore D and McNamara PJ (2001). Aluminum bioavailability from drinking water is very low and is not appreciably influenced by stomach contents or water hardness. Toxicology **161**(1-2): 93-101.

Yokel RA, Rhinehelmer SS, Sharma P, Elmore D and McNamara PJ (2001). Entry, half-life, and desferrioxamine-accelerated clearance of brain aluminum after a single Al-26 exposure. Toxicological Sciences **64(1)**: 77-82.

Yokel RA, Wilson M, Harris WR and Halestrap AP (2002). Aluminum citrate uptake by immortalized brain endothelial cells: implications for its blood-brain barrier transport. Brain Research **930(1-2):** 101-110.

Yoshimura M, Yamanouchi H, Kuzuhara S, Mori H, Sugiura S, Mizutani T, Shimada H, Tomonaga M and Toyokura Y (1992). Dementia in cerebral amyloid angiopathy: a clinicopathological study. J. Neurology **239**: 441-450

Yoshinaga J, Imai H, Nakazawa M, Suzuki T and Morita M (1990). Sci Total Environ **99**: 125-135.

Yousef MI (2004). Aluminium-induced changes in hemato-biochemical parameters, lipid peroxidation and enzyme activities of male rabbits: protective role of ascorbic acid. Toxicology **199**: 47-57.

Yumoto S, Nagai H, Kobayashi K, Tamate A, Kakimi S and Matsuzaki H (2003). ^{26}Al incorporation into the brain of suckling rats through maternal milk. J Inorganic Biochemistry **97**: 155-160.

Yumoto S, Nagai H, Imamura M, Matsuzaki H, Hayashi K, Masuda A, Kumazawa H, Ohashi H and Kobayashi K (1997). Al-26 uptake and accumulation in the rat brain. Nuclear Instruments & Methods in Physics Research. Section B. Beam Interactions with Materials & Atoms **123**(1-4): 279-282.

Zabel M, Lindscheid KR and Mark H (1990). [Copper sulphate allergy with special reference to internal exposure]. Z Hautkr **65**(5): 481-482, 485-486.

Zacarias I, Yanez CG, Araya M, Oraka C, Olivares M and Uauy R. Determination of the taste threshold of copper in water. Chemical Senses **26**: 85-89.

Zafar TA, Weaver CM, Martin BR, Flarend R and Elmore D (1997). Aluminum (Al-26) metabolism in rats. Proceedings of the Society for Experimental Biology & Medicine **216**(1): 81-85.

Zhang ZJ, Qian YH, Hu HT, Yang J and Yang GD (2003). The herbal medicine Dipsacus asper wall extract reduces the cognitive deficits and overexpression of beta-amyloid by aluminum exposure. Life Sci **73**: 2443-2454.

Zorichak R, personal communication to Mr D Young, 20 March 1991

Abbreviations

ADI	acceptable daily intake
ADP	adenosine diphosphate
AML	acute myeloid leukaemia
ATP	adenosine triphosphate
bw	body weight
CI	confidence interval
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Ca-EDTA	calcium (ethylenedinitrilo)tetraacetic acid
DNA	deoxyribonucleic acid
EC	European Community
EU	European Union
EVM	Expert group on Vitamins and Minerals
FAO	Food and Agriculture Organisation
GDWQ	WHO Guidelines for Drinking Water Quality
GP	General Practioner
GST	glutathione-S-transferase
HPA	Health Protection Agency
IPCS	International Programme on Chemical Safety
IQ	intelligence quotient
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LDH	lactate dehydrogenase
LIHAG	Lowermoor Incident Health Advisory Group
LOAEL	lowest observed adverse effect level
MAC	maximum acceptable concentration
NHS	National Health Service
NDNS	National Diet and Nutrition Survey
NOAEL	no observed adverse effect level
NRPB	National Radiation Protection Board
ONS	Office of National Statistics
PTWI	provisional tolerable weekly intake
RNI	Reference Nutrient Intake
SEN	Special Educational Needs
SMR	standardised mortality ratio
SWWA	South West Water Authority
TBARS	thiobarbituric acid reactive substances
TDI	tolerable daily intake
TDS	Total Diet Study
TWI	tolerable weekly intake
WHO	World Health Organization
WRc-NSF	Water Research Centre-National Sanitation Foundation
kg	kilogram
g	gram
mg	milligram

µg	microgram
l	litre
dl	decilitre
w/w	weight for weight

Glossary of terms

Acceptable Daily Intake (ADI): an estimate of the amount of a substance in food or drink, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime by humans without appreciable health risk.

Acidic: adjective relating to acids. Acids are substances that can donate protons, for example, to water molecules, forming the hydronium ion H_3O^+. Common acids include hydrochloric acid and acetic acid. The acidity of a solution is often expressed in terms of its pH. A pH of less than 7 indicates acidity.

Acute: short term, in relation to exposure or effect.

Acute toxicity: effects that occur over a short period of time (up to 14 days) immediately following exposure.

Adenosine diphosphate (ADP): a substance which carries genetic information in cells or viruses and is involved in the transcription or translation of proteins.

ADP-ribosylation: a biochemical reaction involving ADP (qv).

Adverse effect: change in morphology, physiology, biochemistry, growth, development or lifespan of an organism which results in impairment of functional capacity, impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences.

Aetiology: the aetiology of a disease is the cause of that disease.

Age standardised incidence rate: calculated in the same way as standard mortality ratio (see below) but used for the incidence rate of a condition i.e. the number of new cases occurring each year.

Allergic reaction: an adverse reaction elicited by exposure to a previously sensitised individual to the relevant antigen.

Allergy: the adverse health effects that may result from the stimulation of a specific immune response.

Amyloid deposits: deposits of the peptide β-amyloid. They are a characteristic of Alzheimer's disease.

Anaemia: a disease involving a reduction in the number of red cells in the blood or the production of red cells containing inadequate amounts of haemoglobin. Often caused by deficiency in iron.

Anion: an anion is a negatively charged ion. When common salt (soidum chloride) is dissolved in water, the sodium ions (positively charged and described as cations) separate from the negatively charged chloride ions. The chloride ions are anions.

Anthropogenic: man-made or arising from human activities.

Apgar scores: a measure of the physical condition of a newborn infant, obtained by adding points (2, 1, or 0) given for heart rate, respiratory effort, muscle tone, response to stimulation, and skin coloration, a score of ten representing the best possible condition.

Area postrema: part of the brain which triggers vomiting in response to emetic substances.

Axilla: armpit.

Azotemia: excess of urea or other nitrogenous moeties in the blood.

Beta-amyloid: a peptide, also known as amyloid precursor protein.

Bias: in the context of epidemiological studies, an interference which at any stage of an investigation tends to produce results that depart systematically from the true values (to be distinguished from random error) (see Appendix 4 for more detail).

Bioavailability: a term referring to the proportion of a substance which reaches the systemic circulation unchanged after a particular route of administration.

Biomarker: observable change (not necessarily pathological) in an organism, related to a specific exposure or effect.

Body burden: total amount of a chemical present in an organism at a given time.

Bowser: a water tank on wheels.

Caeruloplasmin: a protein found in the blood which is able to transport copper.

Cancer: synonym for a malignant neoplasm – that is, a tumour (qv) that grows progressively, invades local tissues and spreads to distant sites (see also tumour and metastasis).

Carcinogenesis: the origin, causation and development of tumours (qv). The term applies to benign as well as malignant neoplasms and not just to carcinomas (qv).

Carcinogens: the causal agents which induce tumours. They include external factors (chemicals, physical agents, viruses) and internal factors such as hormones. Chemical carcinogens are structurally diverse and include naturally-occurring substances as well as synthetic compounds. Most chemical carcinogens exert their effects after prolonged

exposure, show a dose-response relationship and tend to act on a limited range of susceptible target tissues.

Carcinoma: malignant tumour arising from epithelial cells lining, for example, the alimentary, respiratory and urogenital tracts and from epidermis, also from solid viscera such as the liver, pancreas, kidneys and some endocrine glands (see also 'tumour').

Case-control study: an epidemiological technique in which a group of individuals with a particular disease (cases) is compared with a group of matched individuals without the disease (controls) to try to determine the cause of the disease.

Cation: a positively charged ion – see 'anions'.

Causality: denotes the relationship between one event (called the *cause*) and another event (called the *effect*) which is the consequence of the first.

Choline acetyltransferase: an enzyme which catalyses the transfer of an acetyl group from choline to form acetylcholine.

Chromosomal aberrations: a particular type of damage to the chromosomes.

Chromosome: structures which contain the genetic material (the DNA) of the body.

Chronic effect: consequence which develops slowly and has a long-lasting course (often but not always irreversible).

Chronic exposure: continued exposures occurring over an extended period of time, or a significant fraction of the life-time of a human or test animal.

Cluster: a group of cases of a disease in time, in geographical location, or in both.

Coagulant: 1. (in water treatment): a substance which causes very fine particles to stick together; 2. (in biology): a substance that provokes clotting of the blood.

Cognitive impairment: impairment of the ability to learn.

Cohort: a defined population that continues to exist through time. A birth cohort, for example, would include a group of people all born in the same year.

Cohort study: the study of a group of people defined at a particular point in time (the cohort), who have particular characteristics in common, such as a particular exposure. They are then observed over a period of time for the occurrence of disease. The rate at which the disease develops in the cohort is compared with the rate in a comparison population, in which the characteristics (e.g. exposure) are absent.

Confidence interval (CI): a CI provides an estimate of how accurately a population parameter has been estimated. A 95% CI for a population parameter is an interval constructed from a sample so that, loosely, there is a 95% chance that the interval contains the parameter. Strictly, with repeated sampling, 95% of intervals so constructed would include the population parameter.

Confounding factor (synonym - confounder): an extraneous variable that satisfies BOTH of 2 conditions: (1) it is a risk factor for the disease under study (2) it is associated with the study exposure but is not a consequence of exposure. For example, cigarette smoking is a confounding factor with respect to an association between alcohol consumption and heart disease. Failure to adjust for a confounding factor results in distortion of the apparent magnitude of the effect of the exposure under study. (In the example, smoking is a risk factor for heart disease and is associated with alcohol consumption but is not a consequence of alcohol consumption.)

Cerebral amyloid angiopathy (CAA): a condition characterized by deposition of beta-amyloid (qv) in the blood vessels and membranes of the brain. Sometimes found in association with dementia.

Cupriphore: a substance promoting the absorption of copper.

Cuprosolvent: a fluid which dissolves copper. Acidic water can lead to copper from water pipes being dissolved and to raised concentrations appearing in drinking water.

Cytotoxic: toxic to living cells.

Deprotonation: loss of a hydrogen ion (a proton).

Direct standardisation: a method of standardisation (qv) used in epidemiology studies.

Dog legs: (in the sense in which it is used in the report) a section of mains which leaves the main supply and rejoins it at another point.

Dose: total amount of a substance administered to, taken or absorbed by an organism.

Dyspepsia: indigestion which may, or may not, be associated with the presence of a peptic ulcer.

Ecological studies: epidemiological studies involving the investigation of populations such as those in a particular geographic area or time period. Information is rarely available on exposure at the individual level, nor on confounding factors, and these studies are only of value in generating hypotheses.

Endocytosis: a mechanism by which materials may be taken into cells. The process is an active one in which materials are surrounded by cell membrane and internalised by the cytoplasm of the cell.

Enzymes: protein substances found in cells which act as catalysts to increase the rate of metabolic reactions.

Epidemiology: study of the distribution and the aetiology (qv) of disease in humans.

Epithelium: the tissue covering the outer surface of the body, the mucous membranes and cavities of the body.

Essential element: an essential element is a chemical element that is necessary for the normal functioning of the body. Copper, iron and zinc are examples.

Estrogen: sex hormone or other substance capable of developing and maintaining female characteristics of the body.

Fetotoxic: causing toxic, potentially lethal, effects to the developing fetus.

Finished water: water that has been treated (ie passed through filtration and purification processes at water treatment works) and is ready to be delivered to customers.

Floc: a loose or cloudy precipitate.

Flocculant: (as used in water treatment) a substance which causes a floc to form.

Functional: as in "functional toxicity" – damage to a system which affects its ability to work properly.

Gavage: administration of a liquid via a stomach tube, commonly used as a dosing method in animal toxicity studies.

Gene: the functional unit of inheritance: a specific sequence of nucleotides along the DNA molecule, forming part of a chromosome (qv).

Genotoxic: the ability of a substance to cause DNA damage, either directly or after metabolic activation.

Genotype: the particular genetic pattern seen in the DNA of an individual. "Genotype" is usually used to refer to the particular pair of forms of genes that an individual possesses at a certain location in his or her genetic material.

Haematological malignancies: malignant production of excess numbers of frequently abnormal blood cells. Leukaemia is characterised by excessive numbers of immature white cells in the blood.

Haematopoetic: adjective used to describe tissues where blood cells are produced, for example, the bone marrow.

Haemochromatosis: is an hereditary disorder generally caused by inappropriate absorption of iron by the small intestine that leads to iron deposition in the viscera, in endocrine organs, and at other sites. The toxic effects of iron impair the function of these organs and cause structural injury.

Haem-protein: a protein associated with the blood.

Hand, foot and mouth disease: a typical distribution of vesicular lesions in hands, feet, and mouth (but also buttocks and genitalia) which can be produced by infection with several different viruses.

Hazard: set of inherent properties of a substance, mixture of substances or a process involving substances that make it capable of causing adverse effects to organisms or the environment.

Hepatic: pertaining to the liver

Hepatocellular carcinoma: a malignant tumour i.e. a cancer (qv) of hepatocytes (qv).

Hepatocyte: the principal cell type in the liver, possessing many metabolising enzymes (see 'metabolic activation').

Hepatoma: a benign neoplasm of the liver.

Hepatotoxic: causing toxicity to the liver.

High level intake: as used in this report: (i) for food, the 97.5th centile calculated from the food consumption patterns recorded in the National Diet and Nutrition Survey for the relevant age, and (ii) for water, the 97.5th percentile intake in a 1995 survey of tap water consumption carried out by M.E.L. Research for the Drinking Water Inspectorate.

Homeostasis: a term used to describe a state of physiological equilibrium. Homeostatic mechanisms exist, for example, to regulate the acidity of the blood, the blood pressure and the concentrations of ions such as sodium and calcium in the plasma.

Hydrated: combined with water. Copper sulphate, for example, usually occurs as a hydrated salt. In this state it forms the familiar blue crystals. In the dehydrated (or anhydrous) state, copper sulphate is a white powder.

Hydrophilic: 'water liking' – a substance which has a tendency to partition into water or aqueous solutions.

Hydroxyapatite: the chemical calcium phosphate hydroxide, which is the principal inorganic constituent of tooth enamel and bone.

Hyperplasia: an increase in the size of an organ or tissue due to an increase in the number of cells.

Hyperthyroidism: a condition in which the thyroid gland produces more hormone than normal, resulting in an increased rate of metabolism, often with wasting of muscle and loss of weight together with restlessness and emotional instability.

Hypothyroidism: a condition in which the level of thyroxine in the blood is abnormally low resulting in a decreased metabolic rate.

Incidence: the number of new cases of illness occurring during a given period in a specific population.

Indirect standardisation: a method of standardisation (qv) used in epidemiology studies.

Infant: a child under the age of one year.

In vitro: a Latin term used to describe effects in or studies using biological material outside the living animal (literally 'in glass').

In vivo: a Latin term used to describe effects or studies in living animals (literally 'in life').

Ionic: a chemical term used to describe materials such as common salt (sodium chloride) which, on dissolving in water, form ions (see 'anion' and 'cation').

Isotope: a variety of a chemical element which has a different mass number from, but the same chemical properties as, the other varieties of the element.

Labile: adjective used to describe short lived or unstable substances.

Latency: used in toxicology to describe a period of apparent normality between exposure to a toxic substance and the appearance of adverse effects. Asbestos, for example, has a long latency with regard to the production of cancer. The interval between exposure to asbestos and the appearance of the cancer (a mesothelioma) can be as long as forty years.

LD_{50}: the dose of a toxic compound that causes death in 50% of a group of experimental animals to which it is administered. It can be used to assess the acute toxicity of a compound, but is being superseded by more refined methods.

Leukaemia: a group of neoplastic disorders (see tumour) affecting blood-forming elements in the bone marrow, characterised by uncontrolled proliferation and disordered differentiation or maturation. Examples include the lymphocytic leukaemias which develop from lymphoid cells and the myeloid leukaemias which are derived from myeloid cells (producing red blood cells, mainly in bone marrow).

Ligand: an atom or chemical group that is capable of binding to another chemical.

Lipophilic: 'lipid liking' - a substance which has a tendency to partition into fatty materials.

Lowest Observed Adverse Effect Level (LOAEL): the lowest administered dose of a substance at which an adverse (qv) effect has been observed in studies in animals or humans (see also 'No Observed Adverse Effect Level').

Macrophage: a type of white blood cell.

Macrophagic myofascitiis: inflammation of the myofascial tissue (qv) in which macrophages (qv) are present.

Malignancy: see 'tumour'.

Maximum tolerated dose: in animal toxicity studies, the maximum dose of a compound which the test animals can tolerate without showing adverse effects. The highest dose of a substance in a toxicity study is usually set at or near the maximum tolerated dose.

Menkes' disease: an inherited condition characterised by abnormally low levels of copper in the liver and brain but high levels in other tissues. The disease produces mental retardation, neurological impairment and usually death by the age of three years. The hair is kinked hence the synonym 'kinky-hair syndrome'.

Metabolism: chemical modification of a compound by enzymes within the body. Metabolism may result in activation, inactivation, accumulation or excretion of the compound.

Metabolite: product formed by metabolism of a compound.

mg/kg bw/day: in toxicity studies, chemicals are administered to laboratory animals on a body weight basis so that all animals receive an equivalent amount of chemical regardless of their body size. For example, if the desired dose is 10 milligrams per kilogram body weight (10 mg/kg bw), a rat which weighed 0.2 kg would be administered (10 x 0.2) mg of chemical and a rat which weighed 0.3 kg would be administered (10 x 0.3) mg of chemical. In all except acute toxicity tests, the chemical is administered on a daily basis and the notation used is mg/kg bw/day i.e. milligrams (of chemical) per kilogram body weight per day.

Morphology: the study of structure as applied to zoology and human anatomy.

Morphological: adjective used to describe structural changes in the body.

Mutation: a permanent change in the amount or structure of the genetic material in an organism or cell, which can result in a change in phenotypic characteristics. The alteration may involve a single gene, a block of genes, or a whole chromosome. Mutations involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Changes involving whole chromosomes may be numerical or structural. A mutation in the germ cells of sexually reproducing organisms may be transmitted to the offspring, whereas a mutation that occurs in somatic cells may be transferred only to descendent daughter cells.

Myeloproliferative disorders (MPD): disease characterised by abnormal and frequently neoplastic proliferation of blood forming tissues.

Myofascial tissue: a fibrous membrane sometimes serving as the sheath of a muscle, sometimes forming the connection between muscle and tendon.

Neoplasm: literally means 'new growth', often used as synonymous with tumour.

Nephrotoxicity: toxicity to the kidney.

Neurobehavioural: of behaviour which is determined by the nervous system. In neurobehavioural tests of animals, functions such as sight, hearing, learning ability and social interactions are tested to assess whether they have been damaged by a chemical.

Neuropsychology: the relationship between neural and mental or behavioural processes; a branch of psychology dealing with this.

Neurotoxicity: toxicity to the cells in the brain and elsewhere in the body which comprise the nervous system. This could be caused by a chemical, a physical injury or by certain diseases.

No observed adverse effect level (NOAEL): the lowest administered dose of a substance at which no adverse (qv) effect has been observed in studies in animals or humans. In setting a safe exposure level of a compound for humans, often the lowest NOAEL from all toxicity studies on a compound is selected and divided by a uncertainty factor (qv) to generate a tolerable daily intake (qv). If it is not possible to determine a NOAEL, the LOAEL (qv) is frequently used, and a larger uncertainty factor is applied.

Odds ratio (OR): the odds of disease in an exposed group divided by the odds of disease in an unexposed group.

Onycholysis: separation of the nail plate from the nail bed.

Ossification: the formation of bone; the process of becoming or changing into bone.

Osteomalacia: softening of the bones; especially, that due to inadequate mineralization, resulting from abnormal vitamin D, calcium, or phosphate metabolism.

Osteopenia: reduction in the normal bone mass of the body.

Oestrogen: see Estrogen.

pH: the pH of a solution is a logarithmic measure of its acid or alkaline nature. pH 7 is neutral, acid solutions have a pH less than 7, alkaline solutions have a pH of more than 7. Each sucessive pH unit represents a ten-fold change in acid or alkaline nature:
pH = (- log [H+]) *or* pH = (- log hydrogen ion concentration).

Pineal gland: a gland situated behind the third ventricle of the brain, and containing sand-like particles, which secretes melatonin in various mammals and is concerned with photo-periodicity and circadian rhythms.

Polyelectrolyte: an electrolyte of high molecular weight.

Pre-accident intelligence: intelligence level prior to some event which may have caused a reduction in intelligence.

Prevalence: the number of cases of a disease that are present in a population at a given time.

Provisional Tolerable Weekly Intake (PTWI): a Tolerable Weekly Intake is an estimate of the amount of a substance in food or drink, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested weekly over a lifetime by humans without appreciable health risk. Where this is expressed on a provisional basis, there is usually a requirement for additional data to make a full hazard assessment.

Proximal: an anatomical term used to describe that part of a structure close to its origin. For example, the proximal part of the leg is the thigh.

Receptor: a small, discrete protein in the cell membrane or within the cell with which specific molecules interact to initiate a change in the working of a cell.

Reference nutrient intake (RNI): an amount of the nutrient that is enough, or more than enough, for most (usually at least 97%) of people in a group. If the average intake of a nutrient by a group is at the RNI, then the risk of deficiency in the group is very small.

Reflux oesophagitis: inflammation of the lower part of the oesophagus or gullet caused by acid passing up from the stomach. This causes pain in the chest which may be severe.

Relative risk: a measure of the association between exposure and outcome. The rate of disease in the exposed population divided by the rate of disease among the unexposed population in a cohort study or a population-based case control study. A relative risk of 2

means that the exposed group has twice the disease risk compared to the unexposed group.

Renal: relating to the kidney.

Risk: possibility that a harmful event (death, injury or loss) arising from exposure to a chemical or physical agent may occur under specific conditions.

Saturable: a process which can be saturated. For example, in a saturated absorption process, when the process is saturated, no further absorption can take place.

Sequestration: literally means hiding away. Metals, for example, may be sequestered in bone.

Service reservoir: a service reservoir is located in the supply system and stores finished water (qv) (cf. reservoir which provides storage for water before it enters the treatment works).

Sideroblastic anaemia: a type of anaemia in which immature red blood cells appear in the blood cf. iron-deficiency anaemia.

South West Water Residuary Body: South West Water Authority - a body corporate responsible to the Department of the Environment Food and Rural Affairs. It has remained in existence as a legal entity for limited, specific, legal purposes only, after the transfer of its functions to the Environment Agency and to the current water and sewerage undertaker, South West Water Ltd**.**

Speciation: the chemical or ionic form of an element.

Specific gravity: the density of a substance as compared with the density of water.

Spur mains: where the mains splits into two and each branch ends in a dead end.

Standardised discharge ratio: calculated in the same way as standard mortality ratio (see below) but used for hospital discharges.

Standard mortality ratio (SMR): the standard mortality ratio compares the mortality, from either a specific disease or from all causes, in a particular population with that in a standard population such as the UK (UK standardised rate). It is the ratio of the number of deaths which occurred in the population under study to the number expected if the study population had the same age and sex specific death rates as in the standard population.

$$\text{SMR} = \frac{\text{observed deaths} \times 100}{\text{expected deaths}}$$

If the SMR is greater than 100, it means that the mortality rate is higher in the population being studied than in the standard population. If it is less than 100, the SMR is lower in the study population than in the standard population.

Stoichiometric: containing atoms of different elements in the ratio expected from the formula of the compound which contains them.

Strong acid: an acid which is virtually 100% ionised in solution.

Synergistic: when the combined activity of two substances is greater than the sum of the effects of each one if it was present alone.

Systematic review: a review that has been prepared using a documented systematic approach to minimising biases and random errors.

T-cell: a type of blood cell involved in the immune response.

Talipes: a congenital abnormality of the foot. Commonly known as a 'club foot'.

Teratogen: a substance which, when administered to a pregnant woman or animal, can cause congenital malformations (structural defects) in the baby or offspring.

Teratogenicity: the ability to behave like a teratogen (qv).

Threshold: dose or exposure below which an effect is not expected to occur.

Thyrotoxicosis: a disorder in which there is an excessive amount of thyroid hormones in the blood.

Thyroxine: a hormone produced by the thyroid gland. It is also known as T_4.

Toddler: in the Total Diet Study (TDS), a toddler is defined as a child between 1.5 and 4.5 years of age.

Tolerable Daily Intake (TDI): an estimate of the amount of contaminant, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime without appreciable health risk.

Total Diet Study (TDS): a dietary survey designed to record and measure all components of the diet in order to form a model of the typical UK diet.

Trabecular: a term used by anatomists to describe bone structure. Trabecular bone is bone comprising fine apicules of bone that are not penetrated by blood vessels. The marrow cavity of bones is filled by these trabeculae and the complex structure produced is described as cancellous bone to distinguish it from the compact bone of the walls of the shaft of the whole bone.

Trabeculum: each of the plates of bony substance forming the cancellated tissue of a bone (see Trabecular).

Transcuprein: a protein found in the blood which is able to transport copper.

Transgenic: of an organism: containing genetic material into which DNA (qv) has been artificially introduced into the germ line. Also applied to the cells of a transgenic organism.

Transport Ligand: a chemical group that binds to a compound and facilitates its transport across cell membranes.

Tri-iodothyronine: a hormone produced by the thyroid gland. It is also known as T_3.

Tumour (synonym - neoplasm): a mass of abnormal, disorganised cells, arising from pre-existing tissue, which are characterised by excessive and uncoordinated proliferation and by abnormal differentiation. Benign tumours show a close morphological resemblance to their tissue of origin; grow in a slow expansile fashion; and form circumscribed and (usually) encapsulated masses. They may stop growing and they may regress. Benign tumours do not infiltrate through local tissues and they do not metastasise (qv). They are rarely fatal. Malignant tumours (synonym - cancer) resemble their parent tissues less closely and are composed of increasingly abnormal cells in terms of their form and function. Well differentiated examples still retain recognisable features of their tissue of origin but these characteristics are progressively lost in moderately and poorly differentiated malignancies: undifferentiated or anaplastic tumours are composed of cells which resemble no known normal tissue. Most malignant tumours grow rapidly, spread progressively through adjacent tissues and metastasise to distant sites. Tumours are conventionally classified according to the anatomical site of the primary tumour and its microscopical appearance, rather than by cause.

Uncertainty factor: value used in extrapolation from experimental animals to man (assuming that man may be more sensitive) or from selected individuals to the general population: for example, a value applied to the NOAEL to derive an ADI or TDI. The value depends on the size and type of population to be protected, the toxicological profile of the substance and the quality of the toxicological information available.

Visual analogue scales: visual analogue scales are methods frequently used by psychoanalysts to assess and monitor self-report measures in adults and children in response to a stimulus, particularly those of fear and pain. The measures can be as simple as a horizontal line marked 0 and 10 or 0 and 100 at each end). Sub-divisions may be marked on the line.

Water mains: the network of pipes that carry water from treatment works to homes and businesses.

Weak base: a base which does not convert fully into hydroxide ions in solution.

Wilson's disease: an autosomal recessive inherited disorder of copper metabolism occurring with a frequency of approximately 1 in 30,000 individuals.

Young person: in the Total Diet Study (TDS), a young person is defined as an individual between 4 and 18 years of age.

Appendix 1: Membership of the Lowermoor Subgroup

Chairman

Professor H Frank Woods CBE BM DPhil FFPM FRCP (Lond & Edin) F Med Sci (Formerly Sir George Franklin Professor of Medicine, Division of Molecular and Genetic Medicine, University of Sheffield. Now Emeritus)

Members

Professor J Kevin Chipman BSc PhD CBiol FIBiol FRCPath FBTS FSB (Professor of Cell Toxicology, School of Biosciences, University of Birmingham)
Dr Lesley Rushton OBE BA MSc PhD CStat (Principal Research Fellow, Department of Epidemiology and Public Health, Imperial College London)
Ms Jacquie Salfield BSc MSc MIFST CertEd (Public interest representative)
Professor Stephan Strobel MD PhD FRCP FRCPH (Director of Clinical Education, Peninsula Postgraduate Health Institute)
Dr Anita Donley (formerly Thomas) OBE MB ChB PhD FRCP (Consultant Physician, Plymouth Hospitals NHS Trust)

Local Representatives

Mr Douglas Cross BSc EurProBiol CBiol MIBiol CertEd FSB (From 22 January 2002 to 16 October 2012)
Mr Peter Smith LCH RSHom (From 22 January 2002 to 16 October 2012)

Secretariat

Ms Alison Gowers BSc MSc (From 28 April 2003 to 2 April 2004)
Ms Sue Kennedy Administrative Secretary (From 8 December 2011)
Mr George Kowalczyk BSc MSc DABT CChem FRSC (Until 11 October 2002)
Mr Khandu Mistry Administrative Secretary (Until 5 May 2007)
Ms Frances Pollitt MA DipRCPath Scientific Secretary (From 22 January 2002)
Ms Helen Smethurst BSc MSc (From 10 December 2001 to 28 May 2004)
Mr Michael Waring MA MB BChir BA FRCS LRCP Medical Secretary (Until 31 October 2001: first meeting only)

Appendix 2: Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment[61]

Chairman

Professor David Coggon OBE MA PhD DM FRCP FFOM FFPH FMedSci

Members

Mr Derek Bodey MA (Public interest representative)
Dr Roger Brimblecombe BSc MSc PhD DSc FRCPath FSB Cbiol
Professor Janet Cade BSc PhD PHNutr
Dr Rebecca Dearman BSc PhD
Dr Mark Graham BSc PhD FBTS
Dr Anna Hansell MSc MB BCh PhD MRCP FFPH
Dr David Harrison MD DSc FRCPath FRCPEd FRCSEd
Professor Roy M Harrison OBE PHD DSc FRSC Cchem FRMetS HonMFPHM Hon FFOM Hon MCIEH
Professor Brian Houston BSc PhD DSc
Professor Justin Konje MBBS MB MRCOG Dip Ultrasound
Professor Brian Lake BSc PhD DSc FBTS
Professor Ian Morris BPharm PhD DSc
Dr Nicholas Plant BSc PhD
Professor Robert Smith BA MSc PhD (Public interest representative)
Dr John Thompson FRCP FBTS
Professor Faith Williams MA PhD FTox

Secretariat

Mr Jon M Battershill BSc MSc (Scientific Secretary - HPA) (to 26 September 2012)
Dr Diane J Benford BSc PhD (Scientific Secretary - FSA)
Ms Frances Pollitt MA DipRCPath (Scientific Secretary - HPA) (from 26 September 2012)
Ms Julie Shroff (Administrative Secretary)

[61] As at 11 December 2012

Appendix 3: Health and other professionals who provided information

Those who had meetings with the Subgroup

Professor Freda Alexander (Edinburgh University)
Dr Paul Altmann (Radcliffe Hospital, Oxford)
Mr Malcolm Brandt (Black & Veatch Ltd)
Dr Chris Buckingham (South West Water Authority Residuary Body)
Mr Rolf Clayton (Crowther Clayton Associates)
Dr Ian Coutts (Royal Cornwall Hospitals, Truro)
Professor Jim Edwardson (Newcastle University)
Professor MM Esiri (Oxford University and Oxford Radcliffe NHS Trust)
Dr Chris Exley (Keele University)
Dr David Harris (Aluminium Federation)
Mr Peter Jackson (WRc-NSF)
Dr Chris Jarvis (General Practitioner)
Dr James Lunny (General Practitioner)
Mr Richard Mahoney (Aluminium Federation)
Mrs Jenny McArdle
Professor Tom McMillan[62] (Glasgow University)
Dr David Miles (West of Cornwall Primary Care Trust)
Dr Anthony Nash (General Practitioner)
Ms Pat Owen (West of Cornwall Primary Care Trust)
Mr James Powell (Black & Veatch Ltd)
Professor Nick Priest (Middlesex University)
Professor Michael Rugg (University of California Irvine)
Mr Anthony Wilson
Mr Chris Underwood (South West Water plc)
Dr Neil Ward (Surrey University)

Those who provided written information to the Subgroup

Professor Jim Bridges (Surrey University)
Dr A Davies-Jones (Royal Hallamshire Hospital, Sheffield)
Dr David Gould (Royal Cornwall Hospitals Trust)
Professor ARW Forrest (University of Sheffield)
Dr Norah Frederickson (University College, London)
Dr Alan Foster (formerly Derriford Hospital, Plymouth)
Professor Irvine Gersch (University of East London)
Professor Martin Koltzenburg (Institute of Child Health)
Dr Richard Newman (General Practitioner)
Mr Norman Roberts (Royal Liverpool and Broadgreen University Hospitals NHS Trust)
Dr Tony Wainwright (St Lawrence's Hospital, Bodmin)

[62] By teleconference link

Appendix 4: Discussion of the quality and reliability of scientific data

Introduction

1. The degree of scientific rigour of the available information and the quality of scientific studies affect both the strength of the conclusions which can be drawn from them and the confidence with which the evidence can be used in drawing conclusions about cause and effect, as outlined in Chapter 2 and elsewhere in this report. This appendix outlines some of the principal considerations to be made when assessing the quality of epidemiological and toxicological data[63].

Human Studies

2. Observational studies are often used to examine the influence of substances on human health (see below), whereas experimental studies often assist understanding of the absorption and excretion of the contaminant. Information from human studies may be supported by that from comparable studies in animals.

3. Some human data are available from case reports of accidental or deliberate poisoning incidents but it may be difficult to determine the precise nature of the exposure in such cases. Case reports may be difficult to compare because of the different circumstances of exposure. Supplemental information may be available from data collected on exposure via other routes (e.g. normal exposures via the diet or the medicinal use of a chemical).

Observational studies

4. Observational studies may include ecological studies, which investigate groups of individuals such as those living in a particular city or country, and other types of study (e.g. cross-sectional, cohort and case-control studies) which investigate exposure and health effects (both adverse and beneficial) in individuals. These types of study are described in detail in the following paragraphs.

5. Ecological studies include geographical studies of spatial patterns and time trend studies. In geographical studies, the relationships between the spatial patterns of exposure (for example, region, workplace or school) and disease are described. Time trend studies assess the association between changes in exposure and disease over time.

6. Cross-sectional studies focus on individuals at a specific time i.e. they represent a ‘snapshot ’. They are limited to description of the frequency of the disease at a specific time and the variation between exposure subgroups, where exposure is also ascertained at

[63] Much of this discussion is drawn from the report of the Expert Group on Vitamins and Minerals (Safe upper levels for vitamins and minerals. Food Standards Agency, London, May 2003).

that time. Such studies are most useful for exposures or parameters that cannot change over time e.g. a blood group.

7. Cohort studies (follow-up or prospective studies) follow a group of people with a particular exposure and compare disease occurrence in the exposed group with that in a non-exposed group. Cohort studies enable rates of disease in the exposed and non-exposed populations to be estimated and any associations to be evaluated. However, they may be time consuming and costly and need large numbers of subjects when rare diseases are considered.

8. In case-control studies (retrospective studies), individuals with a particular condition (cases) are compared with a group of individuals without the condition (controls). Information on past exposure to possible risk factors is obtained for both cases and control. The level of exposure in the cases is compared to that of the controls. Case-control studies are useful for studying rare diseases and can be quick and cost efficient. However, recruitment and selection of controls and exposure estimation may present problems when considered retrospectively.

Bias

9. Almost all epidemiological studies are subject to some degree of bias. The three most important types are:

- confounding bias
- information bias
- selection bias

10. Confounding occurs when another variable is associated with both the exposure of interest and the disease of concern. For example, an investigation might find that alcohol consumption is associated with lung cancer. In this case, cigarette smoking (which causes lung cancer) is a confounding factor, because individuals with high alcohol consumption are also more likely to be heavy smokers than those who do not drink alcohol or are only moderate consumers. Confounding factors can be adjusted for either at the design stage, e.g. matching of the factors in a case-control study, or at the analysis stage.

11. Information bias can occur when attempting to correctly identify both the individuals with a disease and in estimating the exposure of an individual (e.g. because of recall bias). This may cause misclassification (in either disease and/or exposure estimation) and can affect estimates of risk.

12. Selection bias arises in the selection of study subjects from the target study population and can be particularly problematic in case-control studies.

Causality

13. An association between an exposure and an effect does not necessarily mean there is a causal relationship. Case-control and cohort studies can both evaluate potential causal relationships. The magnitude of the relative risks or odds ratios gives an indication of a possible causal relationship. Evidence of an exposure-response relationship would also indicate causality. However, such results need to be considered in the context of other epidemiological studies and mechanistic or toxicological investigations.

Assessing human studies

14. When assessing the quality of human studies a number of points should be taken into account, although not all will apply to all studies.

- There should be a clear description of the study objectives and the hypothesis to be tested.
- The study design should be appropriate to achieve the objectives.
- There should be a clear description of the study population (including control or comparison groups if appropriate) and how the main variables were measured, in particular health effects and exposures. Validity and reliability of measurements should be addressed.
- The size of the study should be adequate to provide sufficient power to address the objectives.
- Appropriate statistical analysis methodology should be used and adequately described or referenced.
- Response or tracing rates should be reported and any potential bias through non-response discussed.
- The results should be clearly presented and include both statistical significance levels and confidence intervals if appropriate.
- Potential bias due to confounding, subject selection and data measurement should be addressed in the analyses and discussed.
- The results should be interpreted in the light of evidence from other research, both epidemiological and toxicological, including consistency, strength of association and exposure-response and biological plausibility.

Animal and *in vitro* studies

15. Much of the available information about the absorption and toxicity of chemical contaminants has been generated by studies using laboratory animals. The studies are used to draw inferences about the likely effects of the chemical in humans, and the information from them is extrapolated to estimate the level of exposure which would be expected not to cause adverse effects in humans. The points which need to be considered when assessing toxicological data derived from animal and *in vitro* studies are summarised below.

Types of toxicity data

16. Toxicity studies in animals can be single dose (acute) studies or repeat dose studies of various durations (generally, from 1 week long to studies covering the animals' lifespan). They may be designed to study particular periods or processes during the life of the animal, such as pregnancy, lactation and weaning or skin sensitisation. *In-vitro* studies (studies carried out using biological material taken from an animal) usually investigate specific tissues or cell types to investigate pre-defined end points. The most common *in vitro* studies investigate the potential mutagenicity of chemicals.

17. Toxicity studies can be divided into two broad categories: regulatory studies and investigative studies. Regulatory studies are conducted specifically to assess the safety of a substance in the context of meeting national or international requirements prior to marketing, or in support of health and safety or environmental legislation. Regulatory studies are usually part of a standardised set of investigations and individual studies use well defined methods to study a wide range of body tissues, without any *a priori* hypothesis of possible effects. Investigative studies research a particular issue, such as the mechanism by which a chemical causes a particular effect. These have a more specialised design.

18. Guidelines exist for the conduct of regulatory studies. For example, the Organisation for Economic Cooperation and Development (OECD) sets minimum criteria for acceptability of data on chemicals. There are OECD guidelines for most types of study e.g. *in vitro* mutagenicity studies, multi-generation studies, carcinogencity studies. These provide specific criteria for study design and are formulated to ensure harmonisation of approach and mutual acceptance of data by the different regulatory agencies worldwide. Studies that comply with current OECD guidelines will be of high quality since they reflect the consensus on the most up-to-date practice. Regulatory bodies such as the US Food and Drug Administration or the European Union also produce detailed guidelines for the conduct of regulatory studies. Guidelines for test methods used in mutagenicity studies have been produced by the United Kingdom Environmental Mutagen Society.

19. Other bodies, such as the EU Scientific Committee on Food and the UK Committees on the Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment, have also issued guidelines for regulatory testing of chemicals. These tend to be more flexible, indicating the information or data set required rather than specifying in detail the way in which information should be obtained.

20. Regulatory studies should be conducted in accordance with the principles of Good Laboratory Practice (GLP). This is a system which aims to ensure that laboratory studies are properly planned, performed, monitored and recorded. All information is recorded and tracked so that the results and conclusions can be verified. Quality assurance is an essential component of GLP. Laboratories must be registered for GLP compliance by a

national authority. In the UK, GLP is regulated by the Medicines and Healthcare Products Regulatory Agency, an executive agency of the Department of Health.

21. There are no guidelines covering investigative studies (although they may in some instances be conducted in compliance with GLP). Therefore, professional judgement has to be used to assess the quality of the study. A well-reported study should provide enough information about the methods used to allow the work to be reproduced by others. Data from investigative studies may be used to support or elucidate the findings of regulatory studies.

22. As is often the case for environmental contaminants, few of the data considered by the Subgroup have been generated from studies which were designed to support applications for regulatory approval. Although most of the toxicity studies on environmental contaminants use the same design as regulatory studies, full datasets (i.e. studies examining all of the possible toxicological endpoints) might not always be available.

Assessing animal studies

23. A list of factors considered in assessing the quality of an animal toxicity study is given below and is similar to that given above for human studies. Other, more specialised points will apply to different types of study. Not all the factors below will apply to every study and, where information is missing, this does not always indicate that the study is of poor quality, although it may reduce the amount of confidence which can be put on the results of a study.

- The methods used should be clearly stated and adequate details provided about the results.
- The appropriate species and strain of animal should have been used.
- The numbers should be such that the study has adequate statistical power. For example, at least 50 animals of each sex per dose group should be used in rodent carcinogenicity studies to ensure that a carcinogenic chemical produced an increased incidence of neoplasms in the treated groups. Fewer animals are used in studies of shorter duration or those using non-rodent species (although, in the latter case, this is largely dictated by factors other than statistical considerations).
- The animals should be healthy and housed in suitable conditions. Infections may occur in laboratory animal populations and affect the results and interpretation of a study. It is important to have information on body weights and, preferably, on food and water consumption, because substances that affect the palatability of food or water may confuse toxicological findings by reducing intakes of food and/or water and causing, for example, weight loss and dehydration. Where animals have died during the study it must be clear whether this was a planned sacrifice or an incidental occurrence i.e.whether the animals were found dead or moribund. The cause of death should be stated as this may not always be treatment related.
- In regulatory animal studies, fixed doses of chemical are given to a number (usually 3) groups of animals for the duration of the study. Ideally, the doses used should be adequately spaced to encompass the range which causes adverse effects, through

subtle effects to clear effects, and that which produces no adverse effect. There must also be at least one control group, which receives either no treatment or an inert solution of similar physico-chemical characteristics as the test chemical (the latter in studies in which the substance is administered by gavage). In long-term studies, the dose should not exceed the maximum tolerated dose. Use of excessive doses may affect survival and thus shorten duration of treatment, as well as leaving too few survivors to assess the statistical significance of the effect. It may also produce secondary toxic effects that are of little or no relevance at lower doses. Treatment should cover the appropriate periods in the animals' life. This is particularly important for reproductive and development toxicity studies.

- Appropriate statistical analyses should be conducted.
- Appropriate measures of effect, adequate pathology of all major organs (macroscopic and microscopic), biochemistry, haematology and optimised methods should be used.

Assessing *in vitro* studies

24. Many of the points discussed above have analogies in *in-vitro* testing. For example:

- The methods used should be clearly stated and adequate results provided.
- Appropriate concentrations should be used, taking into account the possible effects of the test article on the test system (e.g. pH, osmolality, cytotoxicity etc). This also depends on the test concerned since some may require testing into the cytotoxic range. The cells or tissues should be exposed in the correct part of the cell cycle.
- Appropriate exogenous activation systems and both negative and positive controls should be used. In addition, it is important to consider whether the tests have been validated. Test methods which are included in regulatory guidelines can be considered adequately validated. Other assays may provide supporting information, but may not be adequate in the absence of results from the accepted test battery.

Interpretation

25. When considering the interpretation of the study, it is important to consider whether the data support the conclusions that have been drawn. It is not possible to conclude that a chemical does not produce adverse effects from an inadequate study and the interpretation of the significance of adverse effects may be confounded by poor conduct or poor reporting of a study. Where there are uncertainties due to a limited study or a poor database, these may sometimes be accounted for by the use of uncertainty factors. Other factors to consider include whether there was a dose-related response (an effect in a single group may indicate a random effect such as a statistical anomaly, a design problem or a highly specific adverse effect).

Peer-review

26. Peer-review is the process used by scientists to control the quality of scientific work and of scientific publications i.e. to ensure that the methods used in the study are sound and the conclusions drawn from the work are justified. The usual process by

which scientists obtain peer-review is by submitting the report of a study, drafted in the form of a scientific paper, to a 'peer-reviewed scientific journal'. The journal submits the paper to at least two respected scientists who work in the same area of work as that discussed in the paper (eg epidemiology, toxicology, ecology). These 'peer-reviewers' make an assessment of the work and advise on whether the conclusions are sound and the paper should be published or not. They may recommend that it could be published after changes to the text or some additional work, in which case it is sent back to the author for amendment.

27. All scientific work should be peer-reviewed before publication. Work which is not peer-reviewed cannot be regarded with the same confidence as peer-reviewed work, as there has been no independent, expert assessment of its quality. Therefore, those assessing scientific data distinguish between unpublished reports and papers from peer-reviewed journals, and place less reliance on results from unpublished than on published scientific papers.

Appendix 5: Consultation Responses

Introduction

Most consultation responses are published in full below, with the consent of the author. Where permission to publish was not received, only a brief description of the content is provided.

In two cases the responses contained only personal medical information and these have not been published, for reasons of confidentiality. Published papers, articles or book chapters sent with some responses have not been reproduced for copyright reasons.

List of those who provided consultation responses

Date	From	Comments
1/2/05	Dr R Handy Plymouth University	Enclosed published book chapter and article.
17/2/05	Mrs C Wyatt Cornwall	Letter with personal medical information.
17/2/05	Mr T Chadwick Cornwall	Document with observations made at the time of the incident and comments on the remit of the investigation and the nature of the contamination after the incident and flushing programme.
23/2/05	Mr R Bowler Cornwall	Enclosed published article: 'Probe overcomes hairy problem' (New Scientist, 1 April 1995).
24/2/05	Mrs J Young Cornwall	Enclosed published article: 'Clash over water analysis results' (Surveyor, 31 May 1990).
1/3/05	Black & Veatch Ltd Surrey	Attached
9/3/05	Mr P Stewart Australia	Attached
14/3/05	Mr P Stewart Australia	Attached
29/3/05	Mr P Stewart Australia	Attached
20/4/05	Mr P Stewart Australia	Attached
9/3/05	Mr and Mrs I Clewes Devon	Letter with comments on remit of investigation, draft report and presentations at public meeting.

14/3/05	Dr D Miles West of Cornwall Primary Care Trust	Letter with comments on paragraphs 5.47 to 5.50 of draft report.
28/3/05	Mrs E Sigmund Cornwall	Document with comments about personal experience of events and on Subgroup's failure to review medical records and undertake clinical investigations.
21/3/0	Mr D Cross Somerset	Attached
8/04/05	Mr D Cross, Somerset, and Mr P Smith, Cornwall	Attached
12/4/05	Ms S Hazell Cornwall	Letter with personal medical information.
15/4/05	Dr C Exley Keele University	Attached
21/4/05	Mr C Buckingham Pennon Group plc	Letter with comments on the report.
21/4/05	Dr R Burnham Royal College of Physicians	Attached
214/05	Dr Bettina Platt University of Aberdeen	Attached
22/4/05	Mr E Jansson Department of the Planet Earth Washington	Attached
22/4/05	Dr M Waring Health Protection Agency	Attached
22/2/05	Mrs S Joiner Cornwall	Attached*
13/4/05	Leigh, Day & Co Solicitors London	Attached*
21/4/05	Mr A Wilson Cornwall	Attached*
19/5/05 and 31/3/06	Dr W Rea Environmental Health Center - Dallas	Attached*

* These responses can be found on our website as a scanned copy

01/03/2005

Frances

I have attached a list of typos/errors/comments for the consultation report. It mainly relates to our report (Appendix 10). There are four relatively important points which I have highlighted in red – these definitely should be amended. The other points are less important. I have made the amendments which relate to our report using track changes. Let me know if you would like a PDF version.

Regards

James

James Powell
Black & Veatch Ltd
69 Grosvenor House
London Rd
Redhill
Surrey RH1 1LQ

Ref	Page/Para/Line	Comments
A	181/7.29/3	I am not familiar with the 'Margin of Safety' concept, but I suspect the equation is incorrect. Surely it should be: $MoS = \frac{NOAEL}{Daily\ intake}$ i.e. higher intake gives lower margin of safety
B	196/6/2	Not sure if this definition of MoS is correct (see A)
C	Abbreviations and Glossary	Margin of Safety is not listed in glossary or abbreviations
D	Glossary	Definition of coagulant could cause concern as in water treatment terms, Aluminium Sulphate is a coagulant: In water treatment, the a coagulant is a substance which causes very fine particles to stick together (it is an ionic process)
Appendix 10 – BV report		
1	264/5/2	Minor Typo – Replace '*of*' with '*for*'
2	264/5/4	Minor Typo – Replace '*on*' with '*of*'
3	265/2/2	Minor Typo – Delete '*and*'
4	270/6/1	Minor Typo – Replace '*of*' with '*for*'
5	270/7/6	Minor Typo – Replace '*which*' with '*that*'
6	275 Fig 12	Zero minutes graphic is printed as black it should be blue
7	277/4/3	Minor Typo – Lower case '*aluminium sulphate*'
8	279/16/1	Serious Typo – Replace '*contact*' with '*clear water*'
9	281/1/2	Serious Typo – Replace '*12*' with '*24*'
10	281/3/3	Minor Typo – Replace '*affect*' with '*effect*'
11	281/3/8	Minor Typo – Replace '*affect*' with '*effect*'
12	283/1/2	Minor Typo – Delete space after 'Table 1'
13	284/1/29	Minor Typo – Replace '*with*' with '*within*'
14	284/2/6	Delete sentence *'BVCs has been unable to locate the fifth private supply, that titled "Mount Camel"'* – Following discussions at the public meeting, we realise that we had already accounted for this sample
15	285 Fig 22	Dates are all one day too late i.e. should run 6 July to 9 July not 7 July to 10 July
16	286/5/	After paragraph 5 insert new paragraph "*One private sample was taken on the morning of 7th July and analysed by the Laboratory of the Government Chemist, Taunton in December 1988. The measured aluminium concentration of 28 mg/l is consistent with the modelled results.*" – see comment 14
17	290/2/1	Minor Typo – Insert '*the*' between '*for*' and '*area*'
18	293/2/3	Minor Typo – Replace '*for*' with '*of*'
19	295/2/14	Incorrect statement - Delete "*At worst the contaminant concentration would be no greater than the CFD modelling predicts. If the density of the sludge blanket was greater than the contaminant, the latter would be a layer above the sludge blanket and therefore dilution and dispersion would have been accelerated.*"
20	296 Point 5	On reflection we would prefer to remove the word '*serious*'. It is a bit emotive and our conclusion relies on the assumptions about the set up of the tank e.g. outlet level, the sludge issue. If these assumptions prove to be incorrect then the level of doubt would be reduced NB. This is also quoted on page 67 Para 3.70
21	Appendix 10 general	Throughout our report we have used the term 'Clear Water Tank'. We note that in the main report the term 'Treated Water Reservoir' is generally used (e.g. Page 29).

09/03/2005

Dear Sir,
Please find attached a case study report which supports the toxicity of aluminium. If you have any questions, please feel free to contact me.
Peter Stewart

A Case Study In Human Aluminium Toxicity.

Background.

The subject was employed in an aluminium remelting plant in the period from February 1996 until December 1998. The plant processed 1200 tonnes/month of aluminium by ingot melting, continuous casting, rolling reduction, annealing, drawing, winding, & scrap reprocessing.

Occupational contamination levels were not determined at the time of exposure; however, anecdotal evidence of exposure relates that after being in the plant for more than 20 minutes, a film of oil and metal dust would be present on the skin, and that the plant contained a visible haze.

In July 1996 the subject presented to the on-site medical centre complaining of fatigue. Blood glucose was tested and the random result was 4.91 mmol/l, a normal result with no indications of diabetes. In May 1998 the subject's health had deteriorated, so he attended a private hospital health assessment centre for a full check-up. The symptoms evident were gastro-intestinal (IBS), fatigue, and increased number of respiratory infections.

Blood test results indicated mildly elevated liver enzymes (GGT and ALT), characteristic of Non Alcoholic Liver Disease (NALD), and anisocytosis, reflected in a high RDW. The problem was incorrectly diagnosed as due to lifestyle factors, and no further tests were conducted.

At the same time the subject had been experiencing significant problems with neurological dysfunction, as indicated by short-term memory, decision making, mood, irritability, aggressiveness, and anxiety.

There is no history of any other exposure to aluminium. The local water authority has regularly tested for aluminium as per their quality assurance program, and low levels are maintained. There have been no incidences of chemical overdosing to the water supply, or use of Al-based antacids.

Discovery.

In 2003 the subject contracted cellulitis, which was taking a long time to heal. In the investigation of the reason for the delayed healing, a hair sample was taken on the 16th July 2003 and submitted for mineral analysis. The result reported for Aluminium was 248 parts per million (ppm).

The reference interval established by the laboratory in accordance with normal clinical laboratory protocol is less than 18 ppm. A recheck of the result was performed and confirmed prior to release of the data.

The test was conducted by Trace Elements Inc. (TEI), which is a licensed and certified clinical laboratory that undergoes regular inspections with Clinical Laboratory Division of the Dept. of Health and Human Services, HCFA, USA. Analysis is by ICP-Mass Spectrometry (Sciex Elan 6100) methodology for all trace element determinations. The laboratory is equipped with a trace element class clean room utilizing HEPA filtration systems. The level of Al in the range reported (248 ppm) is found in less than 0.04% within the population tested of over 27,000 patient samples (samples obtained in accordance with established collection protocol) processed by the laboratory.

Subsequently the initial hair tissue mineral analysis was supported by tests of other tissues including Toenail, Fingernail, Foot Skin, Semen, and Underarm Hair, with other laboratories, and over a significant period of time. Refer to Graph One for the results mapped over the duration of stage one chelation.
In order to confirm the likely source of exposure, semen from 2000 was tested and allowed the construction of the probable contamination curve. The aluminium levels are consistent with a biological half-life of 3 years, and indicate that the level of tissue contamination in 1998 would have been about three times the level detected in 2003. Refer to Graph Two for the backward projection of aluminium levels.

Exposure Estimate.

Exposure is estimated using actual and estimated physical conditions:

- Assumed airborne contamination Level, 15 mg/m3
- Elevated temperature environment due metal remelting
- High breathing rates due heat, activity, & level of contamination.
- Respiration, 10 breaths/minute
- Lung Volume, 4.5 litres at end, (5.7 litres at start)
- Duration, 10 hours/day, 50% presence, 1074 days
- Uptake, at saturation conditions, 15%
- Total uptake over 3 years = 32,622 mg.
- Half Life, (non-repeating exposure) = 3 years
- Calculated body burden 5 years after exp. = **10,765 mg.**

Exposure is compared to projections based on tissue test results:

- Tissue tests, (mean) = 102 mg/kg
- Body weight = 140 kgs.
- Calculated body burden from tests = **10,529 mg.**

Hypothetical Clearance of Sequestered Aluminium:

Based on possible biological clearance rates for aluminium, the following projection can be made for the reduction in sequestered tissue levels between 1998 and 2003:

- Av. Biological Fluids Al Content = 6.55 ppm, 5/9/2003
- Urinary Clearance at this Rate = 17,930 mg
- Sweat Clearance, (0.3 l/day) = 3,586 mg (impaired)

- Hair Tissue Clearance = 16.25 mg
- Nails Tissue Clearance = 15.00 mg
- Faecal Clearance, (from 3.1) = 3.3 mg/day = 6,022 mg
- Calculated Clearance over 5 years = 27,569 mg.
- Calculated body burden from hypothetical clce = 5,053 mg.

The clearance of sequestered aluminium from the body is consistent with the calculated half-life, the tissue test results, and the occupational exposure, with the hypothetical clearance being higher than the actual clearance due to the mobilisation at the time of fluids testing (5/9/2003).

The Estimated Occupational Exposure exceeds the Recommended Tolerable Weekly Intake (RTWI) of 7 milligrams per Kg body weight for all age groups, as set by the FAO/WHO Joint Expert Committee on Food Additives, (JECFA), by a significant amount, (being factor 3.37).

Adverse Health Effects.

Adverse health effects from aluminium, experienced by the subject both at exposure, and during chelation, and also reported in medical research are as follows:

- Psychological dysfunction, tested by QEEG 17/6/2003
- Cognitive Impairment, tested by ERP 24/10/2003
- CNS Balance Disturbance, tested 26/2/2004
- Cognitive Impairment, tested by Neuropsychological Series 6/8/2004
- Vareta Neurofunctional Assessment, evaluated 3/6/2004
- Neural Plaque, high-resolution Spect scan 8/4/2004
- Gastro Intestinal disturbance (IBS)
- Intestinal Flora Imbalance and Leaky Gut
- Anisocytosis and Haemolytic Anaemia
- Lymphocytopenia
- Chronic Fatigue Syndrome
- Sperm Hyperactivation Dysfunction, as per SPA 9/4/2004
- Sperm Morphology, Head Defects, as per SCSA 3/5/2004
- Renal Impairment
- Hepatic Impairment
- Solar Hyperkeratosis from sweat gland exudation of Al

Neuropsychological Testing revealed a pattern of dysfunction which had some similar findings to that of Altmann (19), in a retrospective study of people exposed to contaminated drinking water at Camelford, who found reduced performance on psychomotor speed relative to estimated premorbid IQ, which could not be attributed to anxiety.

Reproductive Effects.

Metals in semen appear to inhibit the function of enzymes contained in the acrosome, the membrane that covers the head of the sperm. The effect is to disrupt the acrosome reaction and inhibit capacitation. The enzyme acrosin, contained in non-reacted acrosome, is thought to have a role in digestion of the sperm path through the zona pellucida, or in the zona binding process. The acrosome reaction occurs following tight binding to the ZP3 receptor located on the zona pellucida of the oocyte and is a prerequisite for the fertilisation process. Sperm that acrosome-react prematurely will be unable to bind to the zona pellucida. Sperm which are unable to bind to the oocyte and/or unable to acrosome-react, will also be unable to fertilise the oocyte, Dana (74).

The study of Aluminium in Finnish Men, Hovatta (1), found a definite correlation between aluminium in the spermatozoa and motility and morphology of the spermatozoa, but there was no correlation between the concentration of aluminium in the seminal plasma and the semen analysis parameters. In addition, "The semen analysis of the three men with clearly the highest aluminium concentrations in their spermatozoa, (from 8.7 to 21.5 ppm), showed asthenozoospermia in all three cases, (A + B motilities from 16 to 46%)".

In this case the subject recorded an aluminium level of 16.7 ppm in 2000, which is of both semen and spermatozoa, and scored an A + B motility of 53% in 2004. Morphology in 2000 was unknown, and in 2004 was unusually low.

In a study of seminal plasma metal levels, Dawson (45), found an inverse relation between aluminium in seminal plasma and sperm viability. Apparently the presence of the metal in the seminal plasma exerts a toxic effect on sperm.

The subject's reproductive status is therefore consistent with aluminium toxicity in the period c2000 to the current day.

Current Situation.

The chelation of aluminium continues in a pulsed manner as allowed by the renal and hepatic capacity. Although the level is within the reference range, it rebounds after the chelation run, indicating that tissue stores still exist.

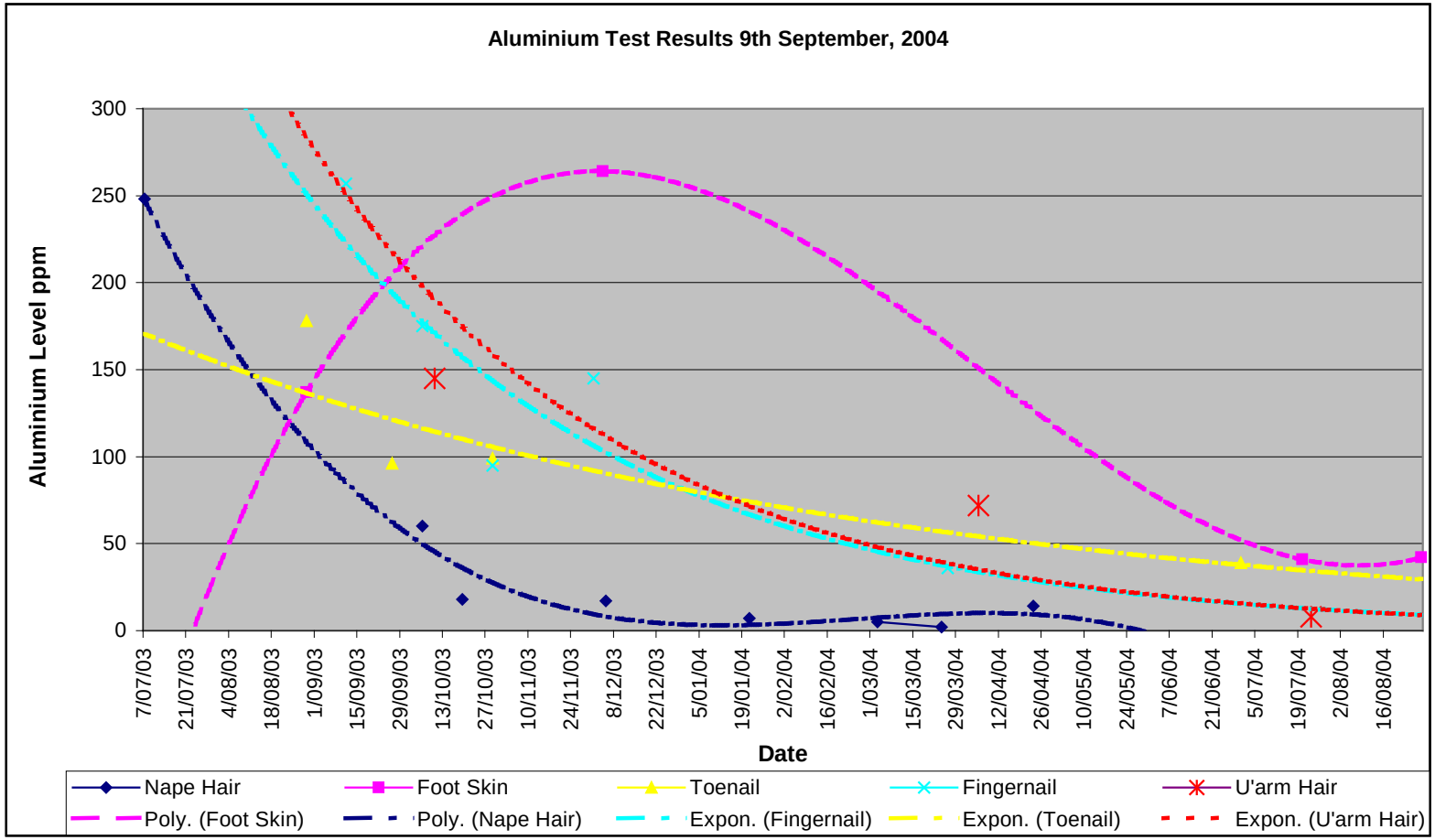
The test of removal will be the no-rebound test, plus a clear brain scan using the PET isotope PIB C-11, which is said to be capable of detecting neural plaques and is currently under clinical trials.

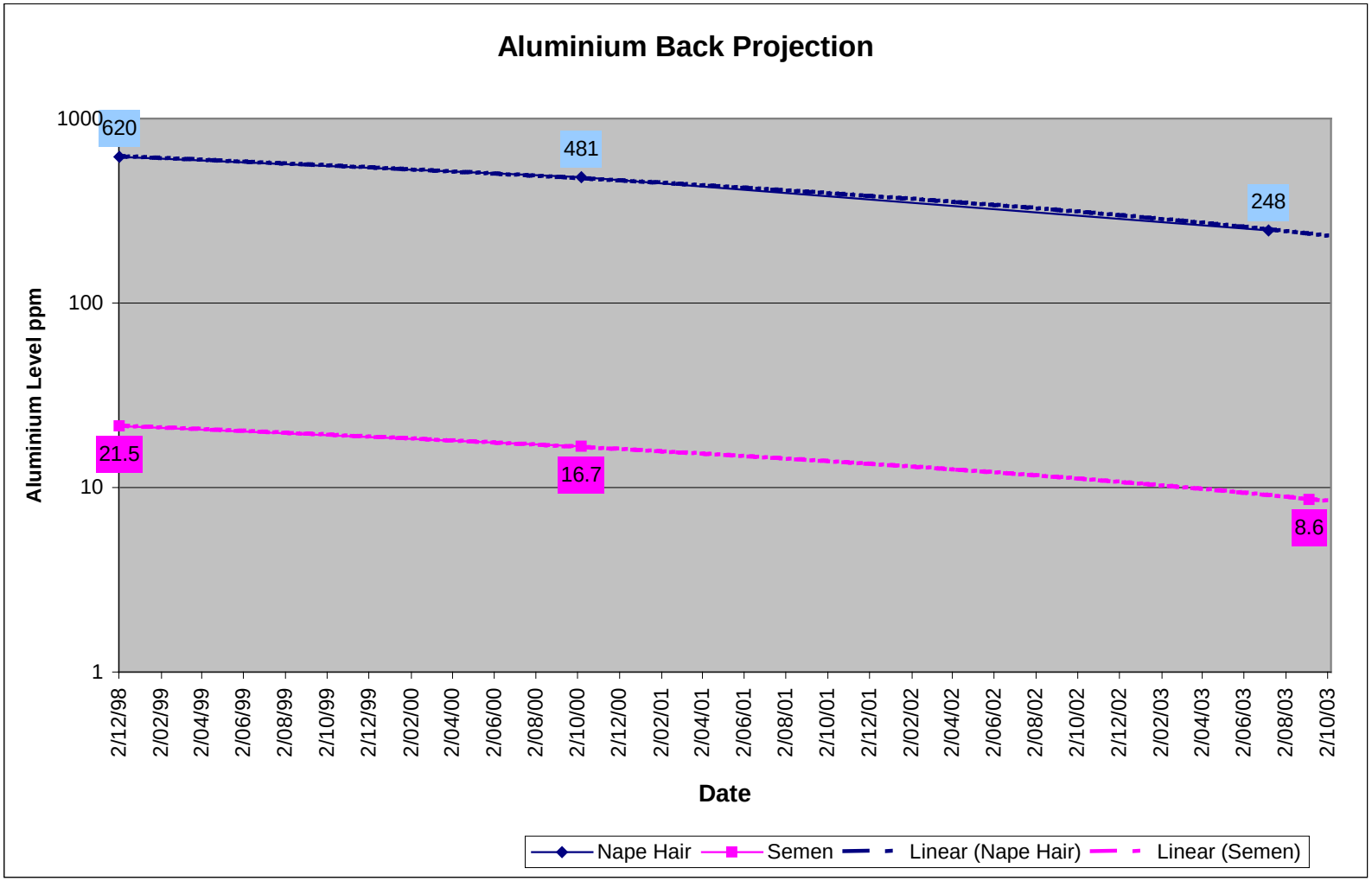
Peter Stewart.
8th March 2005.

Attached:

- Aluminium Tissue Test Results, 9th September 2004
- Aluminium Back Projection, to 1998

- Bibliography/References


Aluminium Test Results 9th September, 2004
Aluminium Level ppm
300
250
200
150
100
50
0
7/07/03
21/07/03
4/08/03
18/08/03
1/09/03
15/09/03
29/09/03
13/10/03
27/10/03
10/11/03
24/11/03
8/12/03
22/12/03
5/01/04
19/01/04
2/02/04
16/02/04
1/03/04
15/03/04
29/03/04
12/04/04
26/04/04
10/05/04
24/05/04
7/06/04
21/06/04
5/07/04
19/07/04
2/08/04
16/08/04
Date
Nape Hair
Foot Skin
Toenail
Fingernail
U'arm Hair
Poly. (Foot Skin)
Poly. (Nape Hair)
Expon. (Fingernail)
Expon. (Toenail)
Expon. (U'arm Hair)


Aluminium Back Projection
1000
100
10
1
Aluminium Level ppm
620
481
248
21.5
16.7
8.6
2/12/98
2/02/99
2/04/99
2/06/99
2/08/99
2/10/99
2/12/99
2/02/00
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Linear (Semen)

Bibliography/References:

1. Aluminium, lead and cadmium concentrations in seminal plasma and spermatozoa, and semen quality in Finnish men.
   Hovatta, Venalainen, Kuusimaki, Heikkila, Hirvi, and Reima. Human Reproduction, vol 13, no 1, pp115-119, 1998
2. Glutathione as a treatment for male infertility.
   D Stewart Irvine. Review of Reproduction, (1996), 1, 6-12.
3. A prospective analysis of the accuracy of the TEST-yolk buffer enhanced hamster egg penetration test and acrosin activity in discriminating fertile from infertile males.
   Romano, Santucci, Marrone, Gabriele, Necozione, Valenti, Francavilla, and Francavilla. Human Reproduction, vol 13, no 3, pp2115-2121, 1998.
4. Analysis of the impact of intracellular reactive oxygen species generation on the structural and functional integrity of human spermatozoa: lipid peroxidation, DNA fragmentation and effectiveness of antioxidants.
   Twigg, Fulton, Gomez, Irvine, and Aitken. Human Reproduction, vol 13, no 6, pp1429-1436, 1998.
5. **Does exposure to fine aluminium dust affect the brain?**
   Kaye Kilburn The *Lancet*, Vol 354, Nov. 6, 1999, 1575-1577.
6. **Aluminum, iron, zinc, and copper influence the in vitro formation of amyloid fibrils of Aβ_{42} in a manner which may have consequences for metal chelation therapy in Alzheimer's disease.**
   Emily House, Joanna Collingwood, Ayesha Khan, Olga Korchazazhina, Guy Berthon, and Christopher Exley. *Journal of Alzheimer's Disease*, 4 (2002), 1-11.
7. **Neurotransmitter dopamine applied in electrochemical determination of aluminum in drinking waters and biological samples.**
   Fuping Zhang, Li Yang, Shuping Bi, Jian Liu, Feng Liu, Xianlong Wang, Xiaodi Yang, Ning Gan, Yu Tsing, Jun Hu, Hongzhao Liu, and Tainming Yang. *Journal of Inorganic Chemistry*, 87, 2001, 105-113.
8. **Interactions of Al(III) with a neurofilament heptapeptide fragment AcLysSerProValGluGly.**
   T. Kiss, M. Kilyen, A. Lakatos, F. Evanics, T. Kortvelyesi, Gy. Dombi, Zs. Majer, M. Hollosi. *Coodination Chemistry Reviews*, 278, (2002), 237-236.
9. **Decrements in cognitive performance in metal inert gas welders exposed to aluminium.**
   Akila, R., Stollery, B. T., & Riihimaki, V. (1999). Occup Environ Med, 56, 632-639.
10. **Neuropsychological deficit among elderly workers in aluminum production.**
    Bast-Pettersen, R., Drablos, P. A., Goffeng, L. O., Thomassen, Y., & Torres, C. G. (1994). Am J Ind Med, 25, 649-662.
11. **Longitudinal study examining the neurotoxicity of occupational exposure to aluminium-containing welding fumes.**
    Buchta, M., Kiesswetter, E., Otto, A., Schaller, K. H., Seeber, A., Hilla, W., Windorfer, K., Stork, J., Kuhlmann, A., Gefeller, O., & Letzel, S. (2003). Int Arch Occup Environ Health, 76, 539-548.
12. **Effects of metals on the nervous system of humans and animals.**
    Carpenter, D. O. (2001). Int J Occup Med Environ Health, 14, 209-218.
13. **Internal load of aluminum and the central nervous system function of aluminum welders.**

Hanninen, H., Matikainen, E., Kovala, T., Valkonen, S., & Riihimaki, V. (1994) Scand J Work Environ Health, 20, 279-285.

14. **Neuropsychological toxicology. Identification and assessment of human neurotoxic syndrome (2nd ed.).**
Hartman, D. E. (1995). New York: Plenum Press.
15. **Mental abilities of workers exposed to aluminium.**
Hosovski, E., Mastelica, Z., Sunderic, D., & Radulovic, D. (1990). Med Lav, 81, 119-123.
16. **Potroom palsy? Neurologic disorder in three aluminum smelter workers.**
Longstreth, W. T., Jr., Rosenstock, L., & Heyer, N. J. (1985). Arch Intern Med, 145, 1972-1975.
17. **Pulmonary fibrosis and encephalopathy associated with the inhalation of aluminum dust.**
McGlaughlin A et al (1962) British Journal of Industrial Medicine 19, 253.
18. **Camelford water poisoning accident: serial neuropsychological assessments and further observations on bone aluminium.**
McMillan, T. M., Freemont, A. J., Herxheimer, A., Denton, J., Taylor, A. P., Pazianas, M., Cummin, A. R., & Eastwood, J. B. (1993). Hum Exp Toxicol, 12, 37-42.
19. **Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident.**
Altmann, P., *et al.,* BMJ 1999 Sep 25, 319 (7213), 807-811.
20. **Neurotoxic effects of aluminium among foundry workers and Alzheimer's disease.**
Polizzi, S., Pira, E., Ferrara, M., Bugiani, M., Papaleo, A., Albera, R., & Palmi, S. (2002). Neurotoxicology, 23, 761-774.
21. **Effect of exposure of miners to aluminium powder.**
Rifat, S. L., Eastwood, M. R., McLachlan, D. R., & Corey, P. N. (1990). Lancet, 336, 1162-1165.
22. **Are aluminium potroom workers at increased risk of neurological disorders?**
Sim, M., Dick, R., Russo, J., Bernard, B., Grubb, P., Krieg, E., Jr., Mueller, C., & McCammon, C. (1997). Occup Environ Med, 54, 229-235.
23. **Effects on the nervous system among welders exposed to aluminium and manganese.**
Sjogren, B., Iregren, A., Frech, W., Hagman, M., Johansson, L., Tesarz, M., & Wennberg, A. (1996). Occup Environ Med, 53, 32-40.
24. **Safety evaluation of dietary aluminum.**
Soni, M. G., White, S. M., Flamm, W. G., & Burdock, G. A. (2001). Regul Toxicol Pharmacol, 33, 66-79.
25. **Aluminum poisoning: dialysis encephalopathy, osteomalacia and anemia.**
Wills, MR and Savory J (1983) Lancet 2, 29-34
26. **The toxicology of aluminum in the brain: a review.**
Yokel RA (2000). Neurotoxicology. 2000 Oct;21(5):813-28.
27. **Reproductive and developmental toxicity of aluminium: a review.**
Domingo JL. Neurotoxicol Teratol. 1995 Jul-Aug;17(4):515-21.
28. **Hair as an indicator of excessive aluminium exposure.**
Yokel R.A., Clinical Chemistry, 28 (1982), 662-665.
29. **Toenail trace element levels as biomarkers: reproducibility over a 6-year period.**

Garland, M., *et al.*, Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA.

30. **The nail and hair in forensic science.**
    Ralph Daniel III, C., *et al.*, J Am Acad Dermatology, Feb. 2004. 258-261.
31. **Selective accumulations of aluminium in five human arteries.**
    Minami, T., *et al.*, Biol Trace Element Res., Vol. 79, 2001, 29-38.
32. **Hair Analysis Panel Discussion: Exploring The State Of The Science.**
    Prep for the ATSDR, by Eastern Research Group, December, 2001.
33. **Toxic and essential metal interactions.**
    Goyer RA. Annu Rev Nutr. 1997;17:37-50.
34. **Membrane composition can influence the rate of Al3+-mediated lipid oxidation:**
    effect of galactolipids.
    Verstraeten SV, Keen CL, Golub MS, Oteiza PI. Biochem J. 1998 Aug 1;333 (Pt 3):833-8.
35. **Aluminum: impacts and disease.**
    Nayak P. Environ Res. 2002 Jun;89(2):101-15.
36. **Effect of different solid metals and metallic pairs on human sperm motility.**
    Kesseru E, Leon F. Int J Fertil. 1974;19(2):81-4.
37. **Experimental study of biological effects of leads and aluminum following oral administration.**
    Krasovskii GN, Vasukovich LY, Chariev OG. Environ Health Perspect. 1979 Jun;30:47-51.
38. **Effects of aluminium chloride on human spermatozoa.**
    Kaur S. Bull Environ Contam Toxicol. 1988 Mar;40(3):444-6.
39. **Cytogenetic, developmental, and biochemical effects of aluminum, iron, and their mixture in sea urchins and mussels.**
    Pagano G, His E, Beiras R, De Biase A, Korkina LG, Iaccarino M, Oral R, Quiniou F, Warnau M, Trieff NM. Arch Environ Contam Toxicol. 1996 Nov;31(4):466-74.
40. **Presence of several elements in normal and pathological human semen samples and its origin.**
    Skandhan KP, Abraham KC. Andrologia. 1984 Nov-Dec;16(6):587-8.
41. **Genetic monitoring of aluminum workers exposed to coal tar pitch volatiles.**
    Heussner JC, Ward JB Jr, Legator MS. Mutat Res. 1985 Mar;155(3):143-55.
42. **Aluminium, lead and cadmium concentrations in seminal plasma and spermatozoa, and semen quality in Finnish men.**
    Hovatta O, Venalainen ER, Kuusimaki L, Heikkila J, Hirvi T, Reima I. Hum Reprod. 1998 Jan;13(1):115-9.
43. **Comparison of sperm viability with seminal plasma metal levels.**
    Dawson EB, Ritter S, Harris WA, Evans DR, Powell LC. Biol Trace Elem Res. 1998 Summer;64(1-3):215-9.
44. **Effect of potash alum (aluminium potassium sulphate) on human semen and sperm.**
    Singh HP, Singh CK, Singh RR. Indian J Physiol Pharmacol. 1998 Apr;42(2):311-4.
45. **Seminal plasma trace metal levels in industrial workers.**
    Dawson EB, Evans DR, Harris WA, Powell LC. Biol Trace Elem Res. 2000 May;74(2):97-105.
46. **Reproductive toxicology of aluminum in male mice.**

Llobet JM, Colomina MT, Sirvent JJ, Domingo JL, Corbella J.
Fundam Appl Toxicol. 1995 Apr;25(1):45-51.

47. **Assessment of aggression, sexual behavior and fertility in adult male rat following long-term ingestion of four industrial metals salts.**
Bataineh H, Al-Hamood MH, Elbetieha AM. Hum Exp Toxicol. 1998 Oct;17(10):570-6.
48. **Male infertility: nutritional and environmental considerations.**
Sinclair S. Altern Med Rev. 2000 Feb;5(1):28-38.
49. **Biochemistry of the induction and prevention of lipoperoxidative damage in human spermatozoa.**
Storey BT. Mol Hum Reprod. 1997 Mar;3(3):203-13.
50. **Oxidative stress and role of antioxidants in normal and abnormal sperm function.**
Sikka SC. Front Biosci. 1996 Aug 1;1:e78-86.
51. **Seminal plasma reduces exogenous oxidative damage to human sperm, determined by the measurement of DNA strand breaks and lipid peroxidation.**
Potts RJ, Notarianni LJ, Jefferies TM. Mutat Res. 2000 Feb 14;447(2):249-56.
52. **Status of vitamin E and reduced glutathione in semen of oligozoospermic and azoospermic patients.**
Bhardwaj A, Verma A, Majumdar S, Khanduja KL. Asian J Androl. 2000 Sep;2(3):225-8.
53. **Glutathione in spermatozoa and seminal plasma of infertile men.**
Ochsendorf FR, Buhl R, Bastlein A, Beschmann H. Hum Reprod. 1998 Feb;13(2):353-9.
54. **Relationship between oxidative stress, semen characteristics, and clinical diagnosis in men undergoing infertility investigation.**
Pasqualotto FF, Sharma RK, Nelson DR, Thomas AJ, Agarwal A.
Fertil Steril. 2000 Mar;73(3):459-64.
55. **Oxidative stress in normospermic men undergoing infertility evaluation.**
Pasqualotto FF, Sharma RK, Kobayashi H, Nelson DR, Thomas AJ Jr, Agarwal A.
J Androl. 2001 Mar-Apr;22(2):316-22.
56. **Lipoperoxidation damage of spermatozoa polyunsaturated fatty acids (PUFA): scavenger mechanisms and possible scavenger therapies.**
Lenzi A, Gandini L, Picardo M, Tramer F, Sandri G, Panfili E.
Front Biosci. 2000 Jan 1;5:E1-E15.
57. **Polyunsaturated fatty acids of germ cell membranes, glutathione and blutathione-dependent enzyme-PHGPx: from basic to clinic.**
Lenzi A, Gandini L, Lombardo F, Picardo M, Maresca V, Panfili E, Tramer F, Boitani C, Dondero F. Contraception. 2002 Apr;65(4):301-4.
58. **Glutathione treatment of dyspermia: effect on the lipoperoxidation process.**
Lenzi A, Picardo M, Gandini L, Lombardo F, Terminali O, Passi S, Dondero F.
Hum Reprod. 1994 Nov;9(11):2044-50.
59. **Glutathione therapy for male infertility.**
Lenzi A, Lombardo F, Gandini L, Culasso F, Dondero F.
Arch Androl. 1992 Jul-Aug;29(1):65-8.
60. **Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility.**
Lenzi A, Culasso F, Gandini L, Lombardo F, Dondero F.

Hum Reprod. 1993 Oct;8(10):1657-62.
61. **Relative impact of oxidative stress on male reproductive function.**
Sikka SC. Curr Med Chem. 2001 Jun;8(7):851-62.
62. **Heavy metal chelators prolong motility and viability of sea urchin sperm by inhibiting spontaneous acrosome reactions.**
Johnson CH, Epel D. J Exp Zool. 1983 Jun;226(3):431-40
63. **Male infertility and environmental exposure to lead and cadmium.**
Benoff S, Jacob A, Hurley IR. Hum Reprod Update. 2000 Mar-Apr;6(2):107-21.
64. **GABA initiates the acrosome reaction and fertilizing ability in human sperm.**
Yuan YY, He CN, Shi QX. Sheng Li Xue Bao. 1998 Jun;50(3):326-32.
65. **Capacitation-associated changes in protein tyrosine phosphorylation, hyperactivation and acrosome reaction in hamster spermatozoa.**
Kulanand J, Shivaji S. Andrologia. 2001 Mar;33(2):95-104.
66. **Seminal lead concentrations negatively affect outcomes of artificial insemination.**
Benoff S, Hurley IR, Millan C, Napolitano B, Centola GM.
Fertil Steril. 2003 Sep;80(3):517-25.
67. **Molecular identification of Ca2+ channels in human sperm.**
Park JY, Ahn HJ, Gu JG, Lee KH, Kim JS, Kang HW, Lee JH.
Exp Mol Med. 2003 Aug 31;35(4):285-92.
68. **Hyperactivated sperm motility driven by CatSper2 is required for fertilization.**
Quill TA, Sugden SA, Rossi KL, Doolittle LK, Hammer RE, Garbers DL.
Proc Natl Acad Sci U S A. 2003 Dec 9;100(25):14869-74.

69. **Inhibition of human and bovine sperm acrosin by divalent metal ions. Possible role of zinc as a regulator of acrosin activity.**
Steven FS, Griffin MM, Chantler EN. Int J Androl. 1982 Aug;5(4):401-12.
70. **Sperm motility hyperactivation facilitates penetration of the hamster zona pellucida.**
Stauss CR, Votta TJ, Suarez SS. Biol Reprod. 1995 Dec;53(6):1280-5.
71. **Effect of copper ion on the motility, viability, acrosome reaction and fertilizing capacity of human spermatozoa in vitro.**
Roblero L, Guadarrama A, Lopez T, Zegers-Hochschild F. Reprod Fertil Dev. 1996;8(5):871-4.
72. **Lead-induced changes in spermatozoa function and metabolism.**
Hsu PC, Hsu CC, Liu MY, Chen LY, Guo YL.
J Toxicol Environ Health A. 1998 Sep 11;55(1):45-64.
73. **Hyperactivation of mammalian spermatozoa: function and regulation.**
Ho HC, Suarez SS. Reproduction. 2001 Oct;122(4):519-26.
74. **Impaired hyperactivation of human sperm in patients with infertility.**
Munire M, Shimizu Y, Sakata Y, Minaguchi R, Aso T. Med Dent Sci. 2004 Mar;51(1):99-104.
75. **Assessment of sperm function and clinical aspects of impaired sperm function.**
Dana A. Ohl, M.D.[1] and Alan C. Menge, Ph.D.[2]
Frontiers in Bioscience 1, e96-108, September 1,1996
76. **Novel association between sperm reactive oxygen species production, sperm morphological defects, and the sperm deformity index.**

Aziz N, Saleh RA, Sharma RK, Lewis-Jones I, Esfandiari N, Thomas AJ Jr, Agarwal A.
Fertil Steril. 2004 Feb;81(2):349-54.

77. **Sperm Morphology, Motility, and Concentration in Fertile and Infertile Men. David S. Guzick, M.D., Ph.D., James W. Overstreet, M.D., Ph.D., Pam Factor-Litvak, Ph.D., Charlene K. Brazil, B.S., Steven T. Nakajima, M.D., Christos Coutifaris, M.D., Ph.D., Sandra Ann Carson, M.D., Pauline Cisneros, Ph.D., Michael P. Steinkampf, M.D., Joseph A. Hill, M.D., Dong Xu, M.Phil., Donna L. Vogel, M.D., Ph.D., for the National Cooperative Reproductive Medicine Network**
The New England J of M, Volume 345:1388-1393, November 8, 2001,Number 19
78. **Reproductive epidemiology of aluminium foundry workers.**
Prasad, M. H., *et al.,* Institute of Genetics, Osmania University, Hyderabad, India.
79. **The role of quantitative EEG topographic mapping or 'neurometrics' in the diagnosis of psychiatric and neurological disorders: the pros.**
John, E.R., Electroencephalogr Clin Neurophysiol, 1989. 73(1):p. 2-4.
80. **Neurometrics.**
John, E.R., et al., Science, 1977. 196(4297): p. 1393-410.
81. **Neurometrics: computer-assisted differential diagnosis of brain dysfunctions.**
John, E.R., et al., Science, 1988. 239(4836): p. 162-9.
82. **Conventional and quantitative electroencephalography in psychiatry.**
Hughes, J.R. and E.R. John,
Journal of Neuropsychiatry and Clinical Neurosciences, 1999. 11(2): p. 190-208.
83. **Subtyping of psychiatric patients by cluster analysis of QEEG.**
John, E.R., L.S. Prichep, and M. Almas, Brain Topogr, 1992. 4(4): p. 321-6.
84. **QEEG profiles of psychiatric disorders.**
Prichep, L.S. and E.R. John, Brain Topogr, 1992. 4(4): p. 249-57.
85. **Neurometrics.**
Flitter, M.A., Jama, 1982. 248(11): p. 1308-9.
86. **The role of quantitative topographic mapping or 'neurometrics' in the diagnosis of psychiatric and neurological disorders: the cons.**
Fisch, B.J. and T.A. Pedley, Electroencephalogr Clin Neurophysiol, 1989. 73(1): p. 5-9.
87. **The clinical role of computerized EEG in the evaluation and treatment of learning and attention disorders in children and adolescents.**
Chabot, R.J., et al., J Neuropsychiatry Clin Neurosci, 2001. 13(2): p. 171-86.
88. **Sensitivity and specificity of QEEG in children with attention deficit or specific developmental learning disorders.**
Chabot, R.J., et al., Clin Electroencephalogr, 1996. 27(1): p. 26-34.
89. **Quantitative electroencephalographic profiles of children with attention deficit disorder.**
Chabot, R.J. and G. Serfontain, Biological Psychiatry, 1996. Nov 15(10): p. 951-963.
90. **EEG measures of cerebral asymmetry: conceptual and methodological issues.**
Davidson, R.J., Int J Neurosci, 1988. 39(1-2): p. 71-89.
91. **Approach-withdrawal and cerebral asymmetry: emotional expression and brain physiology.**
Davidson, R.J., et al., *I.* J Pers Soc Psychol, 1990. 58(2): p. 330-41.
92. **Anterior cerebral asymmetry and the nature of emotion.**

Davidson, R.J., Brain Cogn, 1992. 20(1): p. 125-51.
93. **Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects.**
Henriques, J.B. and R.J. Davidson, J Abnorm Psychol, 1990. 99(1): p. 22-31.
94. **Frontal brain asymmetry and emotional reactivity: a biological substrate of affective style.**
Wheeler, R.E., R.J. Davidson, and A.J. Tomarken, Psychophysiology, 1993. 30(1): p. 82-9.
95. **Frontal EEG asymmetry and the behavioral activation and inhibition systems.**
Coan, J.A. and J.J. Allen, Psychophysiology, 2003. 40(1): p. 106-14.
96. **[Computerized test as a diagnostic auxiliary--TOVA--another tool in the diagnosis off attention deficit disorders (ADHD)].**
Manor, I., Y. Sever, and A. Weizman, Harefuah, 1999. 136(10): p. 812-5.
97. **Correlation study between WISC-III scores and TOVA performance.**
Chae, P.K., Psychology in the Schools, 1999. 36(3): p. 179-185.
98. **Clinical utility of the Test of Variables of Attention (TOVA) in the diagnosis of attentiondeficit/hyperactivity disorder.**
Forbes, G.B., *Journal* of Clinical Psychology, 1998. 54(4): p. 461-476.
99. **Developmental normative data on the Test of Variables of Attention (T.O.V.A.).**
Greenberg, L.M. and I.D. Waldman, Journal of Child Psychology and Psychiatry, 1993. 34(6): p. 1019-1030.
100. **Effect of aluminium on lipid peroxidation of human high density lipoproteins.**
Ferretti, G., et al., Free Radic Res, 2003. 37(5): p. 515-21.
101. **The role of metals in neurodegenerative processes: aluminum, manganese, and zinc.**
Zatta, P., et al., Brain Res Bull, 2003. 62(1): p. 15-28.
102. **Aluminium-induced impairment of Ca2+ modulatory action on GABA transport in brain cortex nerve terminals.**
Cordeiro, J.M., et al., J Inorg Biochem, 2003. 97(1): p. 132-42.
103. **Effect of aluminum on the blood-brain barrier permeability during nitric oxideblockade-induced chronic hypertension in rats.**
Kaya, M., et al., *Biol* Trace Elem Res, 2003. 92(3): p. 221-30.
104. **Brain uptake, retention, and efflux of aluminum and manganese.**
Yokel, R.A., *Environ* Health Perspect, 2002. 110 Suppl 5: p. 699-704.
105. **Aluminium-induced changes in the rat brain serotonin system.**
Kumar, S., Food Chem Toxicol, 2002. 40(12): p. 1875-80.
106. **Effects of metals on the nervous system of humans and animals.**
Carpenter, D.O., Int J Occup Med Environ Health, 2001. 14(3): p. 209-18.
107. **Aluminum, NO, and nerve growth factor neurotoxicity in cholinergic neurons.**
Szutowicz, A., J Neurosci Res, 2001. 66(5): p. 1009-18.
108. **Aluminum-induced dendritic pathology revisited: cytochemical and electron microscopic studies of rabbit cortical pyramidal neurons.**
Forbes, M.S., et al., Ann Clin Lab Sci, 2002. 32(1): p. 75-86.
109. **Neurotoxicology of the brain barrier system: new implications.**
Zheng, W., J Toxicol Clin Toxicol, 2001. **39**(7): p. 711-9.
110. **Aluminium overload influences cognitive function in patients on dialysis.**

Kambova, L., D. Ionova, and Z. Kirijakov, Nephrol Dial Transplant, 1994. 9(9): p. 1357.

111. Neurotoxic effects of dietary aluminium.
Jope, R.S. and G.V. Johnson, Ciba Found Symp, 1992. 169: p.254-62; & 262-7.

112. Aluminium toxicity and binding to Escherichia coli.
Guida, L., *et al.*, Biosphere Sciences Division, King's College London, UK.

113. Effect of alum on intestinal microecological balance in mice.
Yan, M., *et al.*, Institute of Chinese Materia Medica, China Academy of Traditional Chinese Medicine, Beijing.

114. Influence of alum on intestinal flora in mice.
Yan, M., *et al.*, Institute of Chinese Materia Medica, China Academy of Traditional Chinese Medicine, Beijing.

115. The inactivation of Escherichia Coli by microalloyed aluminium based composite.
Bojic, A., *et al.*, Physics, Chemistry, and Technology, Vol. 2, No. 3, 2001, 115-124.

116. Aluminium and Alzheimer's disease.
Wisniewski, H.M. and G.Y. Wen, Ciba Found Symp, 1992. 169: p. 142-54; discussion 154-64.

117. Internal load of aluminum and the central nervous system function of aluminum welders.
Hanninen, H., et al., Scand J Work Environ Health, 1994. 20(4): p. 279-85.

118. Determination of metal concentrations in animal hair by the ICP Method.
Marta, A., Chyla, and Wieslaw Zyrnicki, Biological Trace Element Research, Vol. 75, 2000, 187-194.

119. Aluminium toxicity: The relevant role of the metal speciation.
Zatta, P., Analusis Magazine, 26 (1998), No. 6, 72-76.

120. Aluminium speciation in relation to aluminium bioavailability, metabolism, and toxicity.
Berthon, G., Coordination Chemistry Reviews, 228 (2002), 319-341.

121. Entry, half-life, and Desferrioxammine-accelerated clearance of brain aluminium after a single Al_{26} exposure.
Yokel, R., Toxicological Sciences, 64 (2001), 77-82.

122. A mechanistic in vitro approach to risk assessment and biomonitoring of neurotoxic metals.
Environmental Health and Chemical Safety Research, Contract ENV4-CT96-0173, Manzo, L..

123. A Cluster of Equine Granulomatous Enteritis cases: the link with Aluminium.
Fogarty, U., *et al.*, NRCET, UQ, Brisbane, Queensland.

124. Scanning electron microscopic study of the eccrine ostia of mouse foot pads after application of antiperspirant.
Sungnack Lee, Dong Sik Bang, and Chung Koo Cho, Yonsei Medical Journal, Vol. 24, No. 2, 1983.

125. Lipid peroxidation as a consequence of aluminium toxicity in human skin fibroblast cultures: prevention by superoxide dismutase + catalase, vitamin E, and vitamin C.
Rachid Anane and Edmond E. Creppy, Laboratory of Toxicology and Applied Hygiene, University of Victor Segalen, France.

126. Effect of aluminium and lead salts on lipid peroxidation and cell survival in human skin fibroblasts.
Dominguez, M.C., *et al.*, Unitat de Recerca BiomAedica, Barcelona, Spain.
127. Effect of long-term aluminium feeding on kinetics attributes of tissue cholinesterases.
Kunian, D., *et al,*. Brain Research Bulletin, Vol. 58, No. 2, pp. 225-233, 2002.
128. Morphological and functional alterations of erythroid cells induced by long-term ingestion of aluminium.
Vittori, D., *et al.*, Journal of Inorganic Biochemistry, 76 (1999), 113-120.
129. Disturbance of cellular iron uptake and utilization by aluminium.
Perez, G., *et al.*, Journal of Inorganic Biochemistry, 87 (2001), 21-27.
130. Human erythroid cells are affected by aluminium. Alteration of membrane band 3 protein.
Vittori, D., *et al.*, Biochimica et Biophysica Acta, 1558 (2002), 142-150.
131. Effect of chronic poisoning with aluminium on the renal handling of phosphate in the rat.
Mahieu, S., and Calvo, M. L., Toxicology Letters, 94 (1998), 47-56.
132. Aluminium fluoride affects the structure and functions of cell membranes.
Suwalsky, M., *et al.*, Food and Chemical Toxicology, 42 (2004), 925-933.
133. Transport and subcellular distribution of intranasally administered zinc in the olfactory system of rats and pikes.
Persson, E., *et al.*, Toxicology, 191 (2003), 97-108.
134. Transport of manganese via the olfactory pathway in rats; Dosage dependency of the uptake and subcellular distribution of the metal in the olfactory epithelium and the brain.
Hendriksson, J., *et al.*, Toxicology and Applied Pharmaco;ogy, 156 (1999), 119-128.
135. Accumulation of manganese in rat brain following intranasal administration.
Gianutsos, G., *et al.*, Fundamental and Applied Toxicology, 37 (1997), 102-105.
136. Quantitative particle-induced X-ray emission imaging of rat olfactory epithelium applied to the permeability of rat epithelium to inhaled aluminium.
Divine, K., *et al.*, Chem. Res. Toxicol. 12 (1999), 575-581.
137. Uptake of cobalt from the nasal mucosa into the brain via olfactory pathways in rats.
Persson, E., *et al.*, Toxicology Letters, 145 (2003), 19-27.
138. Fine particle deposition within human nasal airways.
Martonen, T., *et al.*, Inhalation Toxicology, 15 (2003), 283-303.
139. Review: Nasal toxicity, Carcinogenicity, and olfactory uptake of metals.
F. W. Sunderman, Jr., Annals of Clinical & Lab. Science, Vol. 31, No. 1, 2001.
140. Hazard Prevention and Control In The Workplace: Airborne Dust.
WHO/SDE/OEH/99.14.
141. Transcription of the Escherichia coli fliC Gene is regulated by metal ions.
Guzzo, A., *et al.*, Applied and Experimental Microbiology, Aug 1991, Vol. 57, No. 8, 2255-2259.
142. Leptin, gut, and food intake.
Attele, A., *et al.*, Biochemical Pharmacology, 63 (2002), 1579-1583.
143. Aluminium uptake by the in situ rat gut preparation.

Provan S.D., Yokel R.A., J Pharmacological Exp Ther, 245 (1988), 928-931.

144. Does either the gastrointestinal peptide PYY or the neuropeptide NPY bind aluminium?
Korchazhkina, O., *et al.,* Journal of Inorganic Biochemistry, 94 (2003), 372-380.

145. Neuropeptide Y, peptide YY and aluminium in Alzheimer's disease: Is there an etiological relationship?
Croom, J. and Taylor, I., Journal of Inorganic Biochemistry, 87 (2001), 51-56.

146. Changes in catecholamine levels of cerebellum, mid-brain, and brain-cortex in aluminium intoxified rats.
Moshtaghie, A., *et al.,* Indian Journal of Pharmacology, 28 (1998), 244-248.

147. Myelin is a preferred target of aluminium-mediated oxidative damage.
Verstraeten, S., *et al.,* Archives of Biochemistry and Biophysics, Vol. 344, No. 2, 1997, 289-294.

148. Selective modulation of $GABA_A$ Receptors by aluminium.
Trombley, P., The American Physiological Society, 1998, 755-761.

149. Chronic administration of aluminium L-glutamate in young mature rats; effects on iron levels and lipid peroxidation in selected brain areas.
Deloncle, R., *et al.,* Toxicology Letters, 104 (1999), 65-73.

150. A molecular mechanism of aluminium-induced Alzheimer's disease.
Exley, C., Journal of Inorganic Biochemistry, 76 (1999), 133-140.

151. Aluminium enhances iron uptake and expression of neurofibrillary tangle protein in neuroblastoma cells.
Abreo, K., *et al.,* Journal of Neurochemistry, 1999, Vol. 72, No. 5, 2059-2064.

152. Effects of aluminium exposure on glutamate metabolism; a possible explanation for its toxicity.
Struys-Ponsar, C., *et al.*,Experimental Neurology, 163, (2000), 157-164.

153. Effect of aluminium-induced Alzheimer like condition on oxidative energy metabolism in rat liver, brain, and heart mitochondria.
Swegert, C., *et al.,* Mechanisms of Ageing and Development 112 (1999), 27-42.

154. Oxidative and hydrolytic properties of B-amyloid.
Brzyska, M., *et al.,* Eur. Journal of Biochemistry, 268 (2001), 3443-3454.

155. Effects of aluminium on the neurotoxicity of primary cultured neurons and on the aggregation of B-amyloid protein.
Kawahara, M., *et al.,* Brain Research Bulletin, Vol. 55, No. 2, (2001), 211-217.

156. Aluminium affects membrane physical properties in human neuroblastoma (IMR-32) cells both before and after differentiation.
Verstraeten, S., *et al.,* Archives of Biochemistry & Biophysics, Vol. 399, No. 2, (2002), 167-173.

157. Aluminium toxicity in the rat brain: Histochemical and immunocytochemical evidence.
Platt, B., *et al.,* Brain Research Bulletin, Vol. 55, No. 2, (2001), 257-267.

158. Aluminium and iron in the brain-prospects for chelation.
Crichton, R., *et al.,* Coordination Chemistry Reviews, 228 (2002), 365-371.

159. Spectroscopic and voltammetric study on the binding of aluminium (III) to DNA.
Zhang, R., *et al.,* Analytical Sciences, July 2002, Vol. 18, 761-766.

160. In vivo and In vitro effects of aluminium on the activity of mouse brain acetylcholinesterase.
Zatta, P., *et al.,* Brain Research Bulletin, Vol. 59, No. 1, (2002), 41-45.

161. Pro-inflammatory effects of aluminium in human glioblastoma cells.

Campbell, A., *et al.,* Brain Research, 933 (2002), 60-65.

162. Intracellular mechanisms underlying aluminium-induced apoptosis in rabbit brain.
Savory, J., *et al.,* Journal of Inorganic Biochemistry, 97 (2003), 151-154.

163. Neuropathology of aluminium toxicity in rats (glutamate and GABA impairment).
Sahar S. Abd El-Rahman, Pharmacological Research, 47 (2003), 189-194.

164. Aluminium and copper interact in the promotion of oxidative but not inflammatory events: Implications for Alzheimer's disease.
Becaria, A., *et al.,* Journal of Alzheimer's Disease, 5 (2003), 31-38.

165. Aluminium maltolate-induced toxicity in NT2 cells occurs through apoptosis and cytochrome-c release.
Griffioen, K., *et al.,* NeuroToxicology, 25 (2004), 859-867.

166. First evidence for helical transitions in supercoiled DNA by amyloid B peptide (1-42) and aluminium.
Hegde, M., *et al.,* Journal of Molecular Neuroscience, Vol. 22, (2004), 19-31.

167. Aluminium, iron, zinc, and copper influence the in vitro formation of amyloid fibrils of AB_{42} in a manner which may have consequences for metal chelation therapy in Alzheimer's disease.
House, E., *et al.,* Journal of Alzheimer's Disease, 4 (2002), 1-11.

168. Metal-protein attenuation with Iodochlorhydroxyquin (Clioquinol) targeting AB amyloid deposition and toxicity in Alzheimer's Disease.
Ritchie, C., *et al.,* Archives of Neurology, Vol. 60, Dec. 2003, 1685-1690.

169. Molecular shuttle chelation: The use of ascorbate, desferrioxammine, and Feralex-G in combination to remove nuclear bound aluminium.
Kruck, T., *et al.,* Cellular and Molecular Neurobiology, Vol. 24, No. 3, June, 2004, 443-459.

170. Environmental Health Criteria 194, Aluminium.
World Health Organization, International Program on Chemical Safety, 1997.

171. Aluminium, a neurotoxin which affects diverse metabolic reactions.
Joshi, J.G., Biofactors July 1990, 2(3), 163-169.

172. Sepsis: A cause of aluminium release from tissue stores associated with acute neurological dysfunction and mortality.
Davenport, A., *et al.,* Clinical Nephrology, July 1998, 30(1), 48-51.

173. Guidelines on metals and alloys used as food contact materials.
CE Policy Statement Technical Document.

174. Australian Drinking Water Guidelines 1996.
NH&MRC, National Water Quality Management Strategy.

175. Intraneuronal aluminium potentiates iron-induced oxidative stress in cultured rat hippocampal neurons.
Xie, C.X., *et al.,* Brain Research, 743 (1996), 271-277.

176. The role of experimental chronic renal failure and aluminium intoxication in cellular immune response.
Tzanno-Martins, C., *et al.,* Immunology Division, University of Sao Paulo Medical School, Brazil.

177. Aluminium-induced injury to kidney cells: Effects on markers of oxidative damage.
Sargazi, M., *et al.,* J Inorganic Biochemistry, 87 (2001), 37-43.

178. Apoptosis; not the mechanism of aluminium related cell damage to renal proximal tubular cells.

Sargazi, M., *et al.,* J Inorganic Biochemistry, 87 (2001), 37-43.

179. Managing Health In The Aluminium Industry.
Priest, N., and O'Donnell, T., Middlesex University Press, London, England.

180. Cognitive Impairments in Siblings of Alzheimer's disease patients: possible preclinical signs of the disease.
Palsson, S., Dept of Psychology, University of Cophenhagen, Denmark, 2002.

Good Morning Khandu
Please add the attached “Hyperlinked References” to the case study, which I have submitted earlier.
Thank you.
Regards, Peter Stewart.

Aluminium Toxicity References (Hyperlinked)

Version:one 14th March 2005

The metallobiology of Alzheimer's disease.	PubMed 12689772
Neurobehavioural symptoms assoc with Al remelting.	PubMed 9766477
Effect of Al on skin lipid peroxidation.	PubMed 7779576
Metal chelators inhibit Abeta accumulation.	PubMed 11430801
Metals contribute to the accumulation of Abeta.	PubMed 12032279
Copper, Abeta, and Alzheimer's disease.	PubMed 14506299
Metals, oxidation, and Alzheimer's disease.	PubMed 15105262
Neurological effects of aluminium dust.	PubMed 10560668
Metal protein attenuation of Abeta toxicity.	PubMed 14676042
Neurotoxic effects of Al among foundry workers.	PubMed 12520766
Al influences the formation of AB42 fibrils.	PubMed 15201484
Al affects scDNA helicity and superhelicity.	PubMed 14742907
Copper induces aggregation of Abeta protein.	PubMed 14659627
Effect of Aluminium on the AChE enzyme.	PubMed 12372547
Aluminium and brain lipid peroxidation.	PubMed 10048751
Myelin is a preferential target for Aluminium damage.	PubMed 9264541
Aluminium effect on reproduction.	PubMed 9512240
Peptide YY may complex with Aluminium.	PubMed 12667709
Aluminium induces aggregation of Abeta protein.	PubMed 11470317
Aluminium and copper interact in oxidative events.	PubMed 12590164
Aluminium enhances NFT protein in euro 2A cells.	PubMed 10217285
Selective accumulation of Aluminium in arteries.	PubMed 11318235
Aluminium induced toxicity in NT2 Cells.	PubMed 15288516
Aluminium accelerates aberrant presenilin 2.	PubMed 15009634
Toxicity of Aluminium; a historical review. Part 2	PubMed=8218719
Aluminium Toxicity	PubMed=4112209
Aluminium Toxicity	PubMed=4119214
Aluminium Intoxification	PubMed=6708992
The cellular toxicity of aluminium	PubMed=291812
The neurotoxicity of aluminium salts in patients with renal insufficiency	PubMed=2669059
The effect of aluminium on the structure and metabolism of collagen	PubMed=7923326
Immune system to uremia	PubMed=13322
Immunological impairment in renal insufficiency and dialysis	PubMed=7456804
An experimental animal model of aluminium overload	PubMed=7842302
Distribution of aluminium between plasma and erythrocytes	PubMed=4077077
Renal effects of Al in uraemic rats and rats with intact kidney function	PubMed=3958430
T-Lymphocytes in chronic renal failure	PubMed=318095
The immunological state in chronic renal insufficiency	PubMed=6981610
Impaired renal function and aluminium metabolism	PubMed=6617895
T-Lymphocyte & serum inhibitors of cell-mediated immunity in CRI	PubMed=1079332
Effects of short-term JP-8 jet fuel exposure on cell-mediated immunity	PubMed=10798625
Effect of chronic accumulation of aluminium on renal function and stress	PubMed=12928767
Influence of Al on the immune system-a study on volunteers	PubMed=11016399
T cell function in chronic renal failure and dialysis	PubMed=7986474
The effect of DFO on tissue Al concentration in rats with renal failure	PubMed=2980801

Interaction of Al & gallium with lymphocytes; the role of transferrin	PubMed=1958694
Impaired cell immune responses in chronic renal failure; a T cell defect	PubMed=3489122
Animal model of Al-induced osteomalacia; role of chronic renal failure	PubMed=6842959
T cell subsets and cellular immunity in end stage renal disease	PubMed=6227236
The role of experimental Al intoxication in allogenic immunoresponse	PubMed=7576023
Cellular immunity and lymphocyte no's in developing uraemia in the rat	PubMed=2946817
The role of experimental CRF and Al intox in cell immune response	PubMed=8671818
Macrophagic myofasciitis & vacine-derived AlOH in muscle	OUPJournals/124/9/1821
Increased gene expression of APP in senescent cultured fibroblasts	PubMed=1702541
Human erythroid cells affected by Al; Alteration of membrane B-3 protein	PubMed=11779564
B-APP is detectable on monocytes & is inc. in Alzheimer's Disease	PubMed=10588572
B-APP deposition in tissues other than brain in Alzheimer's Disease	PubMed=2528696
Al released from tissues causes acute neurological dysf. & mortality	PubMed=3208458
Aluminium overload in renal failure	oupjournals abstract/17/suppl_2/9
Effect of Al on cholinergic enzyme of rat brain	PubMed 9654357
Effect of Al on dopamine in the hypothalamus	PubMed=10707345
Effect of Al on thyroid function	ijem/20/2
Effect of Al-citrate on tissue composition of sheep	PubMed=2016205
Effect of Al on the pituitary-testicular axis	PubMed=2109985
Al and Ni in serum and lymphocytes of CRF patients	Pubmed=3971590
Lymphocyte analysis for trace metal analysis	Pubmed=3776600
Effect of metals on DNA synthesis and lymphokines IV	Pubmed=1675963
Al intoxication in renal disease	Pubmed=1490419
Genotoxic effects of PAHs for aluminium plant workers	Pubmed=1297065
Myoinositol in lymphocytes of CRF patients is impaired	Pubmed=7566575
Al toxicity contributes to immunological impairment in CRF	Pubmed=8671818
Effect of Al on cytokine production	Pubmed=8814247
Effect of Al on cytokine response	Pubmed=9278332
Biomonitoring of genotoxicity in occupational exposures	Pubmed=10575430
Al initiates a strong Th-2 responses	Pubmed=10586035
Al induces alterations in neuronal cytokine messages	Pubmed=10650912
Influence of Aluminium on the immune system	Pubmed=11016399
Immonulogical disorders induced by heavy metals	Pubmed=11334498
Immunological effects of Al on lymph cells	Pubmed=11562064
The role of IL-18 in Al induced Th-2 responses	Pubmed=12562321
Neurobehavioural function & Lymph subsets in Al workers	Pubmed=12797904
Effects of heavy metals on immune reactions	Pubmed=12920793
B cell response via an Al induced myeloid cell population	Pubmed=15205534
Al dust exposure causes granulomatous lung diseases	Pubmed=15281437
Immunotoxicity of aluminium chloride	Pubmed=15318624
T-cell subsets in idiopathic CD-4+ T-Lymphocytopenia	Pubmed=8098929
Aluminium in tissues	Pubmed=3915959
Hyperparathyroidism and aluminium overload	Pubmed=6483074
Aluminium toxicity in chronic renal insufficiency	Pubmed=3905084
Septicemia complicating chelation therapy with DFO	Pubmed=3867344
Amyloid deposits associated with aluminium overload	Pubmed=2966951
Anaemia is a well defined complication of Al overload	Pubmed=2623200
DFO as a chelating agent for treatment of Al overload	Pubmed=2697761
The diagnosis of Al-associated microcytic anaemia	Pubmed=2909650
The toxic effects of desferrioxammine	Pubmed=2660937
Pathogenesis and treatment of Al induced anaemia	Pubmed=2615192

Serum Al monitoring in dialysis patients	Pubmed=2109284
Aluminium and secondary hyperparathyroidism	Pubmed=2326587
Al adversely affects myocardial calcium transport	Pubmed=2148851
Al interferes with iron absorption and transfer	Pubmed=1745387
Al affects the response to rHuEpo in dialysis	Pubmed=1328942
Al may contribute to tumoral calcifications	Pubmed=1565177
Al may contribute to urolithiasis in patients with CRF	Pubmed=1552617
Al reduces the effect of rHuEpo on anaemia	Pubmed=1578966
Prurigo nodularis and aluminium overload in dialysis	Pubmed=1351616
Heme oxygenase as a factor in Al induced anaemia	Pubmed=7511925
Al overload influences cognitive function in dialysis	Pubmed=7816312
An experimental animal model of Al overload	Pubmed=7842302
Al overload reduces RBC life via membrane peroxidation	Pubmed=7573188
Mechanisms of aluminium-induced microcytosis	Pubmed=7731142
Comparative efficacy of iron and Al chelating drugs	Pubmed=7482575
Use of the DFO test to diagnose Al overload	Pubmed=8592597
Low-dose DFO treatment for acute Al intoxication	Pubmed=8649620
Aluminium accumulation in clinical nephrology	Pubmed=8804004
Efficacy of low-dose DFO test for Al overload estimation	Pubmed=8933580
HPs as an alternative to DFO for aluminium toxicity	Pubmed=9029049
DFO improves erythropoiesis in dialysis patients	Pubmed=9623553
ATP in cellular calcium-overload by trivalent metal ions	Pubmed=9630430
Low serum Al may be associated with Al overload	Pubmed=9725776
DFO chelates iron and enhances erythropoiesis in dialysis	Pubmed=10586429
Hypochromic anaemia is associated with Al OL in CRF	Pubmed=10778588
Deferiprone does not prevent Al foetal toxicity in mice	Pubmed=10931505
An experimental model of intracerebral Al overload	Pubmed=11039305
Al potentiates GLU-induced neuronal damage	Pubmed=11057035
Al overload leads to parathyroid hormone supression	Pubmed=11274267
Diagnostic utility of serum Al and the DFO test in Al OL	Pubmed=11464651
Dementia in patients undergoing long-term dialysis	Pubmed=11580308
Al OL reduces the efficacy of rHuEpo treatment	Pubmed=11590253
Aluminium toxicity and iron homeostasis	Pubmed=11709207
Synthesis of Feralex, a novel chelating compound	Pubmed=11750021
Serum Al levels in the DFO test are affected by iron status	Pubmed=11777318
The clinical impact of Al overload in renal failure	Pubmed=11904351
Aluminium exposure and Alzheimer's disease	Pubmed=12214020
A study of the effects of LT exposure of adult rats to Al	Pubmed=12959739
Elucidation of endemic neurodegenerative disorders	Pubmed=14577644
Molecular shuttle chelation to remove nuclear bound Al	Pubmed=15206824
Aluminium increases the production of ECF	Pubmed=2864377
Hyperaluminiumemia releted to hepatic granulomata	Pubmed=2802942
Aluminium may induce alterations in cell immune responses	Pubmed=11562064
Aluminium binds to canine duodenal mucosal extracts	Pubmed=3814759
Intestinal Al absorption is pH and concentration dependent	Pubmed=3958427
Metabolism and possible health effects of aluminium	Pubmed=2940082
1,25(OH)2D3 receptors and endorgan response in Al intox.	Pubmed=2821318
Al uptake by the in situ rat gut preparation	Pubmed=2455041
Influence of prolonged antacid administration on rat gut mucosa	Pubmed=3144098
Effect of Al on bidirectional calcium flux in rat everted int. sacs	Pubmed=2782413
Effect of iron and precomplexation on Al intestinal uptake	Pubmed=1745394

Bacterial translocation through the gut mucosa	Pubmed=1902478
Aluminium absorption in the presence of normal kidney function	Pubmed=1896590
Al hydroxide uptake in the gut of the rat	Pubmed=1384259
Al inhibits enzymes related to cell energy metabolism	Pubmed=1328029
Al in brain tissues of rats exposed to inhalation of Al(acac)3	Pubmed=8219037
Aluminium adheres to the intestinal mucosa	Pubmed=7926905
Increased intestinal paracellular permeability enhances Al abs.	Pubmed=8943470
Mechanisms of aluminium absorption in rats	Pubmed=9129475
Intestinal absorption of Al; Effect of Na and Ca	Pubmed=9456083
Al effects on calbindin D9K-linked duodenal transport	Pubmed=10079056
Effect of alum on intestinal microecological balance in mice	Pubmed=11783189
Fine and ultrafine particles of the diet; immune response and Crohns	Pubmed=12002786
Effects of Zr and Al salts on alveolar macrophages	Pubmed=715772
Toxicity of metal ions to alveolar macrophages	Pubmed=6282121
Aluminium in joints of CRF patients on dialysis	Pubmed=6699835
Cellular distribution of Ca, Al, & Si in uremic nephrocalcinosis	Pubmed=4047006
Al ind damage of the lysosomes in the liver, spleen, & kidney of rats	Pubmed=3624785
Toxic organic damage	Pubmed=2650456
Effect of chronic Al loading on lysosomal enzymes	Pubmed=2748708
Aluminium-maltolate induced toxicity in NT2 cells	Pubmed=15288516
Al taken up by transferrin affects iron metabolism in rat cortical cells	Pubmed=9504407
Effects of Al on activity of krebs cycle enzymes & glu-dehydrogenase	Pubmed=10806405
Molecular & cellular mechanisms of iron homostasis & toxicity	Pubmed=12121757
Diff toxicity of NO, Al, & AB in SN56 cholinergic cells of mouse septum	Pubmed=12470706
Al triggers decreased aconitase activity via Fe-S cluster disruption	Pubmed=15548528
Exp study of biological effects of lead & Al following oral administration	Pubmed=446457
Inflammatory effect of aluminium phosphate on rat paws	Pubmed=6283459
Multiorgan Al deposits in a chronic dialysis patient	Pubmed=6438896
What is the value of plasma Al in CRF patients	Pubmed=3842104
Neurochemical abnormalities in brains of RF patients on dialysis	Pubmed=2411864
Al increases C-AMP in rat cerebral cortex in vivo	Pubmed=3020329
Al load in patients with analgesic nepropathy	Pubmed=3627045
Pulmonary response of rat lung to instillation of potroom dust	Pubmed=3569186
Maternal & developmental toxicity of chronic Al exposure in mice	Pubmed=3569705
Serum Al & normal kidney function, effect of age and exposure	Pubmed=2623263
The comparison of fibrogenic dusts by bronchoalveolar lavage	Pubmed=2154066
Effect of propentofylline on the biochemical lesion of the rat brain	Pubmed=2336050
Iron uptake in Al overload, in vivo and in vitro studies	Pubmed=1745387
Al induced chronic myelopathy in rabbits	Pubmed=1901636
Iron, Al, & brain ferritin in normal, AD & CRD patients	Pubmed=1445209
Al in plasma and hair of patients on long-term dialysis	Pubmed=8482317
Toxicity, bioavailability, & metal speciation	Pubmed=7905798
Chronic toxic effects of Al on the nervous system in rabbits	Pubmed=7842872
Neuropsychological deficit among elderly workers in Al production	Pubmed=8030636
Chronic Aluminium fluoride administration, behavioural observations	Pubmed=8067979
Al induced model of motor neuron degeneration in rabbits	Pubmed=8584274
LT action of low-dose Al on the CNS of white rats	Pubmed=8779289
Effect of LT-LD Al on haemoglobin synthesis in CRI	Pubmed=8883017
Al toxicity in patients with CRF on dialysis	Pubmed=9275645
Al toxicity contributes to immunological impairment in CRF patients	Pubmed=8671818
Is Al toxicity responsible for uremic pruritis in CR patients on dialysis	Pubmed=9031270

Al interaction with plasma membrane lipids & enzyme metal-B sites	Pubmed=9000512
Oral Al administration and oxidative injury	Pubmed=9282259
Morphological changes of chronic Al intoxication in rats	Pubmed=9500123
Neuronal & cerebrovascular effects of chronic Al administration to rats	Pubmed=9518651
Chronic administration of Al L-Glutamate in young mature rats	Pubmed=10048751
Motor neuron degeneration due to Al in the spinal cord	Pubmed=10335362
Screening plasma Al levels for ARBD in dialysis patients	Pubmed=10516350
Aluminium toxicity haematological effects	Pubmed=10643868
A comparative study of ALS & Al neurotoxicity in NZ white rabbits	Pubmed=10840278
Chronic exposure to Al decreases NADPH-d+ neurons in rat cortex	Pubmed=11166709
Chronic exposure to Al L-glutamate accelerates the ageing process	Pubmed=11226739
Effect of Al on BBB permeability in hyperglycaemic rats	Pubmed=11437183
AB & Al induce stress in the endoplasmic reticulum in rabbits	Pubmed=11731006
Lack of effect of Vit E on Al induced synaptic plasticity in rats	Pubmed=11893406
Neonatal chronic Al exposure impairs LTP & PPF in the DG of rats	Pubmed=12088747
Deposition of Al L-Glutamate in the rat brain cortex	Pubmed=12137928
Effects of chronic accumulation of Al on renal function in rats	Pubmed=12928767
Dipsacus asper extract reduces AB induced by Al exposure	Pubmed=12954453
A study of the effects of LT exposure of adult rats to Aluminium	Pubmed=12959739
Nicotinamide supresses hyperphosphatemia in HD patients	Pubmed=14871431
A 26Al tracer study of Aluminium biokinetics in humans	Pubmed=14871578
Improving outcomes in hyperphosphatemia	Pubmed=15126649
Use of sevelamer in the treatment of hyperphosphatemia of HD patients	Pubmed=15153763
Effects of Al on ATPase & AChE neural membrane proteins of rats	Pubmed=15254985
Disruption of neuronal calcium homeostasis by Al in rats	Pubmed=15679474
Role of keratinocyte derived cytokines in chemical toxicity	Pubmed=8597097
Anaemia, diarrhoea, & opportunistic infections in Fell ponies	Pubmed=11037259
Overexpression of IL-4 alters the homeostasis in the skin	Pubmed=11982753
Urinary Al excretion following renal transplantation	Pubmed=2310153
Fibroblast response to metallic debris in vitro	Pubmed=8314824
Effect of neurotoxic metal ions on proteolytic enzyme activities	Pubmed=7586572
Argyrophilic inclusions in one case of dialysis encephalopathy	Pubmed=9444364
Uptake & effect of Ga & Al on human neuroblastoma cells	Pubmed=9784293
LT organic brain syndrome in a dialysis associated encephalopathy	Pubmed=10093576
Al inhibits the lysosomal proton pump from rat liver	Pubmed=10855947
Ligand specific effects on Al toxicity in neurons & astrocytes	Pubmed=10986332
Dietary Aluminium and renal failure in the koala	Pubmed=15168340
Hepatic Al accumulation in children on total parenteral nutrition	Pubmed=6438295
Hepatic abnormalities associated with Al loading in piglets	Pubmed=3110447
Al associated hepatobiliary dysfunction in rats	Pubmed=3353174
Altered glycine & taurine conjugation of bile acids after Al administration	Pubmed=2614624
Al loading in premature infants during intensive care	Pubmed=2136283
Parenteral drug products containing Al as an ingredient or contaminant	Pubmed=1904955
Kinetics of Al in rats; Effect of route of administration	Pubmed=1545356
Inc biliary transferrin excretion following parenteral Al admin in rats	Pubmed=8361948
Al contamination of pediatric parenteral nutrition solution	Pubmed=8011795
Al contamination of pediatric parenteral nutritional additives	Pubmed=10467613
Liver granulomatosis is not an exceptional cause of hypercalcinemia	Pubmed=10626831
Parenteral nutrition associated cholestasis in neonates; the role of Al	Pubmed=14552065
Biliary secretory function in rats chronically intoxicated with Aluminium	Pubmed=14976346
Distribution of trace elements in the human body by NAA	Pubmed=7362268

Aluminium-related bone disease	Pubmed=3345241
Alimentary tract and pancreas; effect of antacid treatment	Pubmed=2703138
Intracellular Aluminium inhibits evoked Ca2+ mobilisation	Pubmed=2379588
Effects of Al on cytoplasmic Ca2+ signals in pancreatic acinar cells	Pubmed=1337034
Gastric mucosal calcinosis caused by Al phosphate accumulation	Pubmed=8447508
Biodistribution of trace elements in normal and Cd & Al loaded mice	Pubmed=8908323
Heterotrimeric G-proteins regulate apoptosis in pancreatic beta-cells	Pubmed=8940250
Cancer incidence & mortality among workers in 2 Al reduction plants	Pubmed=10615098
NF degeneration of nerve cells after intracerebral injection of Al	Pubmed=5962855
Neurological dysfunction after Al-induced NF degeneration	Pubmed=4577243
Al accumulation in ALS & PD of Guamanian Chamorros	Pubmed=7112111
Toxicological results from tests in aluminium plant workers	Pubmed=2593966
Influence of Al-citrate & CA on tissue mineral composition of sheep	Pubmed=2016205
Biphasic effect of Al on cholinergic enzyme of rat brain	Pubmed=9654357
Al inhibits dopamine synthesis in the hypothalamus of mice	Pubmed=10707345
Al induced changes in the rat brain seratonin system	Pubmed=12419702
Aluminium uptake by the parathyroid glands	Pubmed=479346
Aluminium alters the permeability of the BBB to some non-peptides	Pubmed=4022265
Elevated Al persists in serum & tissue of rabbits after a 6 hr infusion	Pubmed=2727994
Alzheimer's disease and trace elements	Pubmed=8587175
Intestinal perfusion of dietary levels of aluminium; Mucosal effects	bmjjournals/35/8/1053
Oxidative stress and the progression of acute pancreatitis	bmjjournals/42/6/850
Anaemia screening for Al before EPO treatment may be relevant	Pubmed=9159297
Function of r-HuEPO is inhibited by Aluminium toxicity	Pubmed=9566487
Study of factors impacting on treatment with EPO of HD anaemia	Pubmed=10853198
Relationship between nutrition and dementia in the elderly	Pubmed=6599862
Al in parenteral nutrition solution-sources and possible alternatives	Pubmed=3099003
Overview of anaemia associated with chronic renal disease	Pubmed=2648518
Al OL & response to rHuEPO in CHD patients	Pubmed=1328942
Anaemia of renal failure and the use of EPO	Pubmed=1578966
Dietary guidance for mineral elements with beneficial actions	Pubmed=8811801
Trace elements and cognitive impairment; an elderly cohort study	Pubmed=15207438
Dietary linoleic acid alleviates NAFLD in Zucker rats	Pubmed=15623825
Study of effect of metals used in cooking utensils	Pubmed=6897687
Copper accumulation in primary biliary cirrhosis	Pubmed=7085352
Al concentrates in lysosomes of hepatocytes and causes lesions	Pubmed=7079134
Localization of Al in patients with dialysis-associated osteomalacia	Pubmed=6713639
AlF4- can mimic the effects of Ca2+ mobilising hormones in hepatocytes	Pubmed=2997209
Studies on the hepatic mobilising activity of AlF4- and glucagon	Pubmed=2426266
Systemic toxicity of Al given intraperitoneally to rats	Pubmed=6433509
Al accumulates in hepatocytes and can cause serious lesions	Pubmed=3435610
Effects of Al and Cd in rat hepatocytes	Pubmed=3564053
Uptake & distn. of Al in rat hepatocytes & effects on enzyme leakage	Pubmed=3564054
Al potentiates glycogen phosphorylase activity in hepatocytes	Pubmed=3117043
The toxic effects of desferrioxamine	Pubmed=2660937
Fluoroaluminate mimics agonist appln in single rat hepatocytes	Pubmed=2302191
Al disrupts the oscillatory free Ca2+ responses of hepatocytes	Pubmed=2167073
The perturbation by Al of receptor-generated Ca transients in hepatocytes	Pubmed=2173553
Al mobilisation by DFO assessed by microdialysis of blood, liver & brain	Pubmed=2011855
Al uptake and toxicity in cultured mouse hepatocytes	Pubmed=1912392
Effects of Al overload on hepatocytes in rats	Pubmed=1288831

Extracellular Calcium potentiates the effect of Al on hepatocytes	Pubmed=7840648
P-Cresol, a uremic compound, enhances the uptake of Al in hepatocytes	Pubmed=9189861
Al promotes membrane fusion events between rat liver mitochondria	Pubmed=9570927
Mechanisms of iron homeostasis & toxicity in mammalian cells	Pubmed=12121757
Antioxidants prevent Al-induced toxicity in cultured hepatocytes	Pubmed=15149824
Nonalcoholic fatty liver disease	Pubmed=12122975
The importance of AST/ALT ratio in NASH diagnosis	Pubmed=12184161
Aluminium in renal disease	Pubmed=2674255
Microcytic anaemia in dialysis patients; reversible marker of Al toxicity	Pubmed=3826071
Loss of renal tubule cell mass results in an immune dysregulated state	Pubmed=14732813
A review of septcaemia as a complication of CRF	Pubmed=5923731
The dialysis dementia syndrome and Aluminium intoxication	Pubmed=7110469
Role of plasma Al in the detection & prevention of Al toxicity	Pubmed=3458005
Acute fatal hyperaluminic encephalopathy in uremic patients	Pubmed=3778707
Current concepts of the role of Al in CRF patients	Pubmed=6362201
Neurologic symptomatology ~ to the degree of renal dysfunction	Pubmed=206035
Biliary excretion of aluminium in patients with liver disease	Pubmed=3706930
Low serum Al in dialysis patients with increased bone Al levels	Pubmed=9725776
Factors related to mortality of patients with acute renal failure	Pubmed=12971858
Haemodialysis dementia	Pubmed=6970943
Subacute fatal Al poisoning in dialysis patients; toxicological findings	Pubmed=12208020
Al utensils contribute to Al accumulation in patients with RD	Pubmed=9370180
Bullous dermatosis of ESRD; porphyrin and aluminium	Pubmed=8918623
Precipitation of dialysis dementia by DFO treatment of ARBD	Pubmed=3400633
Haemofiltration removes TNFa & IL-1 from patients with sepsis & ARF	Pubmed=8472571
Serum Al transport & Al uptake in CRF	Pubmed=8413773
Serum Al, platelet aggregation, & lipid peroxidation in HD patients	Pubmed=11887212
Prognostic factors in acute renal failure due to sepsis	Pubmed=8700363
Al & Ni content of serum and lymphocytes in chronic renal failure	Pubmed=3971590
Screening plasma Al levels for ARBD in HD patients	Pubmed=10516350
Aluminium in tissues	Pubmed=3915959
ARF associated with the thrombocytopenia of septicemia	Pubmed=6760708
Renal insufficiency is a marker for poor ICU outcome	Pubmed=12164882
Body burden of Al and CNS function in MIG welders	Pubmed=10817377
Acute renal failure following pulmonary surgery	Pubmed=8040169
What is the value of plasma Al in CRF patients	Pubmed=3842104
Factors influencing serum Al in CAPD patients	Pubmed=9725777
Aluminium toxicity in patients with chronic renal failure	Pubmed=8122300
High serum Al & acute encephalopathy in a patient with ARF	Pubmed=1915506
Al from tissues causes sepsis, neurological dysfunction, & mortality	Pubmed=3208458
Increased IL-1 converting enzyme expression & activity in AD	Pubmed=10374748
AlOH induces Th2 associated IL-4 and IL-5 production	Pubmed=10586035
A study of the immunology of chronic fatigue syndrome	Pubmed=9576011
Cell mediated immune response in chronic liver diseases	Pubmed=9914713
CFS; clinical condition associated with immune activation	Pubmed=1679864
CFS research. Definition & medical outcome assessment	Pubmed=1322076
Absorption and disposition of Aluminium in the rat	Pubmed=3735104
Al ingestion alters behaviour & some neurochemicals in rats	Pubmed=8500814
Lipid composition & neuronal injury in primates after chronic Al exposure	Pubmed=9522055
Effects of Al on the progression of lead-induced nephropathy in rats	Pubmed=11140823
Al induced oxidative stress in rat brain; response to HEDTA & CA	Pubmed=12643979

Influence of Al on neurotoxicity of lead in adult male albino rats	Pubmed=15266904
Aluminium in AD; are we still at a crossroad?	Pubmed=15666086
Blood oxidative stress status in patients with macrophagic myofasciitis	Pubmed=15511609
A study of the dermal absorption of Al from antiperspirants using Al26	Pubmed=11267710
CNS disease in patients with macrophagic myofasciitis	Pubmed=11335699
Macrophagic myofasciitis lesions from vaccine derived AlOH in muscle	Pubmed=11522584
Macrophagic myofasciitis: a summary of Dr Gherardi's presentation	Pubmed=12184366
A 62 YO female with progressive muscular weakness	Pubmed=14997943
Nonalcoholic steatohepatitis: what we know in the new millenium	Pubmed=12425538
NAFLD in patients investigated for elevated liver enzymes	Pubmed=12560853
Serum leptin level a negative marker of hepatocyte damage in NAFLD	Pubmed=12768390
Spectrum of NAFLD associated with normal ALT levels	Pubmed=12774006
NASH and insulin resistance: interface between specialists	Pubmed=12836490
A natural history of NAFLD; a clinical histopathalogical study	Pubmed=14499785
Current biochemical studies of NAFLD & NASH; a new approach	Pubmed=14499793
Insulin resistance & ferritin as major determinants of NAFLD	Pubmed=14610526
Vitamin E & C treatment improves fibrosis in patients with NASH	Pubmed=14638353
No direct role for leptin in the pathogenesis of human NASH	Pubmed=14687831
Increased levels of hepatotoxic TNFa occur in ALD & NASH	Pubmed=14720457
NAFLD among patients with hypothalamic & pituitary dysfunction	Pubmed=15057893
NAFLD; a comprehensive review	Pubmed=15104027
Role of cytokine signaling suppressors in NASH in the mouse	Pubmed=15240880
Mechanisms of apoptosis induction in human SH	Pubmed=15330907
Epidemiology of nonalcoholic fatty liver disease	Pubmed=15331060
The clinical features, diagnosis, and natural history of NAFLD	Pubmed=15331061
NAFLD in individuals with severe obesity	Pubmed=15331062
NAFLD in the pediatric population	Pubmed=15331063
Mitochondria in NAFLD	Pubmed=15331066
TNF & its' potential role in insulin resistance and NAFLD	Pubmed=15331067
Lipid metabolism in hepatic steatosis	Pubmed=15331068
Histologic features and clinical correlations of NASH	Pubmed=15343508
A longitudinal study of repeat liver biopsies for NASH	Pubmed=15382171
Oxidative stress & depletion of LCPUFA's contribute to NAFLD	Pubmed=15454290
Elevated ALT may signify the presence of NAFLD	Pubmed=15492608
NAFLD is an early predictor of metabolic disorders	Pubmed=15505132
Non alcoholic fatty liver disease	Pubmed=15505593
The risk factors of fibrosis in NASH	Pubmed=15526543
NASH	Pubmed=15554595
NASH	Pubmed=15560051
NAFLD; a review	Pubmed=15625647
Progress in understanding the pathogenesis of NAFLD	Pubmed=15619243
Gastric mucosal calcinosis from Al based therapy	Pubmed=8447508
Complexation of aluminium with DNA (calf thymus)	Pubmed=3559548
Polynucleotide cross-linking by Aluminium	Pubmed=2560791
Comparison of DNA adducts from exposures & various human tissues	Pubmed=8319665
Treatment of thymic lobes with Al provoked T cell apoptosis	Pubmed=7621860
A study of calf thymus DNA complexation with Al and Ga cations	Pubmed=8723774
Spectroscopic & voltammetric study on binding of Al to DNA	Pubmed=12137370
Aluminium inhibition of hexokinase	Pubmed=4114525
The relaxing effect of Al & La on gastric smooth muscle in vitro	Pubmed=4715218
Al affects the gastro-intestinal smooth muscle via multiple sites	Pubmed=1156030

The dialysis encephalopathy syndrome. Possible Al intoxication.	Pubmed=1244532
Evidence of aluminium accumulation in renal failure	Pubmed=549003
Dementia, renal failure, and brain aluminium	Pubmed=434672
Metabolic balance of aluminium studied in six men	Pubmed=476923
Immunologic & nonimmunologic activation of macrophages	Pubmed=7391601
Metabolism and toxicity of aluminium in renal failure	Pubmed=7395774
Histoenzymatic study of the effects of Al phosphate on gastric mucosa	Pubmed=7243581
Al-containing dense deposits in the glomerular basement membrane	Pubmed=7072638
Hepatic Al accumulation in children on total parenteral nutrition	Pubmed=6438295
Hyperparathyroidism and bone Al deposits may coexist	Pubmed=3830569
Aluminium in tissues	Pubmed=3915959
Effects of hyperparathyroidism & Al toxicity on bone scan in HD patients	Pubmed=3991531
Al in precipitates of alveolocapillary basement membranes of uremic P	Pubmed=4050886
Pseudohyperparathyroidism syndrome assoc with Al intoxication & RF	Pubmed=4014298
Depressed erythroid progenitor cell activity in Al OL mice	Pubmed=8807624
Chronic Al intoxication in rats; dose dependent morphological changes	Pubmed=9500123
Al accumulation & neurotoxicity in mice after LT feeding with Al/citrate	Pubmed=8412742
Effect of Al on mice wrt infection; immune supression	Pubmed=12474775
Alzheimer's dementia and the Aluminium hypothesis	Pubmed=3412205
Effect of Al ind AD like condition on oxidative energy in mitochondria	Pubmed=10656181
Paired helical filaments of AD share antigens with normal NF	Pubmed=6620982
Dialysis encephalopathy with fractures & muscle weakness	Pubmed=7218657
Animal model of Al-induced osteomalacia	Pubmed=6842959
Renal osteodystrophy in diabetic patients	Pubmed=8355457
The effect of DFO on tissue Al in Al-loaded rats with renal failure	Pubmed=2980801
Al accumulates in experimentally induced carcinomas of rats	Pubmed=7804026
Interaction b/w antacid & gastric mucosa using an "artificial stomach"	Pubmed=1469628
Al in bone of a case of renal osteodystrophy & dialysis encephalopathy	Pubmed=6716213
AlCl is cytotoxic to cultured V-79 fibroblasts in vitro	Pubmed=11844038
Mineral metabolism of rats fed varying amounts of Al compounds	Pubmed=4067662
Al toxicity is altered by diet and kidney function in rats	Pubmed=1941183
SR-B1 may take up oxidatively modified lipoproteins & AB-apoE	Pubmed=11959156
31P NMR spectroscopy of brain in aging and AD	Pubmed=3316499
High-field 19.6T NMR of aluminated brain tissue	Pubmed=15388089
Gut Al permeability & bone deposition with normal renal function	Pubmed=908869
The compartmentalisation & metabolism of Al in uremic rats	Pubmed=3973462
Neither serum Al or DFO chelation reflect skeletal aluminium	Pubmed=4067379
Development & reversibility of Al induced bone lesion in the rat	Pubmed=3794513
Diagnosis of Al-associated microcytic anaemia in dialysis patients	Pubmed=2909650
Effect of CA & Maltol on Al accumulation in rat brain and bone	Pubmed=8445293
Al in the CNS, liver, & kidney of rabbits with atherosclerosis	Pubmed=2340946
Al salts interfere with the absorption of nutrients from the gut	Pubmed=8473881
The binding of Al to protein & mineral components of bone & teeth	Pubmed=9397572
The bioavailability of Al in man, including Al-26, a review	Pubmed=15152306
Al uptake by the parathyroid glands	Pubmed=479346
Evidence for a toxic effect of Al on osteoblasts	Pubmed=3213621
The evolution of osteomalacia in the rat with acute Al toxicity	Pubmed=2816514
Effect of Al & Cd intake on antioxidant status in rat tissues	Pubmed=11673849
Al induces lysosome damage to liver, spleen, and kidneys of rats	Pubmed=3624785
Uremia, dialysis, & Al; Al occurs in all organs and tissues	Pubmed=9422488
Al induces alts. in cell immune response in a dose dependent manner	Pubmed=11562064

Al influences cytokine production & depresses CD4+ immune response	Pubmed=8301020
Al induces IL-18 and can facilitate Th2 induction	Pubmed=12562321
Antigen dose defines T helper & cytokine response in mice	Pubmed=10841947
Hair as an indicator of Al exposure in dialysis; comp to bone & plasma	Pubmed=2785480
Effects of the combined exposure to Al & ethanol in the rat	Pubmed=1673624
Camelford water incident: serial neuropsychological assessments	Pubmed=8094970
Comparative Al mobilising actions of several chelators in rats	Pubmed=7908811
Effects of Al & F on enzymes in the jejunal mucus membrane of rats	Pubmed=1328029
Effect of Al on rat brain is enhanced by calcium deficiency	Pubmed=6479848
Dietary Al and renal failure in the koala	Pubmed=15168340
A study of the cytotoxicity of Al to cultured brain cells	Pubmed=8150659
Intestinal perfusion of dietary Al: association with the mucosa	Pubmed=7926905
Microparticles in human gut associated lymphoid tissue contain Al	Pubmed=8675092
Immunotoxicity of Aluminium chloride	Pubmed=15318624
Effect of oral Al citrate on tissue distribution of Al	Pubmed=8349199
Tissue Al distribution in various age rats & changes in metabolism	Pubmed=7590531
AlF affects the structure & functions of cell membranes	Pubmed=15110101
Influence of organic acids on Al absorption & storage in rat tissues	Pubmed=8647304
The influence of complexing agents on the kinetics of Al in rats	Pubmed=11407750
The competition of Fe & Al for transferrin = Al deposition?	Pubmed=9208284
The Al induced acceleration of the aging process in rat hippocampus	Pubmed=11226739
CT mediastinal lymph nodes after Al exposition	Pubmed=11305576
Aluminium: impacts and disease	Pubmed=12123643
Water content of aluminium, dialysis dementia, and osteomalacia	Pubmed=3908086
Metabolism and possible health effects of aluminium	Pubmed=2940082
Iron and aluminium homeostasis in neural disorders	Pubmed=7843099
Effects of ingested Al on essential metals, esp. zinc, in treated mice	Pubmed=3428182
Bone Aluminium content in Alzheimer's disease	Pubmed=7606282
Al & chronic renal failure: sources, absorption, transport, & toxicity	Pubmed=2647415
Diagnosis & treatment of Al bone disease	Pubmed=8840316
Al chelation by 3-HP-4-ones in the rat demonstrated by microdialysis	Pubmed=8862748
Al deposits in the brain & affects the cholinergic neurotransmission	Pubmed=9116693
The causes, diagnosis, & treatment of Al toxicity in CRF patients	Pubmed=9275645
The promotion of Fe-induced generation of ROS in nerve tissue by Al	Pubmed=8962602
Al toxicity may contribute to immunological impairment in CRF	Pubmed=8671818
Effect of AlOH on Al tissue distribution & localisation in liver	Pubmed=8882343
Al accumulation in tissues of rats with compromised kidney function	Pubmed=8737962
Distribution of Al in different brain regions & organs of rat	Pubmed=8773759
Bile is an important route of elimination of ingested Al by rats	Pubmed=8658541
Hormone rel. diffs. in the effect of Al on Ca tspt in the small of the rat	Pubmed=8644129
Status & future concerns of clinical & env. Al toxicology	Pubmed=8772797
Systemic Al toxicity: effects on bone, hematopoietic tissue & kidney	Pubmed=8772804
Age dependent Al accumulation in the human aorta & cerebral artery	Pubmed=8971367
Effects of Al on mineral metabolism of rats IRT age	Pubmed=9148276
Al-sensitive degradation of AB 1-40 by murine & human intracellular enzymes	Pubmed=8947944
The effect of age on Al retention in rats	Pubmed=9020501
ST oral 3-HP-4-one inc. Al excretion & reverses Al toxicity in the rabbit	Pubmed=9029049
Mechanisms of Al absorption in rats	Pubmed=9129475
Analysis of intestinal absorption & storage of Al in uremic rats	Pubmed=9249771
Myelin is a preferred target of Al-mediated oxidative damage	Pubmed=9264541
Al metabolism in rats by Al26 isotope	Pubmed=9316614

Interactions of AB's with the BBB	Pubmed=9329690
Uremia, dialysis, and aluminium	Pubmed=9422488
Relative roles of intestinal absorption & dialysis fluid exposure in HDP	Pubmed=9430871
Aluminium, Alzheimer's disease, and bone fragility	Pubmed=9462346
Al decreases the Mg conc of SC & trab bone in rats	Pubmed=9600675
Action of Al-ATP on the isolated working rat heart	Pubmed=9629673
Uptake of Al & Ga into rat tissues & the influence of antibodies	Pubmed=9630424
Silicon reduces gastrointestinal absorption in rats	Pubmed=9651136
Membrane comp can influence the rate of Al3+ mediated lipid oxidation	Pubmed=9677347
A comparative study of several chelating agents in rats	Pubmed=9677621
A cluster of equine granulomatous enteritis cases and the link to Al	Pubmed=9778770
Effect of Al & Al citrate on blood & tissue Al levels in the rat	Pubmed=9823440
Effect of Al on K-induced contraction in ileal longitudinal smooth muscle	Pubmed=9827026
Effects of Al, Fe, Cr, & Y on rat intestinal smooth muscle in vitro	Pubmed=9845462
Metabolism of aluminium in rats	Pubmed=9863066
Effect of Al on SOD activity in adult rat brain	Pubmed=9877534
Vit E protects against oxidative injury stimulated by excess Al intake	Pubmed=9891850
Low serum Al in dialysis patients with increased bone Al levels	Pubmed=9725776
Variations in Al concentration of caprine, bovine, & human bone samples	Pubmed=10328341
Permeability of rat epithelium to inhaled aluminium	Pubmed=10409396
Al and other metals in bone of ESRF patients	Pubmed=10471660
Behavioural effects of Al in mice: influence of restraint stress	Pubmed=10494050
Effect of Al induced AD condition on oxidative energy of mitochondria	Pubmed=10656181
Myelination of the SC in mice exposed to aluminium	Pubmed=10693976
Evaluation of deferiprone protective effect on Al toxicity in mice	Pubmed=10931505
Al mobilisation by chelating agents in al loaded rats	Pubmed=10987213
Effects of Al comps on tissue distn. & concs. of essential elements	Pubmed=10752672
Al toxicokinetics: an updated minireview	Pubmed=11322172
Changes in mouse brain tissues after prolonged Al ingestion	Pubmed=11393311
Daignostic utility of serum Al & the DFO test	Pubmed=11464651
Effects of Al & DFO on essential elements in Al exposed animals	Pubmed=11757400
The role of trace elements in uraemic toxicity	Pubmed=11904350
The effect of pleurodosis caused by AlOH on lung/chest wall mechanics	Pubmed=11976897
Al induces DNA synthesis in human fibroblasts in vitro	Pubmed=12002655
Effect of LT Al feeding on tissue cholinesterases	Pubmed=12127022
Effect of Al on activity of mouse brain AChE	Pubmed=12372547
Melantonin & pinoline prevent Al induced lipid peroxidation in rat synaps	Pubmed=12755500
Al-induced pro-ox effect in rats: protective role of exogenous melantonin	Pubmed=12823611
A model of Al exposure & lipid peroxidation in rat brain	Pubmed=14716098
Effects of Al on phosphate metabolism in rats	Pubmed=15221202
Comp study of intestinal absorption of Al, Mg, Ni, & Pb in rats	Pubmed=15235150
Molecular exchange of metal ions & tissular calcium overload	Pubmed=15235153
Selective binding of sucralfate to mucosal resection-induced gastric ulcer	Pubmed=15458285
Antioxidant effects of VitE & Se on lipid peroxidation in Al loaded rats	Pubmed=15487771

Peter Stewart.
14th March 2005.

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Phone: 9560 3992
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26th March 2005

The Managing Editor,
Hong Kong Medical Journal,
By e-mail: hkmj@hkam.org.hk

Re: "Use of hair analysis in the diagnosis of heavy metal poisoning: report of three cases", HKMJ 2004; 10: 197-200.

Dear Sir,

Please allow me to correct some misconceptions that are expressed in this article:

- The level of heavy metals in blood or urine will only reflect a recent exposure since the liver, kidney, and spleen perform an effective filtration function,
- An overload of a metal entering the bloodstream will be sequestered into tissues and organs, including the brain. The body will excrete the metal with tissues as they grow-out, but will not re-metabolise it into blood without chelation,
- In all cases of a significantly abnormal reading that is being used as the basis of chelation therapy, the result should be validated by a retest,
- In Case One involving dyslexia, there is a low-level overload of twice the reference range. It is noted; "the patient did not receive any treatment and developed normally thereafter", confirms the overload grew-out naturally,
- In Case Two involving epilepsy or autism, the actual metal levels are not cited. It is noted; "The child showed no signs or symptoms suggestive of metal poisoning, and gave no history of exposure to heavy metals". Autism itself is a possible indicator of metal poisoning, and the first check for a 3-yo would be to perform the same test on the mother,
- In Case Three involving feeding problems and drowsiness, the actual metal levels are not cited. They may not have been the main problem,
- A real case study is attached and is self-explanatory. The problem would not have been diagnosed without hair analysis. I suggest that all practitioners consider hair analysis as a valuable tool if used correctly, and recognise that blood and urine analyses are not suitable screening tools for past metal exposures.

Yours sincerely,

Peter Stewart.

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26th March 2005

Mr Khandu Mistry,
Administrative Secretary,
COT: Lowermoor Sub-group,
DOH London.

Re: COT Report References, Yoshinaga (1990), (two papers).

Dear Sir,

Please note our comments regarding the research articles referenced:

1. **Interrelationship between the concentrations of some elements in the organs of Japanese with special reference to selenium-heavy metal relationships, Yoshinaga *et al,* 1990.**
    - In the elemental concentrations between organs, there is generally good correlation, with the following predictable exceptions:
        i. Cadmium accumulates in the liver and kidneys.
        ii. Copper accumulates in the liver.
        iii. Iron accumulates in the liver, and to a lesser extent, the kidneys.
        iv. Selenium accumulates in the liver and kidneys,
        v. Mercury accumulates in the liver and kidneys,
        vi. Zinc accumulates in the liver and kidneys.
    - There were also some non-predictable exceptions:
        i. Calcium was lower than the RR in all tissues except the kidney,
        ii. Potassium readings are all about 20 times normal hair RR,
        iii. Sodium levels are all about 10 times normal hair RR,
        iv. Phosphorus levels are all about 15 times normal hair RR,
        v. Zinc was lower than the RR in all tissues except as noted above.
    - The study purports to identify correlations between the antioxidants Zn & Se, and the toxic elements Hg & Cd in human organs, particularly the liver & kidney, and achieves this. However, there were some unusual levels obtained for essential elements that warrant further investigation. The causes of the deaths were not given in this paper. <u>The study does show there is a good correlation between element levels in different organs</u>, including brain, & also accumulation in kidney & liver.
2. **Lack of significantly positive correlations between elemental concentrations in hair and in organs, Yoshinaga *et al,* 1990.**
    - Original statistical data appeared in the study in (1) above. Rib data was added from another study which was not reviewed,
    - Please note that individual readings were NOT supplied, and abnormal readings do not appear to have been eliminated or validated,
    - Magnesium hair readings are consistent with tissue readings,
    - Phosphorus readings are consistent with normal hair RR, (tissues high),

- Calcium readings for tissues are in fact low. The hair statistical result is high, due probably to a max reading of 7 times normal. Otherwise there is probably reasonable correlation between the hair and tissue readings,
- Iron hair readings are consistent with tissue readings,
- Copper readings are consistent, with some distortion by a high value/s,
- Zinc in hair is normal, although low in all tissues,
- Selenium is consistent with a mean of all tissues,
- The method of statistical analysis is totally inappropriate for the purpose of the study. Abnormal readings do not appear to have been filtered out or validated. Correlation analysis should be performed on each series, and then condensed. The analysis for this study should be repeated using a more appropriate methodology,
- Hair samples were taken of distal hair and the length of the hair sample was NOT CONSTANT for all subjects. Normally hair length may vary from 10mm in males to 300mm+ in females. At a growth rate of about 3-5 mm/week, the time delay between hair sample and analysis could be anything from 1.0 week to 1.5 years, compared to a notional delay of 1.0 week for tissue samples,
- Even though the hair elemental readings are consistent with the tissue readings (except calcium and phosphorus), and the quoted hair reference ranges, there are abnormalities in the data.
- Due to the faulty hair sampling protocol, this study is **fatally flawed** and should be discounted as a reference. Reworking of the analysis is not possible from the data supplied.

Yours sincerely,

Peter Stewart.

COT Lowermoor Subgroup Report Response

1. Major Reference Source

- Appendix 16 includes the document:
  "Report On Toxicity Of Aluminium.
  An update of the 1997 WHO IPCS Report with emphasis on neurotoxicity."
  This will be referred to by the designation RTA.
  In the RTA, some of the conclusions detailed in the original document, which is WHO EHC-194, 1997, appear to have been edited out.

  In **EHC-194**, the toxicity of aluminium is clearly acknowledged in certain risk populations, and those populations are as follows:
  - Impaired renal function
  - Occupationally exposed
  - Premature infants

  The definition of Risk Population is therefore determined by **the probability of an accumulation**, not by any inherent differences in the biokinetics of the metal or the exposure situation.

  In addition, it is acknowledged in 1.10, 8.6, and 11.1 that aluminium causes the following serious conditions:
  - Encephalopathy / neurotoxicity
  - Vitamin-D resistant osteomalacia
  - Microcytic anaemia

- There is NO indication that aluminium does NOT follow the normal dose dependent relationship for a toxin, ranging from the NOEL, to acute & toxic iatrogenic exposure during dialysis, causing encephalopathy.

- There is every indication in the research that the effects of aluminium are linear within the effective band between the NOEL and the saturation level.

- Therefore, the requirement for demonstration of the toxic effects of aluminium in any person is **the validation of elevated aluminium levels**, which will be in tissues rather than serum for delayed testing scenarios.

2. Implications For Lowermoor

- The Lowermoor incident reflects a poor evidence profile in regard to primary levels contributing to the exposure. This arose due to the incorrect analysis of the initial water problem, its' short duration & high intensity, the distributed nature of the effects, the operation of line flushing, and other factors.

- Given that there are no reliable blood or urine results that focus on the peak exposure period, the measure of exposure must be tissue test results.

- So, for example, the neuropsychological tests very clearly indicate abnormal results in exposed persons, & the effect is MCI (Mild Cognitive Impairment), which is on the damage scale from zero to dialysis encephalopathy.

- Therefore, the conclusion in 1.14 that; “It is not anticipated that the increased exposure to aluminium would have caused, or would be expected to cause, delayed or persistent harm to health in those who were adults or toddlers at the time of the incident…” is not consistent with the evidence.

- In addition, the statement in 1.22 that; “On the basis of the available data, it is not anticipated that the combination of metals which occurred as a result of the pollution incident would have caused or would be expected to cause delayed or persistent additive or synergistic effects” is unsupportable, in that no epidemiological studies have tested or reported the particular scenario, and the Report has ignored the recent studies by Bush *et al*., and Exley *et al*., that identify iron, zinc, copper, and aluminium as contributors to the amyloid cascade in neurodegeneration.

3. Effects Of The Poisoning

- There is a serious lack of hard data in regard to the reported symptoms. The symptoms reported included neuropsychological effects, joint pains and/or swelling, nail problems, cancer, thyroid disease, malaise, tiredness, exhaustion, dry thirst, sensitization, skin problems, gastro problems, arrhythmia, diabetes, & reproductive problems. For example, tiredness and exhaustion are symptoms of haemolytic anaemia caused by aluminium poisoning, yet no data has been presented of actual test results. All of the symptoms listed are linked by research and/or reports to aluminium.

- It is stated in 1.26 that “There is no indication from the toxicological data that the estimated exposures to the contaminants which occurred after the incident can cause effects on joints, and it is not possible to conclude that there is a causal relationship between the joint pains and/or swelling reported and exposure to the contaminants.” It is an undisputable fact that metals cause lipid peroxidation, and in so doing, interfere with the essential fatty acid cascade. Since it is this cascade that is responsible for prostaglandin production and inflammation on a large scale (and not related to infection), the association between aluminium and joint pains is highly probable.

- Research clearly identifies a link between aluminium and skin problems, which would give rise to a condition similar to eczema or dermatitis in certain individuals.

- In regard to cancer, the size of the aluminium dose may be such that the metal will grow out before it can initiate a cancer. Brain deposits of aluminium are a different problem, they do not grow out; they cause neural degeneration and premature ageing, and most certainly contribute in some way to the onset of dementias.

- Aluminium is associated with a decrease in lymphocyte count. I do not recall any results of lymphocyte subset testing in the Report. The onset of lymphocytopenia represents a severely depressed immune condition with a high risk of infection, and hence the link to leukaemia. The statement that “the pollution incident did not cause an increased incidence of infection” does not seem consistent with the patient feedback.

- The neuropsychological test results from Altmann are consistent with the toxicity profile for aluminium as stated in WHO EHC-194, and summarized in 5.111 "The authors concluded that the pattern of abnormalities seen was similar to findings they had previously described in "aluminium loaded but asymptomatic patients undergoing dialysis" (Altmann *et al*, 1989; Altmann, 1991). The authors also concluded "these studies suggest the participants responded to (their) tests, as a group, in a manner compatible with the presence of organic brain disease and in a way similar to dialysis patients exposed to aluminium".

4. Estimation Of The Contamination

- The water sampling conducted by SWWL was flawed and the data is therefore not reliable. As stated in the Report:
    - In the case of the 2-minute flush sample, most of the contaminants from the domestic pipework (copper, lead or zinc) would have been flushed away before the sample was taken. Therefore, the monitoring data for these metals for water from the cold tap may not have revealed the highest concentrations that occurred after the incident.
    - The exact location of the sampling sites was not supplied to us as South West Water Ltd consider that they cannot supply the names of customers at the address from which the sample was taken or information which could identify the customers

- The data from other sources may be more reliable than that from modeling. As per the Report: "The highest aluminium and sulphate concentrations were recorded in a sample collected at a farm in Helstone near St Teath at 5.00 am on 7 July 1988. This contained 620 mg aluminium/l and 4,500 mg sulphate/l. This sample also contained 9.0 mg zinc/l, the highest concentration recorded in the immediate post-incident period."

- In contrast, it was stated: "BVCs concluded: "Given that this is the only major anomaly with the modeling results, it raises serious doubt about the validity of the sample."" Modeling had predicted that the peak outlet concentration entering the network would be 325 ppm.
- In the case of reservoir mixing, the following scenario would apply, which is consistent with the Helstone test. The capacity of the treated water reservoir is approximately 2,300 cubic metres (m3), but it was believed at the time to be about 60% full, (1,380 m3 water). Therefore, if all the added aluminium sulphate were completely mixed into this volume, the maximum concentration in the reservoir would have been approximately **615 ppm** of aluminium and 3,300 mg sulphate/l. (Crowther Clayton Associates, 2003).

- The WHO utilizes 2 litres/day as the standard consumption of drinking water. At the concentration derived above, the daily dose of aluminium would have been 615 ppm X 2 Litres/day = 1230 mg.

- The WHO recommended maximum daily allowance of aluminium is 7 mg/kg bw/ day, applied to a notional 60 kg person, equates to a RDA of 420 mg/day. Consequently, **the RDA has been exceeded by a factor of 3**, reflecting the sequestration into tissues and the elevated tissue test results.

- The ATSDR Minimal Risk Level Publication (MRL) Jan 2003, cites the MRL for aluminium as 2.0 mg/kg/day with an endpoint noted as "neurological". The exposure **has exceeded the MRL by a factor of 10** and has resulted in adverse neurological consequences for many of those exposed.

5. Tissue Test Results

- Tissue test results details are generally not available. For example:
    - Taylor (1990)
    - Ward (1989)
    - Ward (1990)
    - Cross (1990) b
    - Powell (1995), & does not indicate they tested for aluminium
    - Howard (1993), but positive correlation concluded
- Other tissue test results have shown positive, but source data is not provided:
    - Eastwood (1990) reported positive and discrete bone staining in exposed healthy individuals
    - McMillan (1993) reported that the stainable aluminium had disappeared within 18 months in normal individuals

- In the Report, section 5.40, it is stated: " Dr Newman also reported that he arranged for "approximately 435" patients to give samples of blood, hair, nails and/or saliva for analyses by Dr Neil Ward of the University of Surrey (see paragraph 5.150). These were tested for concentrations of metals (Newman, personal communication, 2002)." This data was available in summary from only.

- The results are discussed in the Homeopathic Report, Appendix 4. Aluminium, copper, and lead all show elevated levels reflecting the contamination exposure, and the sequestration of elements into tissues.

- More detailed results are available from the tissue testing of pigs at the piggery at Treburgett, and are reported in the document:

  "Multielement tissue status of sows exposed to aluminium in North Cornwall as a result of the Lowermoor Water Treatment Works Incident", N. I. Ward, Dept of Chemistry, Univ of Surrey.

- The data from these tests is comprehensive and includes a control group with comparative testing. As anticipated, the following results were characteristic:
    - Aluminium, copper, and lead were elevated in the kidneys and livers of the pigs
    - The elevated aluminium and copper levels were reflected in the hair results in a consistent manner
    - The elevated aluminium level was reflected in the bone results in a consistent manner
    - Corresponding reductions in iron and zinc are typical of active metal disturbances

- The conclusion drawn by Dr Ward is totally consistent with the data, and is as follows:

"In conclusion, these results support the case that the chemical nature of the contaminated water supplies following the North Cornwall Lowermoor Water Treatment Works incident is indicative of being responsible for the increased Al, Cu, and Pb levels found in the various body organs and tissues of these affected sows. Moreover, the toxicological effects of such metals in a mixed cocktail of metal species caused imbalances in other essential metals (Zn and Fe) and thereby induced the various behavioural problems and health disorders of those affected sows."

- The adverse health effects reported for the sows associated with the exposure were reported as:
    - Failed matings
    - Decreased litter size
    - Higher post-natal mortality
    - Reduced growth rate
    - Reduced feed conversion efficiency
    - Increased culling of sub-standard breeders

  These effects are consistent with a toxic exposure to metals. The continuation of effects after the event had passed is also indicative of the sequestration of metals into tissues extending their effects.

- The toxic effects of metals is reported in the following references:
    - **Aluminium, lead and cadmium concentrations in seminal plasma and spermatozoa, and semen quality in Finnish men.** Hovatta *et al.*, Human Reproduction, vol 13, no 1, pp115-119, 1998
    - **Glutathione as a treatment for male infertility**. D Stewart Irvine. Review of Reproduction, (1996), 1, 6-12.
    - **A prospective analysis of the accuracy of the TEST-yolk buffer enhanced hamster egg penetration test and acrosin activity in discriminating fertile from infertile males**. Romano *et al.*, Human Reproduction, vol 13, no 3, pp2115-2121, 1998.
    - **Analysis of the impact of intracellular reactive oxygen species generation on the structural and functional integrity of human spermatozoa: lipid peroxidation, DNA fragmentation and effectiveness of antioxidants.** Twigg *et al.*, Human Reproduction, vol 13, no 6, pp1429-1436, 1998.
    - **A Case Study In Human Aluminium Toxicity,** Stewart, 2005, Personal communication.

6. Validity Of Tissue Testing

- In 5.161 it is stated: "The scientific literature indicates that metal concentrations in hair are not a good quantitative indicator of exposure to metals (Poon *et al*, 2004; ASTDR, 2001; Yoshinaga *et al* 1990)." This assertion has no basis in fact. The references were reviewed and commentary is as follows:
    - In **Poon (2004)**, there is an attempt to correlate blood, serum, & urine metal levels with hair analysis, and of course there is NO essential relationship. Metals are filtered from the biological fluids and will appear normal within 30 days. Chelation was offered but

not implemented. There may have been some correlation after chelation.

- In **Yoshinaga (1990)** (1), heavy metals were analysed in internal organs to determine relationships, and it was found that there was a correlation between Se & Zn and Hg & Cd, especially in the liver and kidney. (Precursor to study 2).
- In **Yoshinaga (1990)** (2), it was intended to demonstrate that there was a relationship between internal organ element level and hair element level. Unfortunately they utilized distal hair of different lengths and consequently different time periods. They acknowledge this potential error, and the conclusions are subsequently invalid.
- In **Wilhelm** *et al*., Scalp Hair as an Indicator of Aluminium Exposure; Comparison to Bone and Plasma, Human Toxicology, 1989, Jan, 8(1); 5-9, there appear to be methodological problems with the measurement of hair aluminium during dialysis and its' interpretation.

- Other studies, which did not contain flaws, are supportive of tissue testing in the recording of a historical exposure and that has resulted in sequestration, and they are briefly reviewed as follows:
    - **A Case Study In Human Aluminium Toxicity**, Stewart (2005), (personal communication), indicates that hair analysis is reliable, accurate, consistent over a long period, and has good correlation to physical symptoms.
    - **Hair Lead Levels in Young Children From The F.R.G**., Wilhelm *et al*., (1989), it was stated; "we conclude that by using standardized conditions hair analysis is a valuable screening method."
    - **German Environmental Survey 1990/92 GerES II**, clearly profiles metal levels in human hair and relates them to environmental contaminants.
    - **The Nail and Hair in Forensic Science**, Daniel *et al*., J Am Acad Dermatology, Vol 50, No 2.
    - **Heavy Metal Poisoning and Its' Laboratory Analysis**, Baldwin & Marshall, Ann Clin Biochem; 1999; 36; 267-300.
    - **Hair as a Biopsy Material; Trace Element Data on one Man Over Two Decades**; Klevay *et al*., European J of Clin Nutrition, 2004, 1-6.
    - **Determination of Metal Concentrations in Animal Hair by the ICP Method**, Chyla & Zyrnick; Biol Trace Elem Res, 2000, V75, 187-194.

7. Report Recommendations

- In the Recommendations For Further Research it is proposed that there should be additional and appropriate neuropsychological testing. However, the other recommendations call for monitoring of problems only. This is a totally inappropriate level of response given the evidence of health issues brought forward to the Committee and documented in their Report. The issues associated with aluminium indicate the following should occur:
    - Tissue testing of exposed persons

- Testing for haemolytic anaemia & thyroid for fatigue cases
- Testing for lymphocyte subsets for infection cases
- Testing for lipids and antioxidant status for inflammation
- Bone mineralization and iPTH testing for tissue test +ve cases
- Kidney & liver function testing for fatigue/+ve tissue cases
- Testing of motility, SPA & SCSA for +ve tissue cases or cases involving reproductive problems

- **Further Toxicological Studies are definitely required, however, it can be categorically stated that any individual who has significantly elevated tissue levels of aluminium above the reference range of 16-18 ppm has received an overload, and any such individual who has symptoms of illness has received a dose which is above the NOAEL for that individual, all other factors being equal. Those individuals require testing, treatment, and support until it is demonstrated that the effects are fully discharged.**

P Stewart

20th April 2005.

Dear Frances,

We recently were sent a copy of an email from you to Mrs. Sigmund, in which you stated that the study was a 'toxicological risk assessment' and expressed the view that examining patients' medical records would have been of no assistance in understanding the effects of the Lowermoor Incident. This has now been quoted by Dr. Exley, and must be regarded as being in the public domain.

We strongly disagree with these statements. I have been carrying out risk assessments on a professional basis for over 20 years, as an Environmental Impact Assessor, and these frequently include health issues. A risk assessment, by definition, is a predictive exercise designed to avoid future adverse effects. It is possible to interpret part of the Terms of Reference of the LSG study to include this, in the sense that we were asked to assess whether or not future developments could be anticipated.

However, the primary purpose of this study was to collect all available evidence on what had happened to people up to the time of our study. That cannot be described as a risk assessment. Nor did we anticipate that the study would be regarded primarily as a toxicological assessment, and based almost entirely on the scientific literature. As we have often said, this was a unique incident and there has been continual political opposition to the full investigation, and therefore publication, of any comprehensive accounts of it. The literature will inevitably be a highly defective source of data on which to rely.

The first use of the term 'toxicological assessment' in the context of the Lowermoor Incident that we have been able to identify was by Mr.Michael Waring, on 24th August 1988, in a letter to Dr. Grainger at Truro. In this he expressed the remarkable view that the Lawrence Report was " a toxicological assessment" of the incident that was "to the point and, I believe, accurate". The Lawrence Report was **not** a toxicological assessment. Its primary purpose was to investigate the handling (or perhaps we should say, mishandling) of the incident at the works, and estimate roughly what levels of aluminium might have existed in the water supply as a result.

On both counts the Lawrence Report was defective but, in the case of his highly conservative estimate of the resultant pollution levels, our own analysis of the SWWA water quality data has revealed just how inaccurate his assessment was. Yet Mr. Waring's idiosyncratic assessment of the value of the Lawrence Report as a basis to assess the toxicological risks arising from the incident appears to have formed the basis for all subsequent dismissive views expressed by the DoH ever since.

This highly unreliable conclusion has been incorporated into the Executive Summary of the Draft Report. It was also leaked to the media two days before the official release of the Draft, attracting a substantial amount of concern both amongst the people of North Cornwall and the scientific community, and compromising the reputations of the members of the LSG.

Peter and I are extremely disturbed with sections of the statements contained in the Executive Summary that we believe to be inconsistent with the evidence collected by the LSG. We note with extreme concern that the absence of adequate evidence or

scientific understanding is, in a number of cases, assumed to imply not only the absence of risk that a future adverse effect may occur, but worse, to suggest that existing symptoms reported by the public are almost certainly unrelated to exposure to the contamination.

It is our position that the Lowermoor Incident must be treated as a serious industrial accident, and investigated as such. After any such incident, examination of those involved must be collected and evaluated, thoroughly and impartially. In the case of chemical accidents, this always requires full medical investigation of those exposed to contact. Since this crucial and elementary response has still not been complied with by the health sector, it is essential that this study should now take on this responsibility.

We have recently received a communication from Dr. Exley expressing similar concern,. He indicates that even now suitable medical investigations could be carried out to identify those who may still carry a body burden of aluminium. Any that do may have an increased risk of developing aluminium-related pathological conditions in the future. We therefore consider that the current Consultation Period must not be regarded as the end of the road for this investigation, and that further direct investigations of both the medical records and of the people exposed to the incident should now be instigated. Until all of the remaining evidence - or at least enough to provide a valid assessment - has been collected and weighed, the health effects of this industrial accident will remain unverified.

In the light of these recent developments, we have prepared a review of the Executive Summary. We have identified those - generally very short - sections of the statements included in it on which we have reservations, and provided our perspectives on how these may require amendment in the final version. These comments are designed to be helpful, not destructive, and we trust that they will be accepted in that spirit.

External criticism of the Draft is liable to be based purely on what is included within it. For scientific assessments this is to be expected. But in identifying any perceived defects in the Draft, public concern is liable to include criticism that the LSG has taken a particular approach to the study that is perhaps inadequate. We consider that it is impossible to understand the context of the study adequately without a clear knowledge of the historic and current political constraints that operate upon the work of the LSG. We have therefore included a section that provides at least some of the background to the incident, identifying defects in the past response from the health sector that have led to the appalling shortage of monitoring date that has been such an obstacle to the work of the LSG.

Finally, we feel that the recommendations provided in the Draft do not go nearly far enough. Sociological impacts of this incident affect the mental health and well-being of a substantial number of people within the local population that we represent. We are concerned that there is no recognition of the need for social action, in addition to purely medical, in dealing with the effects of this incident. We have therefore provided some additional suggestions about what needs to be learned from this incident and its mishandling, so that lessons for future responses may be learned.

Doug Cross and Peter Smith

A Review of the Executive Summary of the Lowermoor Sub-Group's Draft Report of February 2005.

Doug Cross and Peter Smith - Local Representatives
CoT - Lowermoor Sub-Group

3rd April 2005

Statement by the authors.

It is not common practice for members of a specialist group to issue a dissenting version of a consensual document produced by the group. Past reviews of the effects of the Lowermoor Incident have been controversial, and the present study aimed to correct the deficiencies of the earlier studies and shed new light upon the incident and its medical effects. In the circumstances, we feel that the LSG has provided a far better assessment of probable exposure levels than has ever been made before.

However, in our view, the wording of the Executive Summary of the Draft Report of the Lowermoor Sub-Group (LSG) of the Committee on Toxicity (CoT) provides unacceptably optimistic conclusions regarding the long-term medical effects of the incident of July 1988. Whilst these statements reflect to some degree the arguments set out in the main text of the Draft, they nevertheless suggest a degree of unanimity of opinion regarding the interpretation of the evidence available to the LSG that is unjustified.

In reviewing the evidence, too much reliance has been placed by the LSG on the toxicological literature in order to assess whether or not the effects of ill health reported by the people are consistent with published reports on the toxicology of the relevant substances. As a unique incident, no literature sources are entirely relevant, and only clinical assessment of those still affected by medical conditions that they associate with exposure can provide conclusive data on which a true assessment of the impacts of the incident can be made. The LSG has effectively ignored this source of data, refusing to examine medical records unless specifically provided by those giving personal evidence. Even then, no critical debate of the validity and implications of such records has been held in LSG meetings.

As a result, where caution is merited, dismissive reassurances are provided. Where lack of knowledge prevents viable scientific conclusions being drawn, optimistic value judgements are offered. Where inconvenient evidence emerges, it is discarded as unrepresentative of predicted impacts and values.

Discrepancy between the study objectives and the approach of the Department of Health.

We believe that the Executive Summary was compiled by the DoH Secretariat. It contains generalizations that are incompatible with evidence provided to the LSG, but that reflect the adamant refusal of the DoH to acknowledge that this incident could have had any serious medical repercussions.

The stubborn refusal of the DoH to admit that any serious toxic threat was implied by the incident has a long history. The first reference that we have been able to trace in which this attitude is evident is a letter dated 24th August 1988, from Mr. Michael Waring, Senior Medical Officer at the DoH. Writing to Dr. C R Grainger at The Cornwall and Isles of Scilly

Health Authority, he refers to the Lawrence Report of August 1988 as " a toxicological assessment" of the incident that was "to the point and, I believe, accurate". At around this time he circulated a letter to the residents of the area assuring them that no adverse medical effects were likely, yet he appears not to have cited any toxicological authority to support this claim.

In fact Dr. Lawrence's Report was nothing of the kind. It investigated the incident in its context as an industrial accident, and provided an initial rough but extremely inaccurate estimate of the extent of the level of contamination, based largely on what few records were available from SWWA water sample analyses. The approach adopted by Mr. Waring is consistent with official DoH policy regarding the incident, at that time and since.

In the new Draft, this attitude re-emerges. It repeatedly offers value-laden judgements that are inconsistent with a disinterested assessment of the evidence presented to the LSG, as does the Press Release issued by the Department of Health (DoH) two days before the release of the Draft. Both assure readers that adverse health effects are not expected to occur. This implies that it is possible to judge the relative probabilities of adverse effects developing or not. LSG members have repeatedly stated that there are often insufficient data, or too much scientific uncertainty, to allow them to make any realistic assessments of the level of probability of the risk of delayed effects developing.

Such optimism is inappropriate in the face of evidence provided to the LSG over the past three years. Indeed, members have felt it appropriate to recommend renewed studies of selected groups of people exposed to the incident, particularly with respect to neuropsychological conditions and the achievements and welfare of children exposed to the contamination. In our view, claiming that the LSG holds opinions that imply a higher level of certainty than the data justify misrepresents the views of members. It is mischievous and unacceptable.

What was the real objective of this study?

Within the last few days the reason for the dichotomy between the intent of the original Terms of Reference for the Sub-Group's study and the approach adopted by the Secretariat in the preparation of the Draft Report's Executive Summary has become clear. In response to an inquiry from a member of the public the Secretariat stated,
"The committee took at face value the information which members of the public told them about their health. Members did not consider that there was a need to confirm what they were told by looking at medical notes or by commissioning medical assessments, neither was this the purpose of the investigation. The assessment made by the committee was a toxicological risk assessment, in which the key questions were:

1. *what levels of exposure were individuals likely to have had to the contaminants and,*
2. *given what is known about the toxicity of the contaminants, were they likely to have caused harm to health at these exposures.*

Medical notes and clinical investigations of individuals claiming persistent ill-health would not have assisted in this risk assessment."

(DoH Secretariat, 17th March 2005)

This is the first indication that we have had that the DoH considered this study to be a toxicological risk assessment. The statement bears a disturbing similarity to the ill-founded

view expressed by Waring about the Lawrence Report almost sixteen years ago. However, the quote above is the key to understanding the root of our concern about the general direction of this Draft. The first Term of Reference for the LSG's work requires it to examine whether or not the incident "caused, or was likely to cause, delayed or persistent harm to human health". The key issue was not, was exposure "likely to have caused harm to health", but did it **actually** do so in the past, and on the basis of that evidence, is it possible that it will do so in the future?

A risk assessment is predictive; except as a purely academic exercise it cannot refer to a historic event. Motorway crashes are not investigated as 'risk assessments', but as analyses of facts, based on verifiable forensic evidence collected about the incident. The Lowermoor Incident should be analysed in exactly the same way, and this is clearly implied by the first Term of Reference. Also, in order to carry out a risk assessment of the possible future implications of a historic event, the assessors must always draw upon the actual historic case evidence to validate its conclusions. In examining the effects of a chemical accident such as this, it is imperative that the medical condition of those exposed to its should be investigated by expert toxicologists in the relevant fields.

To ignore such evidence, particularly when the event under examination was unique, is bad science. Attempting then draw unvalidated conclusions about a historic event, and then to rely on these to extrapolate predictions as to what additional risks the exposed population may face in the future, is irresponsible.

We agreed to work as Local Representatives on the assumption that the LSG would examine all of the available evidence, to decide if the reported health effects were real or not. We did not agree to make a theoretical and retrospective analysis of the risk of a toxicological response developing, especially one that relied heavily on published literature sources but not the actual medical records of the exposed population. This incident was unique, and detailed analysis of it has been continually suppressed. Inevitably, the scientific literature cannot be an adequate source of data on which to assess the its medical risks. Dr. Exley's recent criticism of the adequacy of the literature cited in the Draft implies that there may be additional sources of toxicological data so far unexamined by the LSG. This in no way invalidates our perspective that without data specifically from this or a very similar incident, examination of the literature must always be subservient to examination of the people themselves.

The Sub-Group has in fact assembled a considerable amount of valuable data within the constraints of the scope of its brief and the inordinate delay in commissioning such work. But since no medical records have been examined, the Sub-Group has been forced to rely upon anecdotal evidence from individuals who think that they have experienced some sort of adverse response to their exposure. This is not to decry the claims of those giving evidence - some, indeed, have been examined by reputable medical specialists, and can demonstrate real medical damage.

But in strict evidential terms, verbal evidence from unqualified victims of the incident is an unsatisfactory basis on which to attempt to establish the damage done and what may occur in future, just as eye-witness accounts from bystanders at an accident must be treated with caution. Without detailed examination of actual medical records this approach cannot develop a rigorous and scientifically valid analysis. The validity of at least some (and therefore by association, all) of the medical records of people claiming medical damage has apparently been compromised, and the practice of 'flagging' is so fraught with defects and inadequacies.

We therefore have serious reservations about the validity of any analysis or risk assessment (whatever it may be called) that fails to look in critical detail at the only tangible evidence available.

The DoH's extraordinary claim that

"Medical notes and clinical investigations of individuals claiming persistent ill-health would not have assisted in this risk assessment."

immediately raises a pertinent question. If this is so, then why did the Sub-Group spend so much time reviewing, and in many cases, rejecting or downgrading the validity of published data from those few such sources of direct medical and biochemical evidence as were accessible? We read the papers published by Altmann, Miles, Exley, Ward, Macmillan, and many others, and even interviewed them personally. Now it appears that we may all have been simply wasting time, engaging in displacement activity. We therefore stress that without professional (and now, independent) examination of those who appear to exhibit symptoms of a toxic syndrome, we believe that it is impossible to assess adequately the full extent of the actual medical damage caused by this incident.

On such a flawed basis, no risk assessment (retrospective or otherwise) can ever be prepared. Without evidence, science is powerless. Without science, there can be no interpretation.

Understanding the background of the Lowermoor Incident

For a balanced understanding of the impacts of the Lowermoor Incident, an informed knowledge of its political context is essential. An appreciation of the extraordinarily sustained political opposition to investigating the health effects and long-term implications of exposure to the contaminated water reveals how dramatically the scope of the study and its effectiveness have been compromised. The following notes therefore summarize this neglected aspect of the background to the study, because they reveal the constraints that exist on the work of the LSG in its attempts to obtain sufficient medical data to be able to draw viable conclusions.

In the second part of this document, we have reviewed the statements contained in the Executive Summary of the Draft Report, in an effort to direct attention to possible alternative, and perhaps more balanced, interpretations and the existence of confounding evidence. The dissenting opinions expressed are entirely our own, and may not be taken to represent those of any other member of the LSG. Where we dissent, we have provided the substance of our arguments and the evidence on which we rely. All of this evidence has been presented to the LSG, yet some does not appear in the Draft, despite being central to the interpretation of evidence presented in the Draft Report. In this review, we take the opportunity to place this additional evidence in the public domain, in the hope that others better qualified than we may find it helpful in drawing their own conclusions, and that the Final Report will provide a more reliable assessment of the health effects of this incident.

Our personal backgrounds.

The authors of this document were appointed to the LSG in October 2001, on the recommendations of Mr. Paul Tyler, MP for North Cornwall, and Mr. Michael Meacher, who was at that time Minister for the Environment. Peter Smith is a Registered Homeopath, and

has practiced with the people of North Cornwall for many years. He is Chairman of the Lowermoor Support Group, a local self-help body established to communicate information amongst those affected by the incident and to others who wished to be kept abreast of the progress of investigations. (This privately-run self-help group should not be confused with the CoT Lowermoor Sub-Group, which is referred to throughout this document as the LSG)

Douglas Cross is an independent professional Environmental Analyst and Forensic Ecologist, who was a resident of Camelford at the time of the Lowermoor Incident. He has extensive experience the investigation of environmental and public health issues in water supply and water pollution incidents in many countries. He acts as a Team Leader for International Development Agencies preparing Environmental Impact Assessments - i.e., predictive risk assessments - of a very wide range of developments.

Our role as members of the Lowermoor Sub-Group

Our role has been to provide local knowledge of the incident and facilitate contact between the LSG and the local community. Both of us had, and continue to acquire, detailed knowledge of the incident and of the effects experienced by some, but certainly not by all, local people. Our experience of unacceptable water quality in the area extends back many years, to well before the date of the incident itself (6th July 1988). After the event we both worked to salvage data that the public sector persistently ignored, and for many years we have continued to collect new information as it became available. We have no financial or other compromising interests in relation to this independent investigative work, or that could affect our position as members of the LSG.

General comments on the political constraints on the Draft Report.

The Draft Report of the LSG was published in February 2005. It is not the final version, but a consultation document that aims to provide a comprehensive interim review of all available data on the Lowermoor Incident that occurred on 6th July 1988. This study began in October 2001, and 19 meetings were held in London and two in Camelford. In addition, four visits to Camelford were made between July 2002 and October 2003 to collect evidence directly from local residents. Evidence was taken orally at both venues, as well as from written submissions, and additional research evidence came directly from some authors and from the literature. We provided data from our own records, as well as new evidence based on practical investigations during the course of the study.

Political obstruction and the scope of the LSG study.

The consequences of the politicization on all investigations related to the Lowermoor Incident have been dramatic, and it is impossible understand this incident fully without a clear understanding of the political dimension within which all subsequent officially sanctioned follow-up work has been rigidly controlled. Members of the Lowermoor Support Group (that is, the local group, not the CoT sub-group) have been aware throughout the entire life of this incident of covert attempts to block or subvert independent investigations of the incident and of its medical effects. Such misdirection has continued during the course of the LSG's study.

The obstruction of adequate (or indeed, of any) comprehensive medical investigation of the medical effects following the incident has made it impossible to obtain properly researched

and analysed epidemiological or clinical data on the exposed population. The Draft Report makes no significant comment on the effect of this obstruction on the availability of relevant data. Yet many people were surprised and alarmed that the original remit for the LSG's scope of work, that would have permitted it to take evidence on the handling of the incident, was summarily removed immediately after news of the study was first announced to the public. This is not irrelevant: even now, sixteen years after the incident, we hear that legal actions initiated by some of those affected by the incident are being subjected to pressure to desist.

The question arises, precisely what (or whose) interests are threatened by providing victims of this incident with the comprehensive medical attention and legal support that should have been available to them? We deplore these attempts to prevent the exposure of unethical political objectives and of professional incompetence, especially as it appears to take precedence over determining the extent of the very real medical problems that some people exposed to the incident still experience.

It is evident that these spoiling activities originated at a very high level within the Department of Health. But it is also clear that the water sector was implicated; water was a Government-managed asset, and the sector was under the control of the then Minister, Mr. Michael Howard. It was planned to privatize the industry 18 months later, and the chaotic response to the incident within the Water Authority undoubtedly alarmed many in Government. Pressure to carry out a covert damage limitation exercise appears to have become a Government priority, through concern that exposure of the startling incompetence underlying the incident would damage the commercial value of the Water Authority.

International implications - not just 'a minor local affair'.

The exposure of the defects in the management of the Lowermoor Water Treatment Works has played an important part in alerting the water industry world-wide to the potential hazards of accidents involving aluminium sulphate. Yet despite the publicity surrounding the Lowermoor Incident there have been many subsequent instances of accidents involving the loss of, or environmental pollution by, this substance, right up to the present day. Even in February this year, spilled aluminium sulphate was recycled through the water treatment process at a facility in the UK, instead of being treated as a toxic, acidic or hazardous waste as is required by law. No formal risk assessment in advance of the decision by management to recycle this waste back into the food chain has been reported to us.

The need to ensure that all of the lessons implicit in the incident are fully appreciated remains as urgent and important today as it was sixteen years ago. Only by gaining a full understanding of the political dimensions that underlay attempts to conceal the effects of the incident can the limitations, constraints and defects of the Draft Report be adequately appreciated.

Until this perception is countered and corrected by a balanced and truly authoritative Report, industry will continue to regard accidents involving this substance as trivial and of little concern. After all, if this 20 tonne spillage directly into a water supply system really was innocuous, then any lesser spillage to a less sensitive environment will inevitably be viewed as being of no real consequence.

Scope and limitations of the LSG study

The new Draft Report is the third official attempt to publish an account of the evidence about the health impacts of the 1988 incident. Unlike the original study group, headed by Prof Dame Barbara Clayton, the LSG has obtained access to a wide variety of formerly unavailable records, and has interviewed a far greater number of people with direct experience of the incident and its health effects. In consequence, the LSG has been able to compile a larger database of evidence than has ever been available to researchers into this affair.

The LSG's Draft Report issued in February 2005 is a working document, and not a definitive final report. It is intended that this document should be used as the basis for constructive peer review, and to encourage those with relevant expertise and experience to provide comment and new insight into the evidence and its implications. The Draft has assembled mainly anecdotal evidence on the immediate (acute) medical effects of exposure and the subsequent (chronic) medical complaints that have been attributed to it by people who were present at the time of the incident. This forms the substance of the first of the two Terms of Reference for the LSG's work, and we consider that the LSG has carried out that obligation as well as can be expected under the circumstances.

Indeed, the LSG has widened the scope of studies on this incident into fields not considered by earlier studies. For example, it has recognised the significance of secondary contamination of the water supply within domestic plumbing systems, caused by the solution of additional metals in the highly acidic water. By commissioning a hydraulic model of the water treatment and distribution system, for the first time it has been possible to demonstrate the timing and approximate peak concentrations of the primary contaminants, both within the Lowermoor Works and in the distribution system close to the Works. Sadly, even in this important work discrepancies have been allowed to enter the calculations, compromising the value of the model. This is examined in detail at the end of the Review section of this document.

Reliable new sources of medical information have become available, providing analytical data on human tissues (blood, bone, nails, hair) and urine. The LSG has also had access to a limited number of investigative medical reports produced after the event by independent specialists, and scientific understanding of the toxicology of the main contaminants has developed considerably during the years following the incident. With these innovations, the new Draft is unquestionably the most comprehensive compilation of still accessible evidence, and provides an invaluable resource for further analysis and debate.

Inadequacies in the medical data that obstruct the LSG's investigation.

But against this, in the sixteen years following this serious industrial accident there has been no planned and comprehensive medical assessment of the entire population on which the LSG could draw for medical data and analysis. It is an unfortunate fact that those few clinical studies that have been carried out after the event provide no more than very limited and almost random hints of the more complex issues underlying the incident. A group such as the LSG should have been convened much closer to the time of the Incident, when far more contemporary data would have been easily available. On the other hand, it is also true to observe that with the passage of time long-term and delayed effects that were not evident closer to the time of the incident have now become evident.

We deplore the failure of the health sector to take seriously the need to carry out professional quality monitoring of the health of the community in the wake of what is officially known as

Britain's worst water poisoning incident. It is tragic that the absence of a comprehensive health monitoring system means that once more there is a real risk that medical information on the conditions of some of those affected may still be lost.

Critical comment has been made regarding the apparently limited references cited in the Draft. The literature review examined scientific publications up to 2003. The shortness of the list of cited references is due purely to considerations of space; many more documents and sources were examined than have been noted in the Draft. However, the Draft should not be seen as a definitive assessment of the literature on the toxicology of the various primary and secondary contaminants involved in this incident. For such detailed information the reader should rely on a systematic review of all of the relevant literature.

The system of 'flagging' medical records. The Clayton Committee recommended that the local health authority should set up a post-incident health monitoring system. The health authority appears to have interpreted this as requiring it to compile statistics on cancer rates and hospital discharge rates. It relies on the system known as 'flagging' medical records, which identifies individuals whose records are of interest to some research or monitoring programme within the Health Service. The objective is that the local health authority will be alerted when a flagged individual develops a particular condition.

This system is seriously compromised. At present it relies on hand-annotated medical records: there is no computer-based system that automatically identifies any cluster or trend of unusual medical conditions that might become evident in the flagged group of records relating to the exposed population. It appears that flagging does not guarantee that the records of the considerable number of people who have subsequently moved out of the area are always reported back to the health authority in Cornwall. Nor does it appear to apply to those infants that were unborn but in the womb at the time of the incident.

Failure to collect pathological samples on the decease of people exposed to the incident. Following a serious incident involving any potentially toxic chemical, whenever any person from the flagged populace has died, pathological tissue samples should be retained and examined specifically to determine whether or not the deceased reveals any evidence of medical conditions that might be related to the exposure. Since metal toxicity has been linked with progressive neurodegenerative conditions, this requirement is especially relevant to the Lowermoor Incident. Only detailed examination of appropriate brain and spinal chord preparations post mortem will reveal possible cryptic toxicological indicators of exposure to any or all of the contaminants experienced during this incident.

We understand that no such investigative pathological examinations have been carried out by the health authority. There is therefore no reliable diagnostic evidence based upon prepared tissue specimens (as opposed to symptomatic evidence) on the incidences of Alzheimer's Disease and other neurodegenerative conditions within defined groups of people known to have been exposed to the contaminated water. Yet within the local community, the risk of developing such conditions is now an issue of paramount concern and anxiety.

In short, there is no evidence of willingness within the health sector to set up adequate monitoring of the full range of conditions that might develop as a result of exposure to the pollution. The scope of what ineffective health monitoring has been carried out was apparently founded on the inadequate investigations and placatory assurances issued by the Clayton Committee, and by DoH advisors with no professional expertise in the relevant

toxicological fields. Because of the prolonged delay in setting up the present study, the range of possible follow-up investigations that could now be recommended has been severely limited.

We consider that the public health sector policy relating to monitoring this incident has been based on incompetent initial advice by unqualified advisers, reluctance to investigate the incident by adopting the precautionary principle, and reliance on a less-than-adequate selection of published data from largely superceded scientific research. It is surely obvious that since the incident was unprecedented, inevitably there can be no clear published guidance on which to identify a specific range of resultant medical conditions that might be relevant.

Rejecting evidence from 'unofficial' tissue samples. In contrast to this lax approach within the public sector, human and/or animal tissue samples were collected by a few concerned health professionals, and by both of us. In a number of cases these tissue samples provided data on metal contamination levels that were significantly different from established 'normal' ranges. Remarkably, the relevance of the animal data has been summarily dismissed by the health sector, with the argument that animal models are inappropriate when dealing with human populations. This attitude rejects at a stroke the validity of all animal experimentation in the fields of medical and pharmacological research.

A similar bias is evident in the Draft. The largely worthless water sample data collected from samples taken far too late in the incident by SWWA are provided in exhaustive detail. In stark contrast, Cross's unique and robust data on the effect of drinking contaminated water by pregnant sows, the subsequent declines in pre- and post-partem survival of the fetuses, and on the growth rates and food conversion rates of the surviving piglets, are given only limited and passing mention. The concerned reader is left to attempt to recover the original material from relatively inaccessible sources.

Dismissing evidence from 'self selected' patients. Privately organised surveys have been dismissed by the health sector as 'self selected', as if the only randomized surveys carried out by professional epidemiologists can provide evidence of serious medical damage within a population. In any instance of a disease or environmental contamination affecting more than a single person, the only way that the medical sector is likely to become aware of it is through those people who are affected selecting themselves to report the problem to their local health care professional. Cross and Newman's 1988 survey of acute symptoms was purely aimed at alerting the health sector to the existence of widespread and severe health problems in the local community, and its main findings were replicated by subsequent more formal studies. Yet this original study has been repeatedly dismissed on the grounds that its data originated from 'self selected' sources. The results of other clinical studies - even by professional specialists such as Altmann et al - were dismissed for the same spurious reason by the establishment. We have repeatedly argued that the victims of any serious accident are not identified by random epidemiological surveys; they either refer themselves for medical assistance or are identified at the scene of the accident by emergency service investigators. It is a matter of deep concern to us that the DoH ordered the emergency response team at Guy's Hospital Poisons Unit not to attend this accident, or to have any contact with the people of North Cornwall.

Applying inappropriate statistical analysis. The majority of those few attempts at data analysis that have been made by establishment health sector professionals have themselves

been severely flawed by defects in both the methodology and the statistical interpretation. Some have obscured possibly significant adverse effects by diluting specific sub-groups with overwhelming numbers of irrelevant and largely unexposed 'controls' - people who were not exposed to the worst (or even any) of the contaminated water. The North Cornwall cancer incidence analysis adopted this defective approach. The attempt to discount the Camelford School leukaemia cluster by this means is another example of confounding data from a specific sub-group by including large numbers of non-members. We find unacceptable in this Draft Report the apparently summary dismissal of the significance of these cases with the claim that they could have been caused by infection. In the text of the Draft Report this was offered as no more than a hypothesis about the possible cause of leukaemias in general. But it was then inflated to justify the suggestion that these three specific instances of childhood leukaemia in a single class were caused by infection. This is a wholly spurious inference in the absence of any corroborative evidence.

The case for a Lowermoor Syndrome.

Although many people exposed to the contamination did not experience long-term adverse medical effects, a small group does appear to exhibit a common group of health problems that developed immediately after the incident. These include the acknowledged joint pain and swelling and 'neuropsychological' complaints. Within this group, the latter condition is often referred to as memory loss or confusion, but in a number of cases clinical investigation has revealed the existence of some form of what is generally referred to as 'brain damage' – either cognitive dysfunction or actual physical changes within the tissues of some part of the brain that has been demonstrated in CT and MRI scans. The sufferers are adamant that the symptoms that they experienced immediately or very shortly after exposure led to them seeking medical assistance that eventually led to the discovery of this damage.

Other symptoms that are common to this group are the loss of finger and toe nails, persistent skin rashes that are highly resistant to any form of treatment, a continuing reduced ability to carry out tasks and occupations that they were previously able to do with ease, and difficulties with tasks such as writing and dealing with numbers.

The Draft effectively separates such symptoms and deals with them – often dismissively – as if they are entirely unrelated. We consider this to be a serious defect, and suggest instead that these associated symptoms should properly be regarded as constituting a distinct syndrome caused by severe exposure or individual susceptibility to the toxic insult that they all experienced.

It is therefore worth recording that in the course of the investigations by the North Cornwall Homoeopathic Project, the epidemiological data gathered by Smith et al on 70 individuals clearly delineated such a syndrome. This was so widely shared that continuing to gather repetitive data seemed superfluous at the time of the study. These data were unaccountably omitted from the Appendices of the Draft Report when it was released, and yet the same syndrome emerged as a distinct feature when the LSG interviewed sufferers – many of them unknown even to the NCHP – to the extent that a member of the LSG used the expression " … pattern recognition …" to describe the repeated description of the condition by local people giving their evidence.

Conclusion.

The shortcomings and defects in the database of available medical evidence on which the LSG has been able to draw for its analysis have had a severe effect on the ability of the members to reach robust conclusions. The misrepresentation introduced into the Draft by the opinions expressed in the Executive Summary confound unfortunate ignorance with unnecessary bias and confusion. The failure of the health sector to recognise the common symptoms of sufferers exhibiting what we refer to as the Lowermoor Syndrome is reinforced by the LSG's division of individual symptoms and considering them as if they are unrelated.

Review of the Executive Summary

In the following pages, original text taken directly from the Electronic Version of the Draft report is in italics; those specific sections to which our comments refer are underlined. Comments follow each extract in turn.

"Who received contaminated water and how long was the water supply contaminated after the pollution incident?"

"1.10 *With the exception of those locations for which monitoring data exist, it is not possible to determine whether any particular point on the Lowermoor distribution network did or did not receive contaminated water because of a large scale flushing exercise which was carried out by the water supplier at different points in the distribution network. The extent and severity of the contamination can only be determined by the analysis of samples of water taken at a particular vicinity and time. Sequential water quality data are not available to enable a description of the progress of the aluminium sulphate as it travelled through the distribution system."*

Comment This is unacceptable. First-hand reports of contaminated water at locations for which no formal monitoring was carried out cannot be discounted purely on the grounds that no analytical data exist. Certainly the 'extent and severity' – presumably this means concentration – of the contamination remains unknown, but in some cases it is possible to say if such contamination existed at such locations. It is also a matter of concern that in several cases where SWWA water samples were analysed by other fully accredited Public Health Laboratories, the level of contamination of the critical components aluminium and sulphate were often found to be higher in the analyses of the independent laboratory than was indicated by the results obtained by SWWA.

"1.11 *The period of contamination with high concentrations of contaminants was short. Both water quality data and modelling of the passage of aluminium in the trunk mains indicate that the concentrations of this metal in the water supply fell rapidly from a high, initial peak. However, thirty per cent of samples taken up to the end of 1988 and 6% in 1989 remained above the 1984 WHO Guideline Value for Drinking Water Quality for aluminium. This value was set to avoid deposits in the distribution system and discolouration of water, not because of a risk of adverse health effects above this concentration. Concentrations of copper and lead were high for approximately a week after the contamination incident and very few water samples exceeded the 1984 WHO Guideline Value for zinc."*

Comment This only applies in the trunk mains. In branches of the distribution system highly contaminated water remained for much longer, and many areas were not flushed for weeks or, in some cases, for up to 18 months after the incident. The reiteration of the mantra that the Aluminium (Al) standard is set, in effect, for aesthetic reasons and not because of any health implications, deliberately diverts attention from the real medical issue. When this standard was set there was very little

appreciation that aluminium was a potential toxin – the implication of the repeated use of this phrase is that there was no relevant health consideration, and not that if any did exist then it could be discounted. This is an example of the use of assertion instead of informed opinion to divert public concern away from the issues before the LSG.

In fact, three out of six studies have found a statistical link between Al concentrations in drinking water and the prevalence of Alzheimer's Disease – hardly a robust assertion of an absolute lack of association between the two. With such uncertainty, the efficacy of the current standard for Al in drinking water to protect health interests must be considered unproven, and is indeed the subject of official concern elsewhere.

The study has been totally unable to interpret information that reveals that water quality in the area served by Lowermoor has been unreliable for a long period before the 6th July 1988 incident. For example: -

- In 1967 a discharge of sludge from the Lowermoor Works into the Tregoodwell Stream in Camelford resulted in a substantial fish kill. As the result of the research by Cross, for over twenty years the water quality regulators in the South West had the only environmental standard in the UK for aluminium in freshwaters designed to protect fish life.

- During the summer of 1986 a number of ducklings at Helstone died after drinking tap water, and the owner received a substantial compensation payment from SWWA.

- On 28th June 1988, only eight days before the Lowermoor Incident, mains water fed into a new plastic-lined swimming pool in Helstone was so acidic that adolescents who jumped into the pool quickly left it again, complaining of a stinging sensation. Shortly after they developed sores and blisters over their bodies. Attempts to neutralise the acidity of this water failed when the supply of sodium bicarbonate proved inadequate.

- On the morning of 6th July 1988, some hours before the Lowermoor Incident itself, a young woman at Treveighan, just south of Camelford, experienced ulceration of the mouth when drinking a cup of coffee.

The implication is that there have been persistent and repeated failures over the years to manage the water treatment process at the Lowermoor Works. Lime pump failure alone cannot account for the extreme reduction of pH in the swimming pool at Helstone shortly before the main incident, and it seems probable that there has been over-dosing of aluminium sulphate at least sporadically on a number of occasions in the past. Where this coincided with a lime pump failure, sporadic incidents in which severely acidic water was released to the mains distribution system may account for these earlier instances of acid water delivery.

***"1.12** Water quality data on the contaminants arising from the flushing exercises indicated that the proportion of samples with concentrations of manganese above the relevant 1984 WHO Guideline Value increased in the month after the incident but fell markedly thereafter. <u>The proportion of iron samples exceeding the relevant 1984</u>*

WHO Guideline Value rose in the month after the incident and remained high to the end of 1990."

Comment High iron concentrations indicate that the old scale lining the pipes had been either dislodged or even dissolved by the acidic water. Following flushing, some oxidation of the exposed pipe metal would have occurred. In fact high iron concentrations were recorded for years after the event.

Irrespective of this, however, the toxicological implications of the high levels of **uranium** (up to 0.2 mg per metre length of pipe) reported by Powell et al have never been discussed. (Powell J J et al. Assessment of toxic metal exposure following the Camelford Water Pollution Incident: evidence of acute mobilization of lead into drinking water. *Analyst March 1995 Vol. 120: 793-8)* Although this paper was quoted by the LSG in its discussions of the implications of the presence of lead, it entirely failed to pick up the authors' comment about the need to review the possible toxicological significance of the subsequent exposure of the population to uranium dissolved from pipe linings and entering the public water supply.

"On the basis of the toxicity data in the scientific literature and the estimated exposures, would the contaminants be expected to cause delayed or persistent harm to human health?"

***"1.13** This question is considered separately for each contaminant in Chapter 7. The possibility of additive or synergistic interactions is also addressed. For each contaminant, the implications for health of the worst case estimated intakes are considered in the context of the toxicological and epidemiological data in the scientific literature."*

Comment This is an unsatisfactory approach. Since this incident appears to have been unique, no relevant scientific studies have been published. The literature is therefore not a reliable source on which to base conclusions. The only relevant primary evidence is from the incident itself, yet this report tends to subjugate this in favour of published reports about largely non-comparable studies.

Also it is divisive – it attempts to deal with each of the individual symptoms reported by people providing evidence as if it were a discrete medical condition. The Draft in fact appears to use this technique to discount many of the symptoms revealed, and on that basis it then draws the overall conclusion that further medical developments are unlikely.

But in this incident, there has been a clear pattern of medical effects shared by a number of those who claim to have been most severely affected. In these cases, their symptoms should not be divided and examined individually. Instead, they should be treated collectively, as a discrete syndrome, and the evidence must be weighed in that context.

***"1.14** It is not anticipated that the increased exposure to aluminium would have caused, or would be expected to cause, delayed or persistent harm to health in those*

who were adults or toddlers at the time of the incident. However, the possibility of delayed or persistent harm to health, although unlikely, should be explored further in those who were bottle-fed infants at the time of the incident (i.e. below one year of age)."

Comment This is a value laden statement, and should surely read 'Nothing in the literature appears to indicate this'. Such an optimistic conclusion is entirely unjustified. Similarly, 'although unlikely' implies an ability to judge the relative significance of potential for and against such damage. No adequate foundation for this claim exists.

As evidence of the uncertainty about this subject, recent literature records the development of amyloid plaque (a known associate of the symptoms of Alzheimer's Disease - AD) close to the cuproprotein alpha synuclein in the brain that changes its configuration in the presence of aluminium. Despite claims that aluminium does not enter the blood to any significant degree, there is clear clinically reliable evidence from the medical records of a number of Camelford residents that they experienced extremely high plasma aluminium concentrations for some time after the incident. Contrary to the assumed situation, therefore, exposure of their tissues to aluminium (and possibly even of brain tissue) was possible, and the rejection of any risks from this source is unjustified.

There may be genetic reasons for susceptibility to aluminium absorption in a small number of individuals. Nevertheless, there were thousands of potentially exposed people in the area at the time, and a possible consequential increase in the incidence of AD or other neurodegenerative or neurotoxic conditions cannot reliably be discounted. It has been reported that the cause of death of AD victims may be officially recorded as some other acute development. If this is correct, then the effectiveness of any local health authority monitoring system must be in serious doubt. This conclusion that any consequential effect is unlikely is therefore unsound.

Confining future monitoring to those who were below one year of age and bottle fed at the time is unjustified. Moreover, there is an additional reason for including all unweaned infants in future monitoring (see our notes on section 1.17, below)

Because there is doubt about the potential of an exposure in this incident to initiate delayed effects all exposed people who can be shown to have been at risk should be monitored. Those still exhibiting severe disability that they attribute to exposure should be offered comprehensive medical examination by specialists who are expert in aluminium (and related) toxicology. These experts must also be immune from Government pressures to conform with the politically-acceptable mantra that exposure presents little real health risk. This has prevented both local people and those who were visiting the area at the time from receiving the medical assistance to which they are entitled under the provisions of the Human Rights legislation.

"1.15 *The increased concentrations of copper in the first week or thereabouts after the incident probably contributed to acute, adverse gastrointestinal symptoms. It is not anticipated that they would have caused, or would be expected to cause, delayed or persistent harm to health."*

Comment Again, this is an unsafe conclusion. There are still no reliable data on the actual copper concentrations experienced by some people during this incident. Cross's research contribution to this debate suggests that investigations should be considering the possible effects of exposures of up to around 2000+ mg Cu/l, particularly through dermal absorption, in some cases. The toxicological literature relating to copper is unhelpful in such instances, especially since uniquely in this case such exposure was contemporary with exposure to both aluminium and sulphuric acid. The significance of dermal exposure to some people with skin damaged by sunburn or other existing forms of dermatological damage should be reviewed.

Once again, genetic defects in some individuals may result in abnormalities of copper homeostasis that may make them vulnerable to changed configuration of the brain cuproprotein alpha synuclein. The role of encephalopathies associated with cuproproteins is now becoming of increasing research interest in neuropathological research, especially in the field of atypical Parkinsonism-like neurodegenerative conditions. As with aluminium, alpha synuclein responds to the presence of the cupric ion by changing its configuration; this time Lewy Bodies typical of the development of some forms of Parkinson's Disease are reported to form close to the site of the reconfigured cuproprotein.

These conditions are very often misdiagnosed, and the British (but not other) medical establishment is curiously unwilling to acknowledge the existence of similar neurodegenerative syndromes that result from exposure to copper, aluminium and pesticides, although they are well documented. These conditions can be induced at any time in the life of a person, but typically do not manifest until late middle age, when the damage becomes progressively intolerable, and ultimately fatal. With such a severe health risk, the adoption of the 'Precautionary Principle' is particularly vital.

Without far more effort being put into screening all deaths in the exposed population for all possible (even if improbable or rare) conditions, our understanding of the vulnerability of human populations to such exposures will remain uncertain. The total absence of detailed analysis of tissues taken from people exposed to the incident and who have subsequently died is unacceptable and demonstrates a serious procedural anomaly that merits investigation.

"1.16 The occasional high concentrations of zinc which occurred after the incident may have contributed to acute, adverse gastrointestinal symptoms. It is not anticipated that they would have caused, or would be expected to cause, delayed or persistent harm to health."

Comment This seems to be reasonable overall, but again, such apparent optimism is not justified. Dr. Neil Ward's work on induced zinc deficiency and metabolism seems to suggest otherwise.

***"1.17** It is unlikely that the potential brief period of increased exposure to lead, would have caused, or would be expected to cause, delayed or persistent harm to health. However, any additional exposure of young children to lead is undesirable and the possibility of a delayed or persistent effect should be explored further in those who were bottle-fed infants at the time of the incident, potentially the most highly exposed*

group. Inorganic lead compounds are considered to be possible carcinogens in humans and it is not possible to say whether the small additional exposures to lead will have any effect on cancer incidence.

Comment The statement relies on the fact that the fluid intake of unweaned infants may be as much as 2.5 times as great for each unit of body weight as that of weaned infants. It therefore identifies bottle-fed infants as having a far greater relative exposure level to contaminated water (assuming that their feeds were made with tap water and not bottled water). This is a dangerously flawed assumption.

In fact, Cross recorded a 20-fold increase in the concentration of aluminium in a batch of cows' milk made into ice cream at one dairy near Camelford, only four days after this incident. In considering the capacity of the body to eliminate absorbed aluminium, the Draft identifies no literature source in which lactation has been found to provide such a pathway; the observation of this additional excretory pathway is apparently unprecedented. In the absence of evidence to the contrary, it must be assumed that this indicates a potential new source of exposure for breast-fed infants.

Before this excretory pathway was revealed, the possibility of increased exposure to lead of breast-fed infants would have been rejected, yet it raises the question, can lead (and indeed, both primary and secondary pollutant metal ions involved in this incident) also be excreted via this pathway? If mothers were excreting even a part of any of their own excess lead (or other metal) body burden through lactation, the possible risk of the exposure of their infants to this indirect source of lead contamination is uncertain, but cannot be ignored.

Older children in the Camelford area have been reported to have shown signs of sudden and long-lasting changes in behaviour after the incident, a known effect of even very small increases in blood lead levels. Our comments above relating to possible repeated incidents of acidic water discharges from the Lowermoor Works also imply a need for a much more cautious approach to the claim that any long-term effect from exposure to lead is 'unlikely'

Although it is not directly related to the above extract, it is necessary to refer here to the apparently ignored part of one paper that has been used by LSG in its analysis of the implications of exposure to lead. In their paper on lead contamination extracted by the acid water passing through steel mains pipes, Powell at al (1995) noted that the acid would also have extracted uranium from the pipes, and that this represented a potential toxicological hazard to people drinking the water. It is unclear why the authors' recommendation that the presence of this uranium merited further investigation has not been noted by the LSG in the Draft Report. There is clearly a need to review the toxicological analysis of the health hazards of this entire incident using a much wider view than has been adopted so far.

***"1.18** It is not anticipated that concentrations of manganese after the incident would have caused, or would be expected to cause, delayed or persistent harm to health in those who were adults at the time of the incident, nor is it considered that there would be any substantial increased risk to health to those who were toddlers at the time. It is unlikely that there would have been any delayed or persistent harm to health in those*

who were bottle-fed infants but recommendations have been made for further monitoring of this age group."

Comment Again, the suggestion is that only bottle-fed infants were at particular risk. Until it is certain that manganese is not excreted by lactation, it is unsafe to assume that those infants that were breast-fed were at less risk than those that were bottle-fed.

There was recently a case of a rapidly fatal Parkinson-like neurodegenerative disease in Tintagel (the person concerned was not present during the 1988 incident) where it has been reported that manganese levels have been persistently extremely high recently. Manganese is reported to affect the same brain cuproprotein that is affected by aluminium and copper ions. If there is a link between any of these metals and Parkinson-like or other neurodegenerative conditions, it implies that older people in the population exposed in 1988 may also be at risk. Although evidence of this possible link between these metals, sensitive neuroproteins and neurodegenerative or neurotoxic conditions was presented to the LSG, no mention of this appears in the Draft.

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*"**1.19** It is not anticipated that the concentrations of iron in drinking water after the incident would have caused or would be expected to cause, delayed or persistent harm to health."*

Comment This is based on evidence from the literature sources consulted. However, some characteristics of iron metabolism are increasingly suspected of being a contributory factor in the pathology of Parkinson-like conditions, and this view needs to be subject to expert appraisal.

***"1.20** The sporadic high concentrations of sulphate in drinking water after the incident may have caused acute, adverse gastrointestinal symptoms. It is not anticipated that they would have caused, or would be expected to cause, delayed or persistent harm to health."*

Comment The toxicological implications of drinking what was effectively dilute sulphuric have not been adequately examined by the LSG. Sulphuric acid is a Schedule 2 Poison under the 1972 Poisons Act. Since pH of itself does not appear to be responsible for damage to the mouth mucosa (Cross's measurement of the pH of common consumable products -section 7.40, Fig.33 - is relevant here) there is clearly some unidentified mechanism, possibly but not inevitably associated with the sulphate ions) that the LSG has failed to identify to explain this very common symptom of drinking the highly acidic water (see below also)

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*"**1.21** There may have been an additive effect of those contaminants with the potential to cause adverse gastrointestinal effects and this may have led to an unpleasant, acute gastrointestinal response among those who drank the water, even when the*

concentration of individual contaminants alone was not high enough to cause such a response. The recorded pH values of the water after the incident were not low enough to cause the cases of sore throat and skin irritation which are reported. It may be that high concentrations of sulphate and metal salts rendered the water more irritant than would be anticipated from its pH alone."

Comment Despite the apparently far higher acidity of many common foodstuffs, as demonstrated in the Draft, the mouth and throat ulceration reported by some of the people who drank the acidic water cannot be explained by any mechanism so far proposed. This apparently simple observation is very important. If the pH was not low enough to cause the widely reported mucosal damage (the existence and severity of which is supported by pathological evidence in animals that drank the water, and obtained from creditable veterinary sources) and nothing in the toxicological literature explains it, then the LSG has clearly failed to identify the cause of this damage All toxicological data on the absorption of metals from the gut relies on the assumption that the gut lining is intact, so this is clearly a serious obstruction to the diagnosis of risks and possible consequential effects.

Whilst most of the literature dealing with the toxicology of sulphuric acid deals with the corrosive effects of exposure to more concentrated solutions, the potential synergistic effects of consuming a combination of dilute sulphuric acid and the relevant metals in combination appears not to have been explored. The pH of water is an important ecotoxicological factor in metal pollution, as metals such as aluminium, copper, zinc and lead become much more toxic in acidic solution, and show a greatly enhanced toxicity to fish in waters with a pH value below 7. Although the human stomach may contain considerable amounts of hydrochloric acid, the combined effects of metals and sulphuric acid in the stomach and intestine cannot be assumed to be identical to that of the same metals when present in the naturally acidic human stomach.

***"1.22** <u>On the basis of the available data, it is not anticipated that</u> the combination of metals which occurred as a result of the pollution incident would have caused or would be expected to cause delayed or persistent additive or synergistic effects."*

Comment The literature does not provide adequate data on the possible synergistic effects of consuming two or more of the metals prominent in this study to draw such a conclusion, and is even less forthcoming when dealing with them in conjunction with the extraordinarily improbable presence of the registered poison, sulphuric acid. Nor is it safe to accept the general assumption that the low apparent toxicity of one of the metals present would have indicated relative immunity from toxic effects on all ages and conditions of people exposed to them. This is example of the failure of the compilers of the Executive Summary to recognise that lack of adequate understanding is an unsuitable basis for assuming a consequent lack of risk.

"Are the symptoms or illnesses reported by individuals or identified from epidemiological studies considered to have been caused by delayed or persistent effects of the contaminants?"

***"1.23** The symptoms reported as being health effects of the incident were identified using a number of sources. The types of chronic symptoms and diseases which were most commonly reported to the Subgroup in interviews with, and written submissions from, individuals fell into the categories of neuropsychological effects, joint pains and/or swelling, nail problems, cancer and thyroid disease. These were similar to those reported by 70 people in the report of a homeopathic project in 1992; this also reported malaise, tiredness and exhaustion, a dry thirst, and a sensitivity to tapwater. The Subgroup recognised that the incident was unique and that there was a recognizable pattern of symptoms and diagnoses among the individuals who provided personal evidence. It also recognised, through its contact with the local population, that many individuals were concerned and distressed about the possible health consequences of the incident in relation both to themselves and to the community as a whole."*

Comment The clinical evidence of brain damage in a number of people who complained of severe mental effects, including memory loss, within a short period of exposure is well documented, and is not a matter of opinion. However, information on medical consultation rates is difficult to assess. It is important to bear in mind that many people have reported that they were very actively dissuaded from reporting later symptoms to their medical advisers – indeed, in some cases they claim to have been asked to leave surgeries when they attempted to consult on related issues. Some local GPs are reported to have been reluctant to examine or treat anyone presenting with conditions that they believed to have been caused by the incident. This may be attributed to a letter circulated from Mr. Michael Waring (DoH) in August 1988, in which he assured the local medical sector that adverse health effects were unlikely to occur.

Unlike the detailed critique of published medical papers provided in this Draft, there is no corresponding review of the apparent reliability of verbal evidence about the responses of the medical services following this incident, yet this is relevant to the evaluation of the reliability of data from all sources. Readers without relevant professional qualifications should not be left to infer any inconsistencies in recorded evidence, and thereby decide for themselves on the reliability of the evidence from their own reading of this complex and long document.

We also note with concern that the detailed epidemiological data (referred to above) of the North Cornwall Homoeopathic Project was omitted from the Draft Report, and appeared on the COT website only after its exclusion was drawn to the attention of the Secretariat.

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*"**1.24** In Chapter 8, each of the symptoms, or symptom groups and disease is considered in the context of the evidence relating to the potential exposures to the contaminants, their known toxic effects, and the results of studies on the exposed population. An assessment is made of the likelihood that the reported health effects were caused by the contaminants."*

Comment This is, of course, a fundamental point that must be made clear to the public. The toxic effects of the contaminants are 'known' only as far as past experimentation or study relates to the unique conditions of this incident, and as they

are accordingly reported in the literature. Without an appropriate precedent, there can be no truly relevant literature!

As for the epidemiological studies described and assessed in the text, some that were carried out by medical specialists for lawyers acting for claimants have been wrongly denigrated as having been somehow tainted by association with vulgar financial interests. Other studies have been so obstructed by the inaction of the health sector that vital evidence has been irretrievably lost. And a few, as detailed below, have been of such dubious quality that their value as scientific studies must be rejected. It is improper to draw benign conclusions from such sources – where a potentially lethal or debilitating outcome may be possible, adopting the 'Precautionary Principle' is an absolute requirement. When the balance of probability indicates a possible adverse outcome with a low safety factor, then that should be sufficient to trigger a 'fail safe' response. Adopting scientific aloofness and applying the test of 'beyond reasonable doubt' is a dangerous and unacceptable approach when the health, and even lives, of many may be at risk.

"1.25 *The estimated exposures to the contaminants are not considered to have been sufficient to cause neurotoxic effects in adults nor in those who were children at the time of the incident. However, the Subgroup was advised that the overall pattern of results in one of the neuropsychological studies indicated subtle effects in the individuals tested but that it was not possible to determine whether these effects were due to the contaminated water because of deficiencies in the design of these studies. Further work is recommended on this endpoint."*

Comment These statements are mutually exclusive. The advice indicated that such effects were possibly the result of exposure. There has been abundant evidence, both from the public and from some medical specialists, that in their opinion such a direct causative link was present, even if the mechanism was unclear. This is always the case when a new medical condition appears.

The scope of the neuropsychological effects that appear to have resulted from exposure therefore needs to be clearly defined. The issue is not what the literature does or does not suggest, but what actually appears to have occurred amongst some individuals following their exposure, especially amongst those that were entirely free of such problems immediately before the incident. Any initial monitoring needs to cover the widest possible field. It must attempt to identify those effects that are now amenable to further examination and relevant to the study. Then a targeted series of studies is required to quantify as far as possible the effects on specific conditions.

And also note that a neurodegenerative condition is not necessarily in itself an 'endpoint'. The real endpoint is death.

"1.26 *There is no indication <u>from the toxicological data</u> that the estimated exposures to the contaminants which occurred after the incident can cause effects on joints and <u>it is not possible to conclude that</u> there is a causal relationship between the joint pains and/or swelling reported and exposure to the contaminants. It should be borne in mind that arthritis and related problems occur commonly in the population.*

However, the Subgroup recognised that many individuals with whom they spoke were concerned about joint problems. Therefore, further work is recommended on this endpoint."

Comment Joint pain, especially amongst males, was a prominent finding of the Cross and Newman study in 1988. In many cases people were virtually crippled for weeks or months afterwards. This paragraph suggests that any causal relationship is unlikely – the facts suggest otherwise. Whilst it may not be possible to conclude that there was a direct relationship on the basis of evidence from the literature, or to discover if such an effect has previously been recorded, this does not mean that it is impossible – only that it may result from a novel form of exposure that has triggered a response that is more familiar as the result of other causes.

However, since such conditions naturally do develop and progress as people age, the possibility that any instances that have developed in people exposed can now be recognised as in some way distinct from those that arise naturally is likely now to be remote. Unless exposure caused some new and unique form of joint damage, it is unclear what the recommended study might be capable of revealing at such a late stage.

***"1.27** A consultant dermatologist who, two years after the incident, examined individuals suffering from nail and skin problems reported that the types of nail problems seen were common and that further metabolic investigation of the patients' nails was not required. There is no relevant information in the epidemiological studies nor from the toxicological data on possible effects of the contaminants on nails which can add to this opinion."*

Comment On the contrary, several specialist who also saw some of these patients stated that they could not identify the cause, but in some cases at least the cause was emphatically not fungal. Precisely what 'types of nail problems' did this specialist refer to? How typical were the instances from Camelford people, and how prevalent is non-fungal damage that arises spontaneously and persists for years after its appearance? Why did other specialists say that at least some of these examples were not typical of the usual nail loss conditions?

It is crucial to understand that people reporting nail loss also consistently presented with a number of other conditions that also appeared at the same time – in other words **they exhibited a syndrome**. It is completely unacceptable to discount one of the symptoms within such linked conditions – or indeed, several of them – by dividing them from the entire spectrum of medical conditions shared by the group. This dismissal of any significance in the shedding of finger and toenails is unjustified. At the time local doctors were baffled by the repeated loss of nails. The statement in section 1.27 indicates that this decision is based on the opinion of a single specialist, irrespective of the opinion of others, and is therefore unacceptable. Metals of Group 3A in the periodic table (including aluminium, gallium and thallium) are all known to concentrate in nails after exposure, and skin rashes and nail losses that were commonly reported within this group have been improperly dismissed in isolation.

***"1.28** The results of a study of cancer incidence and mortality between 1988 and 1998 in the population living in the area which received contaminated water provide no evidence of an increased overall cancer risk arising from the incident."*

Comment This dismissal of the significance of cancer rates is based on a single flawed study by Dr. Miles and his colleagues – why is this unreliable study used to support this claim? This study diluted the 'test' group with the entire remaining population of North Cornwall, a technique guaranteed to conceal all but the most overwhelming incidence of abnormal incidence of a pathological condition.

The significance of cancer in the community as a whole is in fact open to interpretation. We have heard a number of local people observe that people from the exposed area seem to have a much shorter life expectancy following initial diagnosis than people elsewhere, but no data have been made available on the survival time of cancer patients that might discredit such a claim. Purely recording mortality rates would not identify any other factor, such as more rapid lethality, that might be relevant.

Unfortunately, the issue of cancer is impossible to evaluate at present, not least because of the uncertainty of the accuracy of either reporting, record keeping or the effectiveness of 'flagging' patients' medical records. The incidence of lost medical records, or the reported alteration of some long after they have been written, has become an issue of concern for some patients. Such records should never be subject to revision, only addition, since this inevitably raises the question of possible attempts to conceal past medical mistakes. Although this Report makes no recommendation regarding the management of medical and other official records, it is our view that all relevant records should be sealed and never subjected to any form of retrospective editing. This would include both medical records, school attendance records, and any other relevant quantitative records that might be of value for statistical analysis after an incident such as this. Their relevance to future investigations needs to be preserved and they should be properly protected from disposal.

Where a large population is exposed to a potentially dangerous emergency, all previous and subsequent medical records should be accessible to official investigation; there is no reason that medical confidentiality should be used to frustrate the identification of population responses that could prove of vital importance in managing the consequential effects. Access to some information is also provided under the new Freedom of Information Act, as well as the Freedom of Access to Environmental Information Act. All relevant records must be preserved and made available to investigators, and medical records should not be exempt from such protection and accessibility.

***"1.29** The results of an investigation of a cluster of three cases of acute leukaemia in children attending a secondary school in the area which had received contaminated water were consistent with the hypothesis that the incidence of leukaemia could be affected by prior exposure to infectious agents. However, the study found that the pollution incident did not cause an increased incidence of infection."*

Comment The LSG did not find that the incident did not cause an increase in leukaemia cases. It has accepted the proposal that some cases of leukaemia may be caused by infection, but has then assumed that this provides sufficient evidence of causation in these cases. It has not established that infection was the only possible such explanation.

In fact, the three leukaemia cases occurred in a singe group of 22 children who were, apparently uniquely, given orange juice with their morning drink in the nursery class at Camelford on 7th July 1988. This forms a valid sub-group against which other matched groups should be compared. Diluting data from such a sub-group with the entire population of North Cornwall is not a scientifically or statistically valid way of examining this cluster. A new analysis of the health of that sub-group of children must be made immediately.

The recommendation that more investigations of properly selected sub-groups should be undertaken to assess possible delayed or persistent neuropsychological effects of exposure should certainly include this sub-group, but should also identify the causes of chronic illness (including morbid psychological conditions) or death in any members of all identifiable sub-groups. During its investigations and case-taking, the North Cornwall Homoeopathic Project recorded many instances in which subjects needed four, five or six prescriptions of antibiotics to clear infections that would normally have been expected to responded to one or two prescriptions. This suggests lowered immunity and, by implication, an impaired ability to hold back the rate of growth of cancers.

***"1.30** There was no indication from the toxicological data on the contaminants of an adverse effect on the thyroid gland. Thyroid disease is common in the population and the cases reported are considered unlikely to be caused by exposure to the contaminants resulting from the incident."*

Comment This is again linear thinking in a situation that demands a lateral approach. Why should there be relevant literature upon which to draw when this incident was unique? The factual evidence of unusual thyroid conditions (Hashimoto's Disease, for example) is available; conclusions should be drawn from it, not 'reverse engineered' to discount the significance of the evidential data. The thyroid gland is sensitive to many forms of infection and toxic assault, and may provide an early warning of developing conditions.

***"1.31** The homeopathic report cited a sensitivity to tap water as a common finding after the incident but, from the symptoms described, this does not appear to be the immune condition termed "sensitisation". It has been proposed that it may be a manifestation of the non-immune condition termed "chemical sensitivity". It is difficult to assess the potential significance of this process in the context of the Lowermoor incident in view of the lack of firm mechanistic evidence and of robust means of diagnosis. Therefore, at this stage, it is not possible to draw conclusions or make recommendations in relation to these symptoms."*

Comment There is abundant research and case-study literature dealing with chemical sensitivity, yet the LSG has failed to treat this topic with the rigour that it deserves. The argument that there is no immunological basis for such 'sensitivity' has been proposed to dismiss conditions such as ME, yet that is now known to be a real and debilitating condition. Sensitisation to local tapwater has been shown to occur under 'double blind' (but non-clinical trial) conditions; its significance should be investigated, not simply dismissed as inexplicable. The 'lack of evidence and of a robust means of diagnosis' blamed for the LSG's inability to reach a conclusion is attributable to the failure of the health sector to consider the claim of sensitivity as a serious issue, despite the ease with which the claims of those reporting it could be tested.

***"1.32** The Subgroup was informed that there was a higher proportion of children with a statement of Special Educational Needs (SEN) ("Statements") in North Cornwall than in the rest of Cornwall and concern was expressed that this might be related to the pollution incident. The Subgroup received expert advice that the determination of children with SEN is influenced by many different factors and that no conclusions could be drawn from SEN figures about the long-term impact of the incident on health. In addition, a detailed investigation did not find there to be any consistent difference between the rates of children with Statements in the secondary school likely to have had the highest proportion of children from the affected area and those in other schools in Cornwall."*

Comment This statement indicates an unwillingness to examine the data critically. The Richmond Test methodology from the USA used as the measurement criterion has been widely dismissed by teachers throughout Britain as inappropriate for British children. Available SEN and Statement data for the area and schools are indeed useless, but this statement fails to highlight the fundamental flaw in relying on any formal method of classifying children that is based upon the economic provisions within the Education Sector for the support of children with special needs.

To put it bluntly, if an Education Authority does not provide adequate funds according to the actual demands of a community, then the rate of Statementing, and any other formal classification of less serious educational problems, will not reflect the needs of the children, but simply the depth of the purse of the School that they attend.

We have received authoritative reports that after the incident the proportion of children in some groups recognised by their teachers (but not by the funding provided) as having special educational needs was over 30%. This is not merely a 'higher proportion' but one far above the national upper average limit of around 16%. This needs to taken at face value and investigated in detail. If there was an increase in children having difficulties, then the possibility that this may be linked to the incident, even if only in a proportion of cases, is of extreme concern and requires immediate investigation.

We have seen from the modelling, and learned from members of the public giving evidence to the LSG, that exposure to extreme levels of contamination could differ wildly, even between adjacent dwellings. Consequently, the validity of attempting to

use residential postal code groupings as the basis for broad-based epidemiological studies is highly questionable. In contrast, children attending the schools (particularly in Camelford where the model shows that exposure levels would have been at their highest) can be identified as members of specific sub-groups, all of whom were subject to similar exposure risks. It is our contention that the achievements and behaviour of sub-groups of children who attended the schools should form the basis of detailed surveys into the possible long-term and delayed effects of the incident.

"Recommendations for further research"

A. Population Studies

Neuropsychological investigations

"1.33 *Further studies should be carried out to explore the neuropsychological status of those individuals who consumed the contaminated water. Expert advice will be required on both the design and conduct of a suitable study or studies. It is suggested that the following groups are investigated:*
• individuals who drank the water and have symptoms
• a matched sample of individuals who drank the water and are without symptoms
• a matched control group from another community where exposure did not occur."

Comment The school classes provide valid sub-groups, since their members were, in general, all in the same large premises at the relevant time of highest contamination within the same area of the water distribution network. If the attendance records still exist, then the actual presence of individuals could be established, and if possible these sub-groups should be identified from class attendance records. The use in the health authority studies of statistics based on subjects' residential post-codes is clearly invalid. This is further exacerbated by the model's indication that the worst affected area was around Camelford itself; many children travelled to the school from outside the worst affected area, but are more likely to have been exposed to similar levels of contamination through the drinking water fountains at the school, even if not at home.

"Investigations of the cognitive, behavioural and educational development of children"

"1.34 *Investigations should be carried out into the cognitive and educational development of individuals who were under 1 year of age at the time of the incident. Expert advice will be required on both the design and conduct of suitable studies."*

Comment We do not accept this; the medical history of ALL children present in the worst affected area must be investigated. There were and are alarming reports concerning some children's behavioral problems that cannot simply be ignored because they were not members of this highly selective age cohort. Extra non-teaching staff had to be recruited to help the teachers to control certain classes.

"Joint pains and/or swelling"

***"1.35** Routine health statistics cannot be used to monitor the prevalence of joint problems. It is recommended that, if feasible, a study should be carried out to assess whether the prevalence of joint pains and/or swelling in the population receiving contaminated water is higher than normal."*

Comment It is almost certainly now too late to carry out any such study. If initial pathological changes did occur after the incident, they may well now be obscured by the subsequent development of more conventional arthrosis at the damaged sites. We know that even the unique aluminium-rich surface layer shown in the bone biopsies disappeared after a year or so. Any persistent physical changes remaining now are likely to be indistinguishable from subsequent consequential or incidental changes.

"Monitoring of routine health statistics"

***"1.36** The monitoring of routine health statistics for the population potentially exposed to contaminated water after the Lowermoor pollution incident, recommended by the Lowermoor Incident Health Advisory Group (1991), should continue. The monitoring should include analysis of overall cancer incidence and mortality rates, and analysis of cancer subgroups. If possible, the assessment of the exposed population should be refined to take account of the fact that some areas experienced a higher level of contamination than others. If such a refinement is possible, it could also be applied retrospectively. It is suggested that monitoring is continued until 2008, twenty years after the incident, and that the burden of this work is removed from the local primary care trust and is, in future, carried out by an academic department familiar with the analysis of routine health statistics.*

Comment The LIHAG monitoring proposal was far too restricted, and credit for the original proposal should not be permitted. Had adequate professional monitoring been carried out, then the LSG might well have had far better evidence on which to base its conclusions now.

Given the history of public sector pressure on scientists and others wishing to investigate this incident, that an independent research body should undertake such studies should not be a recommendation but an absolute requirement. It must have no dependence on research funding from the health sector, and the termination date should not be set merely at 2008. The relevance of the effects of aluminium and copper on neuroproteins, for instance, may cause damage that becomes fatal only as the affected person ages. It is possible that some individuals who were young adults or even middle aged may eventually develop dangerous or lethal conditions in the next twenty five years, whilst those who were infants at the time may eventually develop fatal conditions only in their mid-fifties, as far ahead as 2040.

Since improper medical advice was issued to the public by both the Water Authority (" the water is bacteriologically pure!", and, "If you don't like the taste, mix it with orange juice!") and the health sector at the time of the incident, the possibility that the public prosecutor's office might wish to consider bringing charges of corporate manslaughter and/or medical negligence cannot be ruled out. There is no limitation on the time for bringing such a serious charge against a defendant, and in such

eventuality the requirement for transparently independent forensic analysis of all data and relevant materials is central to the concept of justice.

"Toxicological studies"

"1.37 *The toxicological data on aluminium, although extensive, is insufficient to make a definitive hazard assessment. There is a need for further work on the toxicity of aluminium, including:*

• studies to identify No Observed Adverse Effect Levels for aluminum salts using both acute and chronic exposure and a range of salts of different bioavailabilities

• *mechanistic data on the neurotoxicity of aluminium and of its potential role in neurological disease and other disorders such as macrophagic myofasciitis*

• *further investigations of the bioavailability of aluminium in humans, including of the reasons for the reported interindividual variation."*

Comments This recommendation refers only to the toxicology of aluminium, and not to the possible synergistic effects of a cocktail of contaminants. We still do not (and probably never shall) know what substances might have been leached from the sludge layer within the contact tank at the time of the incident, or the implications of the possible mobilization of uranium proposed by Powell et al.

The refusal of the medical establishment to recognise the potential significance of animal data collected from the affected area as an 'early warning' tool is unacceptable.

Animal data provided new insights into unexpected mechanisms of toxicity that would have alerted health authorities to possible adverse effects in the human population. Examples include the previously unreported excretion pathway of aluminium in lactating cows; the altered metal status of pig tissues; changes in reproductive performance, reduced fetal and neonatal survival of pigs; and the death of livestock forced to drink the worst of the contaminated water. All of these indicated at least a potential risk to human consumers, yet were entirely rejected by both the veterinary specialist employed by SWWA and by those (both lay and medically trained) dealing with requests for advice on the possible hazards and medical consequences of exposure.

No other pathological materials were either available or could ethically have been secured, yet the potential significance of this animal evidence has been repeatedly dismissed.

We suggest that further work on the response of common livestock and their suitability as early warning models for possible effects in humans is merited; they represent important sources of reference data and tissue preparations in investigation future chemical accidents.

The failure of the Health sector to carry out post mortem examinations on people from the exposed area who have subsequently died, with the specific aim of determining whether or not their death was related to the incident, is astonishing. Until exposure

can be conclusively proven not to have been responsible for human fatalities, all such incidents should be subjected to detailed investigations to discover the scope of any pathological or biochemical changes that may have occurred in those subjected to the incident.

The relationship between the metals – specifically aluminium, copper and manganese - involved in this incident and possible induced changes in neurological tissues and biochemical components is an emerging issue as a result of this incident. Research should be directed at more reliable identification of rare conditions that may result in unusual sensitivity to exposure to metals, as a marker to the epidemiological implications of chemical accidents in which large populations are exposed.

In particular, the incidence of Alzheimer's Disease, and of Parkinson-like neurodegenerative and neurotoxic conditions over long periods following such incidents may be of relevance to the Lowermoor Incident. Special attention needs to be paid to identifying appropriate methods of assessing the neurotoxicology of these metals, and the long-term implications of the response of critical brain components to them. The possibility that rare genetic conditions may be implicated in the expression of neurological conditions, even if only in a small minority within a population, should be discussed.

"Future handling of similar incidents"

"1.38 *There have been considerable improvements in contingency arrangements for and the management of any future chemical incidents since 1988. However, it is noted that the following areas may require particular consideration in the management of a future incident of the type which occurred in Cornwall:*
• the early identification of populations which may need to be monitored in any later epidemiological studies
• rapid, widespread dissemination of clear and accurate advice. Individuals should be informed about what has happened, the likely consequences and any action they may need to take as promptly as possible. An information point, such as an enquiry line or drop-in centre, should be set up and should continue to operate for some time after the incident so that individuals can seek advice on new concerns if and when they arise
• if the exposed population includes a large number of transient individuals e.g. holiday makers who are in the area temporarily at the time of the incident, consideration must be given as to how to identify this population for inclusion in any future monitoring programme
• consideration of the effect of contamination upon the intake of chemical species from food when there are either direct or indirect routes for the contamination of food."

Comment What improvements have been made? An internationally important effect of the initial analyses of the 1988 incident was that the Clayton Reports were adopted by the Food and Agricultural Organization of the United Nations as an example of how to manage a chemical spillage – which is simply bizarre! Unless the LSG is prepared to spell out these improvements, this section is worthless as a discussion of the lessons that should be learned about handling such incidents

Nor do these recommendations relate to the need for a more precautionary approach to the response to chemical spillages of aluminium sulphate. In a recent incident, approximately 1.3 tonnes of concentrated aluminium sulphate solution was spilled at South West Water plc's Pynes Water Treatment Works in Exeter, Devonshire. The spilled chemical, along with an unspecified amount of water from an underground

channel below the works, was ‘recovered and subjected to a cleaning process’ – apparently the dead fish were strained out of the water into which it leaked – and then recycled through the water treatment process. There appears to have been no consideration of the possible chemical effects of the extremely acidic water on unspecified detritus lying in that channel before the dirty solution was recovered and recycled into the food chain. This illustrates the extent of the industry’s failure to appreciate the potential hazards of spillages of this chemical, and brings into question whether in fact lessons have been learned.

Early identification of vulnerable populations depends on who decides what the threat is and on what basis the risk is assessed. This paragraph provides no proposal on how the manifest defects in the management of this incident could be replaced by an effective non-political response system. The Guy’s Hospital Poisons Unit is reported to have been ordered not to send the emergency team promised immediately after the incident. The lack of authority of the Director of the Unit to over-riding any such political instructions in the face of Britain’s worst ever water poisoning incident is alarming.

It suggests that political expediency may still play a controlling role in obstructing rapid and effective emergency responses, even when the situation presents an overwhelming need for coordinating public responses and essential data salvage in politically sensitive circumstances.

The role of the public in organizing community responses to such incidents is repeatedly ignored by Government. Even quite recently, the public sector’s priority in any chemical emergency was still stated to be to get the public out of an incident area, by military force if necessary, and not to allow local people any autonomy or authority in dealing with local social issues. The Camelford Scientific Advisory Panel is now internationally cited as an example of how such incidents can draw on the skills of local people to deal with their problems. Communities do not always panic if provided with full information, and it is patronizing and insulting to try to exclude them and let ‘authority’ take over.

A crucial question is, who will pay for running the ‘drop-in centre’ proposed above? The reluctance of Government to ensure that emergency funds allocated for even overwhelmingly severe disasters such as the recent Asian tsunami actually get to the target locations does not provide confidence that adequate – or indeed, any – funding would be available in a purely local incident such as this.

It is now quite apparent that the Department of Health does not wish to incur the costs implicit in a full assessment of the health of the people of North Cornwall affected by this incident. Expecting it to pay for a ‘drop-in centre’ for an indefinite period is probably equally naïve. After the Lowermoor Incident, the need for this essential social function was recognised and carried out without funding or support by local people in North Cornwall from the start of the incident until the present day.

Indeed, the demand for this service has actually increased as time has passed. The social dimension of community support has expanded to include many aspects of personal and group interaction and advice that are entirely absent from any official recognition or acknowledgement. The cost of this, if supplied from the public purse, would have been substantial. Instead it has fallen on local people already financially compromised by the failure of the public sector to provide even the most basic of support services to the traumatized population.

Assessment of the hydraulic model of the Lowermoor Works.

As part of its technical investigations, the LSG commissioned a detailed hydraulic model of the Lowermoor Works and the main distribution pipelines and service reservoirs from Black and Veatch Consultants. The purpose was to provide estimates of the time and concentrations of contamination within the Works and as the polluted water travelled through the distribution network to consumers around North Cornwall.

It was hoped that the output from such a model would help to extrapolate from the information provided by the delayed and sporadic water sampling programme carried out by South West Water Authority (SWWA) following the incident. This would give the LSG a clearer over-all picture of the physical characteristics of the incident, and assist it in estimating the limits of exposure of the people in different parts of the area served by the distribution network.

What the model does well.

Previously, the only predictive model was a physical one constructed and tested by Philip Allen of SWWA in 1988-9. On running an aluminium sulphate solution through a wooden mock-up of the contact tank, he found that the outflow could have contained between 600 and 1200 mg Al/l. But no indication of the time scale, or of the concentrations of aluminium that might have appeared in the water distribution system to North Cornwall was possible.

An important benefit of the new model is that it is now possible for the first time to understand the time-scale and approximate levels of contamination that could have been associated with the water distribution system. It describes the rate of mixing of the aluminium sulphate within the treatment works, and identifies the time when it entered the main distribution system. It also predicts the contamination levels over a period of four days, both within the Lowermoor Treatment Works itself and in the water distribution system in at least the more proximal part of the area served by the Lowermoor Works.

The sampling operation initiated by SWWA immediately following the incident was hopelessly inadequate. It collected only ten water samples on the 7th July and twelve on the 8th July, yet the results of the analysis of samples taken on the 8th appear to form the basis of all subsequent official estimates of the health implications of the incident.

The new hydraulic model reveals that in fact the peak concentration of contaminated water passed through the system in the Camelford area many hours before any attempt was made by SWWA to collect samples from the distribution system. It establishes that virtually all of the data obtained by analyzing those water samples that were taken on the 7th and 8th July have very little practical value in helping to assess the level of contamination in the critical few hours immediately after the incident. The value of such delayed sampling in assessing the possible medical implications of the incident is low.

We know that shortly after the incident two SWWA chemists were sent to the Lowermoor Treatment Works on the evening of 6th July. They spent a large part of

the night attempting to find out where the contamination came from, and "they were getting such high aluminium readings that they did not believe their instruments". Unfortunately, no trace of any records that they might have made has emerged, and no reference to such information was made in the Lawrence Report on the incident in 1988. Consequently, data that could have been used to calibrate the new model have been lost.

In the Lawrence Report, the claim was made that concentrations of aluminium of '4 mg/l, peaking at 40 mg/l' were experienced briefly, then fell rapidly. This was misleading, because it was applied only to data collected on the 8th of July and later – at least one and a half to two days after the incident, and long after the actual peak contamination levels had passed through the sections of the system close to Camelford. The very sparse SWWA water quality data relating to conditions on the 7th July indicated the existence of much higher levels of aluminium contamination, including one of 109 mg Al/l, but although briefly acknowledged by Lawrence, remarkably these were not treated as particularly important, and were relegated to a more or less coincidental status.

Yet this assessment formed the foundation of the reassuring reports issued by Waring (DoH) and the Clayton Committee a short time after the incident, and repeated interminably whenever any discussion of the Lowermoor Incident takes place. They also provided the basis on which highly dismissive views on the potential adverse health effects were issued repeatedly by the health sector, right up to the present.

What the model fails to describe adequately

Even in the present study the validity of the new model has been compromised. There is a curious absence of data on the times that SWWA water samples were taken; none of the sample times are recorded in the material provided to the LSG. Yet one of us has direct practical experience in this work with SWWA's predecessor; we can state categorically that recording sampling times has always been a fundamental and routine requirement when collecting water samples for the SWWA.

As a result of this unexplained deletion, the new model has had to assume that all samples from this source were collected at mid-day on the date indicated; this is reflected by plotting of all sample data at the mid-day point for the relevant date in the plots shown in the Draft. The model itself concludes that

'99.9% of the aluminium would have been discharged from the (contact) tank after 10 hours',

'After 24 hours, 92% (by mass) of the aluminium sulphate . . . was predicted to have exited the clear water tank' (paragraphs 3.67 and 3.68).

Introducing an uncertainty factor of up to 12 hours in the times at which these downstream samples were taken seriously compromises capacity to calibrate the model using real-time field data derived from SWWA's own analytical data.

The peak contamination spread to relatively distant sections of the system within 48 hours, yet the SWWA sampling regime still failed to locate the peaks of

contamination that were critical to understanding the incident, because their sampling programme started far too late.

Yet one crucial privately-collected water sample for which the exact time of sampling is available is treated by the modellers as if the time at which it was taken is also uncertain. If the information is correctly re-plotted in Fig 19 (page 68), it reveals that the May Rose Farm sample actually provides the only reliable indication of the concentration of aluminium present in those parts of the distribution system immediately following the incident. Yet the Draft contains the following extraordinary statement,

"*Given that this (sample containing 620 mg Al/l) is the only major anomaly with the modelling results, it raises serious doubt about the validity of the sample."* (para 3.70)

In other words, if the evidence does not fit the theory, then it is the evidence (and not the model) that must be wrong!

It is a fundamental principle of scientific methodology that the test of any theory is whether or not it reflects reality. When evidence indicates a theory is wrong, then it is the theory that should be modified, and not the evidence. Discarding inconvenient evidence is a serious scientific mischief, to be deplored in any research study. Yet at present this new model remains purely a theoretical construct; remarkably, it has not been calibrated.

It is wrongly assumed that since the predicted decay curves of the contamination in the system correspond well with almost all of SWWA analytical results from the 7th and 8th July onwards, they must therefore reflect reasonably well what happened during the crucial early hours after the incident. This is unacceptable – the data that it claims to reflect accurately were all obtained from samples that were taken after the initial slug of highly contaminated water had passed through much of the system. There are also questions regarding the accuracy of some of the analyses.

Evidence of a deep layer of solids in the contact tank.

In fact, data from the May Rose Farm sample could and should be used to calibrate the model. Two witnesses have provided written depositions to the LSG recording the evidence of sludge in the contact tank at the time of the incident. This was given by a former SWWA staff member to a formal meeting of the Lowermoor Incident Liaison Group in Camelford, a few months after the incident. He stated that the contact tank into which the aluminium sulphate was discharged did not in fact contain only treated water under chlorination at the time. Instead, there was

> **"about a metre of sludge on the bed of the contact tank, firm enough for a man to walk on it, and reaching up to the level of the outlet."**

As the modellers themselves state, the contact tank outlet was approximately one metre above the floor of the tank. Unfortunately, the schematic showing the components of the Lowermoor Treatment Works (Fig 2, page 30) shows every component except the contact tank in profile – the tank is in plan. So the vertical relationship between the outlet pipe and the floor of the tank is not evident in the plan of the treatment works.

The configuration of this ‘high level outlet’ has led to a remarkable dispute that has distorted the output of the model. This has resulted in an unduly optimistic (i.e., low) estimate of the concentration of aluminium sulphate that existed in the distributions system near to Camelford immediately after the incident. It also suggests that the estimate of the time when the peak concentration left the works and passed through the distribution system may require revision.

In his original analysis of the incident, Cross (1990) noted that the bottom of the contact tank, below the level of the outlet pipe, effectively formed a ‘sump’ into which the dense solution of aluminium sulphate would have flowed. This would have slowed the rate at which the solution mixed with the water flowing through the tank, and would have provided more time for SWWA to have realized that there was a serious water quality problem, and to have responded more effectively.

The existence of this ‘sump’ has been disputed, yet the original evidence came from a SWWA staff member who had inspected the contact tank shortly after the incident. A cross-sectional view at the location of the outlet of the contact tank shows that the outlet was and remains, as the modellers state, a ‘high-level outlet’, approximately half way up the side wall of the tank. The lower half of the contact tank would therefore have acted as a partial trap for the extremely dense aluminium sulphate solution as it was poured into the contact tank. The claim of the eye-witness that there was a layer of sludge to a depth of one metre is therefore credible, especially in view of the mismanagement at the works for many years before this incident.

In fact the model, as it has been run so far, effectively recognizes the existence of Cross’s ‘sump effect’. He commented that the effect of sludge in this ‘sump’ would have been to accelerate the rate at which the pollutant could have passed out of the system. The model output therefore mirrors the potentially delayed release of the aluminium sulphate into the distribution system had the ‘sump’ been clear of sludge, as postulated by Cross fifteen years ago.

In the account of the modelling the level of the water recorded in the contact tank at the time of the incident indicated an apparent depth of 2.2m, (Appendix 10. Page 267), and the calculated flushing time and concentrations of contaminants entering and leaving the treated water tank downstream were based on the assumption that the true depth of water in the contact tank was indeed 2.2m.

But if the sludge was present as the witness records, then the actual volume of the tank would have been only around half of that assumed in the model. This would have accelerated the rate at which the contamination passed through the works, and increased the peak concentration of the contamination entering the distribution system. Indeed, without the 1 metre high differential between the bottom of the tank and the outlet, the aluminium sulphate solution would have begun to emerge from the contact tank within, at most, a few minutes of the start of the delivery. The model therefore does not provide a reliable description of the time and concentration of pollutant in the outflow in the presence of the sludge deposit filling half of the contact tank.

The so-called ‘anomalous’ May Rose Farm water sample contained 620 mg Al/l, and is the sole evidence of the actual concentration from the distribution mains. It would have been drawn into the long feeder pipe to the Farm during the late evening of the

6th July, exactly when the model indicates that the highest concentration of pollutant would have been in the region of Helstone. It was stored overnight in the pipes and tanks of the cottages on the Farm, and used to make morning drinks at 053o hrs on the 7th July.

The concentration of aluminium in this sample is probably close to the concentration that the model would have predicted had the modellers accepted that the sludge was indeed present as stated. Remarkably, they did not re-run the model to assess this alternative scenario, which would in effect have calibrated the model against the actual field evidence.

Instead they sought the views of a specialist in water treatment who was not present at the time, and indeed may never have visited the Lowermoor Works. They accepted his view that it was extremely improbable that there had been any such sludge in the tank, or that it could support the weight of a man. Instead he apparently proposed that those making the observation must have mistaken the sludge for some hypothetical and non-existent 'benching' in the contact tank.

Yet again, evidence has been rejected to support theory!

Conflicting evidence from 'blue baths' downstream of service reservoirs.

Had the model been adjusted and calibrated as described above, the result would almost certainly have been more consistent with other observations that also raise doubts about the validity of its predictions. For instance, Cross demonstrated to the LSDG that when water containing the secondary contaminant copper comes into contact with some soaps and detergents, it only develops the strong blue coloration reported by many local people if the copper concentration is in excess of 1000mg/l. The aluminium concentration in the polluted water wherever a 'blue bath' was reported would have had to be in the region of 285 mg/l or greater to release sufficient sulphuric acid to dissolve sufficient copper in the acidic water.

The model predicts that the maximum concentrations of aluminium in the outflow of the service reservoirs at Delabole and St Endellion would have been around 125 mg Al/l, yet 'blue baths' were reported downstream of these reservoirs. The concentrations predicted by the model for these reservoir outflows are too low to account for the development of this indicative phenomenon. Had the model accepted the presence of the sludge layer, the resultant output predictions for these reservoirs would have been consistent with the development of the 'blue bath' effects downstream.

Additional toxicological implications of the contamination of the water supply by sludge in the contact tank.

One important potential health implication of the presence of sludge in the contact tank is obscured by the modellers' decision to reject of the evidence of its presence. The extremely acidic water above this layer would have dissolved out some components of the sludge, and possibly more would have been physically mobilized and carried out into the distribution mains. But since there is no information about the composition of that sludge, this is likely to remain an unresolved additional factor in the toxicology of the incident.

In conclusion

- **The Local Representative Members of the LSG Study of the 1988 Lowermoor Incident disassociate themselves from the conclusions expressed in the Executive Summary of the Draft Report. The view that this study was a 'toxicological risk assessment' is inconsistent with the requirements of the Terms of Reference and inappropriate for the analysis of a historic event.**

- **The study has failed to investigate all of the available evidence, notably the past and present medical condition of those exposed to the contamination, and particularly of those who continue to exhibit residual medical conditions that they attribute to their exposure to it.**

- **We note with concern the re-emergence of the reassurance first issued by the DoH immediately after the incident, and repeated interminably for the past sixteen years, that the Lowermoor Incident is not expected to pose any substantial threat to human health. In the Executive Summary this outdated official mantra is resurrected, and implies discredit to the members of the Lowermoor Sub-Group who have worked hard to compile an invaluable summary of evidence on the actual effects of the incident.**

1. Methodology

Because the incident was unprecedented, the Draft's assessment of its medical risks relies far too heavily on inadequate literature sources

- It is not with the collection and recording of data in the Draft that we are concerned, but with the interpretations placed upon that evidence expressed in the Executive Summary. The statements are dependent on analyses based far too heavily on literature sources and previous experience for an understanding of an incident in which the health risks to a large and disparate population were in fact unprecedented and unpredictable.

- Failure examine personal medical records means that the conclusions presented in the Draft are not supported by any clinically robust assessment of the present conditions of those still claiming to be experiencing severe and long-lasting symptoms. Instead, reliance is placed upon a random and extremely small collection of often-controversial studies, most carried out over a decade before this present study.

2. The Lowermoor syndrome

Within a small group of severely affected people there is a distinct syndrome that should be investigated as such; the attempt by the Draft to deal with, and even dismiss, individual symptoms as if they were unrelated is inappropriate.

- In analyzing the individual symptoms, the Draft fails to consider the common set of symptoms exhibited by a small but clearly defined group of complainants as possibly constituting a novel clinical syndrome. We hold that the totality of the symptoms should be regarded as indicative of a toxic overload resulting from

exposure to an undefined mixture of contaminants; individual symptoms should be re-assessed within that framework, and not as if they are unrelated**.**

- The assistance of experts in aluminium (and other metal) toxicology, in relevant associated fields of neurotoxicology, and in the field of chemical sensitivity, should be sought to provide a more comprehensive view of the implications of this incident. Those people exhibiting this condition should receive immediately the detailed medical examination to which they are entitled.

3. Political obstruction

The study has been hamstrung by political obstruction and the failure of the health sector to collect reliable and comprehensive data on the medical effects of the incident. The origins of this obstruction and those responsible for implementing it should be identified and replaced by sound and accountable strategies for dealing with such chemical accidents and their health impacts in the future.

- Political obstruction to providing an effective medical response to the incident has been evident from July 1988, and remains an issue right through to the present day. At the time of the Incident the health sector accepted without question medically unjustified dismissals of the health risks, and has stifled all subsequent dissenting concern. Access to medical services and justice for those affected has been blocked repeatedly, resulting in an absence of critical data on the medical effects of exposure. This has seriously obstructed the work of the LSG in assessing the implications of the evidence now available to it.

- The death of a wide range of livestock forced to drink the contaminated water provided important early warnings of the potential severity of the toxicological risks to people. The persistent dismissal of the relevance of such data when applied to a large and diverse population implies a serious failing in professional standards. Those persons and policies responsible for obstructing the victims of this incident from having such assistance for the past sixteen years should be identified and removed, to ensure that such injustice is not repeated.

- The Terms of Reference for the LSG study were amended at the last moment by the DoH to prohibit the Sub-Group from identifying the reasons and persons responsible for the resultant absence of reliable medical data. The failure of the health sector to advise the population of health risks at the time, without political bias, or to engage subsequently in an adequate monitoring and support programme for those worst affected, must be investigated. Suitable safeguards should be put in place to ensure that such bias and deficiencies in responding to chemical emergencies do not occur again.

- The study's second Term of Reference requires the LSG to make recommendations on future management of the medical monitoring of, and research on, the incident. This is impossible without a full understanding of those aspects of its administrative and political history that are responsible for the present difficulties in collecting and interpreting data. The scope of the all such

studies should be widened to allow them to identify and comment on the defects in the medical management of the incident and their consequences.

4. Public policy in chemical emergencies

The Draft recommends that drop-in centres should be funded in similar circumstances. But it fails to recognise that providing financial and administrative support to local self-help groups is the most socially- and cost-effective method of promoting strong liaisons between public sector authorities, the emergency services and the public exposed to such incidents. The Draft should contain more targeted proposals, which can be used as a model for responding to future chemical emergencies.

- In chemical emergencies of this type, provided that the immediate threats to public safety are abated, public involvement is the only reliable means whereby any resultant social problems may be managed and all possible relevant data salvaged without political interference.

- Public funds should be rapidly available for local self-help groups to establish community contact centres and support services, and liaise with public authorities and experts in the management and recording of such incidents and their impacts.

- The policies and procedures of local and national emergency response services engaged in dealing with such incidents should be reviewed, and robust structures developed to ensure that interference in the name of political expediency does not occur.

5. The hydraulic model of the Lowermoor Works and distribution system.

The hydraulic model used in the study should be revised to take into account evidence that has been improperly rejected in the initial computations. The strengths and limitations of the model to predict the full range of chemical implications in this incident should be identified and explained.

- Whilst providing valuable provisional insights into the timing of the peak contamination levels in and close to Camelford, and in some of the nearby communities, the refusal to recognise evidence on the presence of the sludge layer in the contact tank is unjustified. The model should be re-run to include this additional factor, and the output calibrated against the water quality data from the May Rose Farm water sample, to reflect recorded field conditions. The revised output data should then be re-interpreted.

- The output from the model reveals that the Water Authority failed to act quickly enough to secure crucial water quality data during the critical periods when peak contamination concentrations existed in the distribution mains, but the Draft fails to emphasize this important lesson.

- Contingency planning in industries in which chemical accidents could affect large areas should include provisions to identify critical nodes in the distribution system or potential contamination areas at which recording pollution monitors can be installed to provide adequate monitoring data on the timing and intensity of

public exposure or risk. Such records should be securely sealed and in the possession of local public health authorities to ensure their availability id they become relevant to future incidents or emergent health issues.

- Contemporary analytical data show that secondary chemical reactions were taking place between the primary pollutants and materials deposited over a period within the distribution system itself. The model does not provide information on the potential extent of contamination of secondary pollutants such as copper, lead and manganese.

- There is a clear chemical relationship between the potential of primary contaminants (such as the sulphuric acid released in this incident) to engage in complex secondary chemical reactions. Within broad limits, the theoretical maxima of the resultant secondary contaminants resulting from acid attack of domestic plumbing systems are predictable. The model can be used to estimate some 'worst case' scenarios that could have developed in different parts of the distribution system. The Draft has failed to discuss the use of the calibrated model's predictions to expand understanding of potential 'downstream' effects in incidents of this type.

6. The importance of social factors in community perceptions of the incident.

The social disruption caused by the incident, and the social damage resulting from the defective response of the medical sector, are important but neglected aspects of this study. The Draft should provide a clearer analysis of how socio-economic factors regulated the individual risks of exposure to the contamination. It should also provide a section explaining the relevance of the sociological factors that subsequently affected community relations within the population after this incident.

- Severe social divisions have developed within the local community as a direct result of the public sector's refusal to provide full medical and social support to those needing them. The variability of individual exposure to the contaminated water, of individual medical responses to it, and of the failure of the health sector to be seen to be providing the best possible response and assistance to those in need of support have promoted conflicting entrenched beliefs about the incident. These could have been avoided with full and open admission by the medical establishment of its uncertainty of the implications of the incident.

- Socio-economic factors were highly relevant in affecting the exposure risks experienced in different locations. There were very significant discrepancies between the actual exposure to contaminants of individuals living in different properties, even if they were adjacent. Different houses had widely differing plumbing systems; some had direct cold water supply to their taps, others had header tanks in their lofts; domestic water pipes were of copper, cast iron, polyethylene, or even in some cases of lead. In some holiday accommodation properties, high occupancy rates resulted in large numbers of people using the toilet facilities before retiring on the evening of the 6th July.

- Consequently, some properties were more likely to draw off highly contaminated water passing through the nearby water mains, and become exposed to the worst of the contaminated water during the following morning. The salvage of the most critical water quality data of the entire incident from such a location emphasizes the importance of recognizing such factors in planning emergency and monitoring responses to such incidents.

- The public needs to be helped to understand how variables within the system, the characteristics of different properties, and the physiological differences between individuals can result in highly variable exposures and medical responses in homes and those living in them. This is necessary to reconcile disparate and by now entrenched views of the physical and chemical effects of the contamination in homes and on the health of the population.

- The Draft should provide a clearer explanation of the reasons for the variability in exposure risks, and provide more discussion on the sociological factors that led to the present climate of social division and public distrust of the health sector.

Doug Cross and Peter Smith
4th April 2005

Subgroup Report on the Lowermoor Water Pollution Incident

COMMENTS ON **THE DRAFT FOR CONSULTATION**

General Point

I am extremely disappointed about the general tone of the report. In particular it does not come across as being independent, rather it gives the impression of always looking for ways to dismiss any possibility that individuals were harmed or will be harmed by the poisoning of their drinking water with aluminium sulphate. In doing so the subgroup have chosen to ignore, or have not consulted, large swathes of the scientific literature and have chosen to cite a limited literature which supports what appears to be a prejudiced view of the event. I have no intention of directly addressing these inadequacies in this submission. The subgroup had more than enough time and opportunity to undertake a thorough review of the relevant literature and they have decided that such would not be necessary. Whilst ignorance cannot change the facts it can help to keep them under wraps and this seems to have been the motive of the subgroup. Why the Department of Health should prefer to protect the interests of South West Water Ltd and the Aluminium Federation and not the health of the residents of this area of the United Kingdom is an open question.

Specific Points

1. The subgroup has no expertise in any aspect of the environmental toxicology of aluminium. The subgroup made almost no attempt to remedy this situation. Review data pertaining to aluminium were provided by the Department of Health Toxicology Unit at Imperial College, London, and all documents were written by postgraduate and postdoctoral staff with no direct experience of any aspect of the environmental toxicology of aluminium. The subgroup took oral evidence on aluminium from only **four** individuals with recognised experience in the environmental toxicology of aluminium. I was one of these individuals (the others were, Dr P Altmann, Dr N Ward and Dr N Roberts) though I was not invited to give evidence I, independently, offered to give evidence. In addition to my oral evidence I also provided the subgroup with a written critique of their summary document LSG/02/29. I am not aware that any of the information which I supplied to the subgroup in either oral or written form has formed any part of the consultation document. In addition after I had given my oral evidence to the subgroup the chairman, Professor HF Woods, thanked me and asked if I would be prepared to assist the subgroup in preparing the sections of the final report which pertained to the environmental toxicology of aluminium. In spite of my agreement to this effect I have never had any further communication with Professor Woods. The latter was in spite of the fact that I was in regular contact with members of the secretariat, Mr George Kowalczyk and Mr Khandu Mistry for the entire duration of the enquiry.

2. The subgroup took oral evidence from the Aluminium Federation though they omitted to point out in the report (Appendix 3) that Professor J Edwardson and Professor N Priest gave their evidence on behalf of the Aluminium Federation. Thus the subgroup took oral evidence from **four** representatives of the Aluminium Industry

and only **four** representatives of independent research on the environmental toxicology of aluminium. Why did the subgroup take evidence from an umbrella organisation the members of which are the worldwide aluminium industry which is an industry which does not fund any open research on the environmental toxicology of aluminium ? I have been told that it is only a coincidence that the Aluminium Federation gave evidence at the meeting which immediately followed the meeting at which I gave evidence and that they wrote to the subgroup and requested to give evidence without any prior knowledge that I had given evidence. Documentary evidence to support this chain of events should be made forthcoming as an alternative scenario is that the subgroup or someone associated with the subgroup invited the Aluminium Federation to give evidence at this time. Is it a coincidence that the Department of Health are supporting financially at least one of the individuals, (Priest) who gave evidence on behalf of the Aluminium Federation? Professor N Priest was awarded a contract by the Department of Health to commence on the 1st of January 1999 valued at £95,600 to undertake studies on; 'The development of assays for the determination of aluminium body burden in man' (D.H. Reference No: PRIEST/CHEM/98/1). The individual in the Department of Health whom acted as signatory to this contract was **Miss FD Pollitt**, who also happens to be the **Scientific Secretary to the Lowermoor subgroup**. Questions should be asked as to why the Department of Health funded an individual (who they new to be a representative of the aluminium industry) who, to use Priest's own words as written in the contract, **'is a consultant to the International Aluminium Industry'** !? The award of this contract is even more of a scandal if one considers that even though the contract was due to expire on the 1st of November 2001 the Department of Health have, over three years later, still **not received a single published outcome from the research**. Indeed, upon my latest enquiry I was told that they were still awaiting the interim report on this project! It is also a scandal that this award to a consultant of the aluminium industry represents the **only grant of any kind awarded by government**, including all of the research councils, during the past **ten years** in the subject area of aluminium and human health.

3. The fact that the subgroup took evidence from the Aluminium Federation would not be so important if it was not that the evidence of Priest and Edwardson was the most heavily used and cited in the report. The scandalous misuse of the published literature is one of the subjects of a Letter to the Editor recently published in the British Medical Journal (http://bmj.bmjjournals.com/cgi/eletters/330/7486/275-a?ck=nck). A particular example of the subgroup's misuse of the published literature is their extensive reference to Priest (2004). Not only is this a review article written by a known representative of the Aluminium Federation it is also currently the subject of a Letter to the Editor of the Journal of Environmental Monitoring (the RSC journal which published the paper) concerning the author's **failure to disclose 'conflicts of interest'** relating to his connections with the international aluminium industry. This letter will appear in the May Issue of the journal. Clearly the connections between the Department of Health and the International Aluminium Industry run deep and the Lowermoor subgroup would have been better advised to have steered clear of such complications.

4. The terms of reference of the COT Lowermoor subgroup are outlined in section 2.9 on page 23 of their report;

“To advise on whether the exposure to chemicals resulting from the 1988 Lowermoor water pollution incident has caused, or is expected to cause, delayed or persistent harm to human health; and

To advise whether the existing programme of monitoring and research into the human health effects of the incident should be augmented and, if so, to make recommendations.”

These terms of reference have since been amended to;
"The committee took at face value the information which members of the public told them about their health. Members did not consider that there was a need to confirm what they were told by looking at medical notes or by commissioning medical assessments, neither was this the purpose of the investigation. The assessment made by the committee was a toxicological risk assessment, in which the key questions were:

1. what levels of exposure were individuals likely to have had to the contaminants and,
2. given what is known about the toxicity of the contaminants, were they likely to have caused harm to health at these exposures.

Medical notes and clinical investigations of individuals claiming persistent ill-health would not have assisted in this risk assessment."

(Frances Pollitt, DoH Secretariat, 17th March 2005)

The above is a quotation which was made in response to a question concerning whether or not any assessment was made by the subgroup of the ‘medical’ evidence presented to the subgroup. Clearly, and perhaps in spite of the original terms of reference, **the subgroup were not concerned with the health of individuals who might have been affected by the incident**. They have interpreted the terms of reference such that their remit is limited to a risk assessment of an hypothetical exposure to the poisoned drinking water supply. In this respect the subgroup have employed a number of strategies to try to ascertain the concentration of aluminium to which individuals were exposed and how this concentration would have changed in the days which followed the incident. Much of the available information is contained in Chapter 3. One does not have to read far into this chapter to have the ignorance of the subgroup’s knowledge of anything to do with aluminium confirmed. The equation in section 3.14 and its corresponding footnote are non-sensical and yet the information that the subgroup was trying to deliver by using them was absolutely critical to their understanding of this aspect of the poisoning event. This is not a good start! The majority of the water quality data were provided by the polluters, South West Water Ltd. However, in a similar approach to the medical evidence, the subgroup **have not appraised this data in any way**. Neither the haphazard manner in which water samples were collected for analysis (the sampling) nor the methods by which the samples were analysed have been critically appraised. These water quality data will form the major part of the subgroup’s risk assessment analysis and yet the risks associated with using these potentially flawed data were not determined. From only a preliminary look at the data presented in Table 4 it is immediately obvious that there are some significant discrepancies between the concentrations recorded for aluminium and those recorded for sulphate. (Remember that the aluminium was ‘dumped’ into the water supply as a slurry of aluminium sulphate.) Conveniently, perhaps, there were not any measurements for sulphate on the days immediately

following the incident. However, the measurements for sulphate and aluminium on the 9th of July (three days after the incident) revealed that the measurements given for aluminium are a **significant underestimate** of what would have been expected from the corresponding sulphate concentration. The aluminium concentrations offered by South West Water Ltd are between 2 and 5 times lower than would be predicted by the sulphate concentration. Interestingly the trend of underestimating the aluminium concentration is only continued for water samples collected up to about the 18th of July at which time the measured aluminium concentrations (which are now all at or below 1 mg/L) are exactly as would be predicted by the corresponding sulphate concentrations. The significant discrepancies between the measured concentrations of aluminium and sulphate are mentioned in section 3.65 on page 63 of the report but they do not prevent the subgroup from continuing to use the South West Water Ltd data in their subsequent risk assessments. The data concerning aluminium concentrations in tapwater in the days following the poisoning of the potable supply are clearly flawed in such a way as to underestimate the degree to which individuals were exposed to aluminium. These data, though pretty horrendous in themselves, are clearly what South West Water Ltd. are willing to accept in the terms of their liability though they have little if any scientific credibility and this should have been clear to anyone with any relevant experience on the subgroup. In many ways the subgroup allowed themselves, conveniently, to be confused by the modelling exercise that they commissioned to try to determine how the aluminium which had been dumped into the treatment tank at Lowermoor would subsequently have been distributed throughout the potable water network. Like many models this can only be a very crude approximation of events and as such may be useful to present ideas concerning proportional differences in aluminium concentration throughout the network but it cannot be definitive in terms of the absolute concentrations of aluminium. Indeed, even the modellers have themselves questioned the validity of their model beyond twenty four hours after the event.
The subgroup would have been better served by asking the question as to whether the water quality analyses which were at their disposal were sufficiently reliable to be used in their subsequent risk assessments. Clearly, if they had asked this question they would have concluded that such reliable data were not available to them. No one could have argued with such a conclusion.

5. The subgroup then proceeded to use the flawed water quality data to calculate estimates of human exposure to aluminium and other contaminants in the poisoned tap waters. The futility of the textbook approach taken by the subgroup should be evident to anyone interested in the scientific method. The test of the validity of their approach should be that it would survive peer review and could be published in a quality scientific journal. Irrespective of the fact that the water quality data used in the calculations of exposure were flawed it is the simplistic manner in which these data were used that negates their scientific credibility. I am making my assessment as someone who reviews more than thirty scientific manuscripts each year and as someone who has reviewed for more than fifty different scientific journals. There are members of the subgroup who should have a similar experience in the scientific method and yet they have not questioned the approach taken in the draft report. Why ? For whatever reason, though it cannot have a scientific basis, it is clear that the subgroup believe that their estimates of ‘worst-case exposures’ for aluminium (and other contaminants) are of considerable value and consequently all of their recommendations concerning the likely impact of the pollution incident on human

health have been based upon them. In my original submission to the subgroup I pointed out that it would be **impossible to determine human exposure without looking at the individuals that were exposed**. The subgroup ignored this advice as being outside of their remit, almost certainly their understanding and most probably their budget. Later on in these comments I shall include some brief recommendations on how we might, even today, be able to determine the likely exposure of the Camelford residents to aluminium without relying upon unsatisfactory water quality analyses supplied by the polluters.

6. Chapter 5 of the draft report is at least useful in that it confirms that many individuals were exposed to the contaminated drinking water and suffered ill effects commensurate with aluminium poisoning. All of the ill effects reported in this chapter are documented in the scientific literature in respect of exposure to environmental aluminium. However, what is truly intriguing about the evidence presented in this chapter is not what was reported but indeed what was not reported. Human exposure to aluminium has been linked with a number of classes of disease, namely, (i) **neurodegenerative diseases** such as Alzheimer's disease, Parkinson's disease, motor neurone disease, multiple sclerosis, epilepsy..etc. (ii) **diseases of the bone and connective tissues** including osteomalacia, adynamic bone disease, arthritic conditions..etc. and (iii) **haematological conditions** including an anaemia and an insensitivity to erythropoetin. There is an exhaustive scientific and medical literature covering the role or putative role of aluminium in these diseases (including effects relating to the thyroid !!) and yet the Department of Health, as part of their ongoing assessment of the possible health effects of the incident funded studies looking at, pregnancy outcomes, child growth, mortality, cancer incidence including leukaemia, and educational achievements of schoolchildren. Why were these 'health outcomes' chosen whilst those which might have identified likely exposure to aluminium largely ignored. The subgroup were often dismissive of the accounts of the health of many individuals in that they were criticised for being 'self-reported'. It is quite clear that whoever was responsible for organising the so-called monitoring of the health of the local population following the poisoning was extremely careful in selecting health criteria which were least likely to indicate any influence of the known exposure to aluminium. Why were these criteria chosen ?

7. As someone who lives and breathes the subject of aluminium, whether through its chemistry with silicic acid to form hydroxyaluminosilicates and so to keep aluminium out of biota or its interaction with beta-amyloid in the aetiology of Alzheimer's disease, I am confident when I say that even with the best will in the world and all of the relevant scientific literature immediately available because of the lack of reliable data concerning individual exposure to aluminium during and following the poisoning incident it would not be possible to provide unequivocal answers relating to the terms of reference of the Lowermoor enquiry. We have two unassailable facts; (i) twenty tonnes of aluminium sulphate were dumped into the potable water supply of Camelford and the surrounding areas and (ii) many individuals were exposed to the poisoned water and many of those experienced illnesses following exposure. We now need to know how many people; (i) continued to suffer ill-effects; (ii) have developed ill-effects as a consequence of their exposure and (iii) are still to suffer ill-effects as a consequence of their exposure. This cannot be achieved in any other way than by looking at the affected population. A first approach would be to determine if the population had a higher than normal body burden of aluminium. We are all aware that

our bodies have no requirement for aluminium and so the storage or retention of aluminium in our bodies can only put unneccessary stress upon our physiology. How this may manifest itself will be entirely dependent upon the individual and individual susceptibility to disease. Larger body burdens of aluminium will increase our individual susceptibility to an aluminium-related disease. Thus estimates of the body burden of aluminium will enable a better understanding of the likelihood that an individual has suffered, is suffering or will suffer in the future from an aluminium-related illness. The determination of an estimate of the body burden of aluminium in an individual is not a trivial matter but there are a number of almost completely non-invasive techniques which could be used to achieve this. For example, it was announced at the **Sixth Keele Meeting on Aluminium** (26^{th} Feb – 2^{nd} March, 2005) that the aluminium content of bone, which is an important indicator of a prior exposure to aluminium, can now be measured without the requirement of a biopsy using in vivo neutron activation. The 'patient' will simply be asked to place their hand in small tube for a short period of time during which the hand will be bombarded with neutrons and data corresponding to the aluminium content of the bone will be collected. This is only one of a number of ways that we should be able to make useful estimates of the body burden of aluminium in individuals. These body burdens will be a first step in establishing that people absorbed and retained aluminium in their bodies following the pollution incident. Those individuals showing the highest burdens might then have their past, present and future health scrutinised more thoroughly to establish whether or not their health had been or was being impacted by their exposure to the poisoned drinking water. Only by such a human-based approach will any subgroup be able to make strong conclusions concerning the possible health effects of what happened at Lowermoor treatment works on the 6^{th} of July 1988.
The conclusions drawn by the present subgroup and contained within their draft report have neither scientific foundation nor credibility and can do nothing to allay the very real fears of the individuals who believe that they were poisoned by the polluted drinking water.

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Ms Khandu Mistry
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21 April 2005

Dear Ms Mistry

Re: Subgroup report on the Lowermoor water pollution incident

The Royal College of Physicians welcomes the Report from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment on whether the Lowermoor pollution incident in July 1988 has caused delayed or persistent harm to human health.

On the basis of the available data, the Royal College of Physicians concurs with the conclusion of the Report that the combination of metals which occurred as a result of the pollution incident would not have caused, or would not be expected to cause, delayed or persistent harm to health.

The Royal College of Physicians supports the recommendations that:

(i) Further studies should be carried out to explore the neuropsychological status of those individuals who consumed the contaminated water;

(ii) Investigations should be carried out into the cognitive, behavioural and educational development of individuals who were under one year of age at the time of the incident;

(iii) A study should be performed to assess whether the prevalence of joint pains and/or swelling in the population receiving the contaminated water is higher than normal;

(iv) The monitoring of routine health statistics for the population potentially exposed to contaminated water after the Lowermoor pollution incident should continue;

(v) There is a need for further work on the toxicity of aluminium, specifically studies to identify the NOAEL (no-observed-adverse-effect-level) for aluminium salts, for both acute and chronic exposure and a range of salts at different bioavailabilities;

(vi) Mechanistic data on the neurotoxicity of aluminium and its potential role in neurological disease and other disorders should be generated;

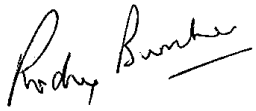
(vii) Further studies on the bioavailability of aluminium in humans should be performed.

The Royal College of Physicians also endorses the recommendation that there should be rapid and widespread dissemination of accurate advice, particularly to medical practitioners, if further chemical incidents of this kind were to take place.

In conclusion the College is reassured by the thoroughness of the evaluations contained in the report and the fact that no neurotoxic effects have been identified almost seven years since the exposure.

I trust these comments are of use.

Yours sincerely



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Re: Lowermoor Water Pollution Incident:
Comments on the DRAFT FOR CONSULTATION

22 April, 2005

Dear Mr Mistry

I herewith would like to submit comments on the above indicate report.

I trust you shall pass this on to the committee.

Sincerely

Dr Bettina Platt

Comments on the subgroup report on the

Lowermoor Water Pollution Incident

As a neuroscientists working in a medical research institute, and with an interest and an expertise in metal toxicity and mental health, I have to express my concern about the enquiry in the above incident. My main concern lies with the lack of medical and epidemiological data sought by the committee from the individuals exposed. It is entirely unacceptable to conduct an enquiry of such an incident without essential medical data and related continuous monitoring of the affected population.
Furthermore, the assessment of parameters *relevant* in cases of aluminium exposure should be the focus of such an assessment, such as repeated cognitive and neurological assessments, particularly in the elderly and in people with pre-existing neurological conditions. Monitoring of the current aluminium load and correlations to relevant neurological parameters are also still possible, and should be investigated in connection with the individuals' medical history.
Other points of concern are:

1) I could not find any evidence that the committee has sought appropriate expert advice on various issues of aluminium toxicology. Aluminium is unique in many aspects related to its chemical properties, interactions with biological system, and analytical problems related to its determination in the environment and in biological samples, and this is not considered appropriately in the your report.
2) The involvement of the Aluminium Federation in the proceedings, and scientists associated with them, is rather questionable and of major concern.
3) Clarification is required with regards to why the company that caused the pollution (South West Water Ltd.) was involved in the water analyses following the incident. The resulting data cannot stand up to scientific and indeed ethical scrutiny.
4) As an expert in the filed of aluminium neurotoxicity, I would like to stress that the scientific data and information considered by the committee appears to be more than inadequate and incomplete.

I sincerely urge the committee to take action to rectify this situation. This incident requires more rigorous scrutiny, firstly to help the affected population, but also to gain insights into the effects of high Al exposure to the human body, and learn necessary lessons on how to deal with other pollution incidents in the future.

Re: Comments on COT Lowermoor Subgroup Report on Water Pollution Incident

Dear Sirs,

We have reviewed the Lowermoor Subgroup report on the 20 ton aluminum sulphate accidental dumping into the water supply at Camelford in July 1988.

We have to totally agree with the comments of Dr. Chris Exley. We have seen so many of these types of reports in the United States, where many pages are produced to generate the illusion that the environmental and public health matter at hand has been considered. We are so regretful to conclude that the report appears to be aimed at whitewashing the issue.

It is well known that aluminum causes cognitive impairment in humans, and the Camelford spill involved a very large dosage. Profound effects are seen in very young children, in elderly persons. For example, there are now 22 drinking water epidemiology studies statistically linking aluminum to either elderly cognitive impairment or Alzheiemr's disease.

Cognitive effects are also seen in high dosage situations like welders for middle-aged persons. (1)

It is documented by many sources that individuals differ in their absorption of aluminum. For example, P.Brian Moore et al found the absorption of aluminum-26 to average higher in Alzheimer's disease patients. But there was a considerable individual scatter of absorption in both the control group and the AD cases. (2) And so, in Camelford one would expect some individuals to be more significantly and aversely affected than others, just based on differing absorption rates. Undoubtedly, there are also metabolic or dietary variables that would make some individuals more prone to injury than others from the massive exposure.

We are most impressed with the study of Paul Altmann et al, of the Camelford incident. Significant differences in cognitive function was found in exposed persons, compared to sibling controls using a range of tests, but most importantly the very sensitive flash and pattern visual evoked potentials. (3) This type of test is not only very sensitive, but it is also non-subjective.

We conclude that Lowermoor Water Pollution Incident Subgroup Report needs to be reworked by experts who have actual experience with aluminum in biology. The public deserves safe drinking water, and alternative safer purification systems such as iron based coagulants are used widely in Europe, in a number of cities in the United States, and undoubtedly in locations in the UK. Many utilities, such as that in Philadelphia, find that they can reduce costs by using iron coagulants.

For all these reasons, we think that you should adopt the recommendations of Dr. Chris Exley on this situation. We are a US-Canadian group, and have worked on the aluminum in health issue since 1989.

Best regards,

Erik Jansson, Pres.
Department of the Planet Earth, Inc.
701 E Street, SE, Ste. 200
Washington, DC 20003

(1) H. Hanninen et al, Internal load of aluminum and the central nervous functioning of aluminum welders, Scand J Work Environ Health 20 (1994) 279-85
(2) P. Brian Moore et al, Absorption of aluminum-26 in Alzheimer's disease, measured using accelerator mass spectrometry, Dement Geriatr Cogn Disord 11 (2000) 66-9
(3) Paul Altmann et al, Disturbance of cerebral function in people exposed to drinking water contaminated with aluminum sulphate: retrospective study of the Camelford water incident, BMJ 319 (1999) 807-11

Khandu, here are my comments on the January 2005 draft subgroup report of the Lowermoor water pollution incident. These are not comments on behalf of the Health Protection Agency.

Para 1.37 The highlighting of macrophagic myofasciitis (here and at para 9.6) seems odd, given that the impression from para 6.55 and page 388 (appx 16, section 6.3.1) is that the basis is speculation in one paper, and little is made of it in para 8.29. It would be helpful if the group could explain its apparent interest in the hypothesis, in the context of the incident. Were any soundings taken from vaccination experts in DH or MHRA or HPA about the status of this hypothesis?

Para 1.38 The order of the bullet points is different from (and less logical than) that in para 9.7. These recommendations are not supported by any discussion or explanation in the body of the report or its appendices. Despite the careful wording of the stem, this paragraph may give the presumably incorrect impression that LSG has identified these points as deficiencies in present-day management of chemical incidents. This impression could be avoided by rewording the paragraph along the lines of "There have been considerable improvements.....The Lowermoor incident highlighted in particular the importance of the following aspects of management…"

Para 2.2. The quote from the first LIHAG report should insert dots after the end of the second sentence, to indicate a deletion.

In the last sentence, insert "the very real current health complaints to" after "attribute".

Para 2.5. The last word in the first paragraph of the quote from the second LIHAG report should be "categorically", not "completely".

Table 3 (p 40). Number of samples for pH should presumably be 130 (since the 50 exceeding the GV make up 39%).

Table 8 (p 58), and Figures 10-14, and Table 9. If the units really are mg rather than micrograms, the maximum concentrations are extremely high if they are samples at the potable water tap.

Figures 11-13 Incorrect metal on y-axis.

Table 10. heading in table should be "number of samples" not "concentration…"

Table 11. If the units really are mg rather than micrograms, the maximum concentration of copper is extremely high.

Table 12. If the units really are mg rather than micrograms, the maximum concentration of copper is extremely high.

Table 11 maxima for Al, Mn and Fe are not reflected in Table 12.

Para 3.70. second sentence "consistent"

Fig 25 the key to the trend lines is the wrong way round.

Para 4.31 1991 not 1999, at end.

Para 6.36 At end, 6.28 not 4.28

Figure 32 the key to the trend lines is the wrong way round.

Para 7.29 The RHS of the equation is "upside-down" (as is the description in the second sentence of point 3 on page 196).

Figure 33 The heading should refer to "concentration of hydrogen ions", not "amount of hydrogen ions present".

Abbreviations In "JECFA", also need to expand "FAO" somewhere?
In "SWWA", Authority not Association.
In "TDS", Study not Survey (or has it changed?)
Re "WRc-NSF", I think that the acronym *per se* is actually the name of the company, although its derivation is as described.

I should be included in Appendix 1 in the Secretariat as:

Mr Michael Waring MA MB BChir BA FRCS LRCP Medical Secretary (until 31 October 2001)

In Appendix 3, maybe "Those who provided written information to the Subgroup" should include "Officials from Department of Health and Department for the Environment Food and Rural Affairs" – or maybe this aspect could be included in the bullet points in para 2.12 of the body of the report.

Michael Waring
Medical Toxicologist
Health Protection Agency
Chemical Hazards and Poisons Division HQ
Chilton.

Appendix 6: Reply to the Consultation Responses

Introduction

1. A draft version of the Subgroup's report was published in January 2005 and a consultation exercise to consider the draft report was run from 26 January to 20 May 2005. Twenty-six consultation responses were received, four of which were from one correspondent. Two submissions were received from one of the lay representatives on the subgroup; one of these reported information provided by an individual who had previously given oral evidence to us. Five submissions were received from individuals who had previously provided personal evidence about the incident to the Subgroup, and one from an individual who provided new personal evidence. This was reviewed but the evidence was not added to Tables 31 and 32 of the report, because it had not been provided in oral form (see Chapter 5, paragraph 5.16). Four responses were received from individuals who had previously provided technical information. Several responses provided new technical information, raised new issues or pointed out minor errors in the report.

2. A public consultation meeting was held in Camelford on 17 February 2005. Thirty-three individuals attended and a number of helpful points were raised. These were considered by the Subgroup with the written consultation responses.

3. The responses were helpful to us and we are grateful to the correspondents for their contribution to the development of this report. The exercise raised issues which we had not previously addressed, such as the question of what other trace contaminants might be present in the contaminated water (see Chapter 3, paragraphs 3.90 to 3.96). It has allowed us to identify issues which require further explanation, such as why we did not review individual medical records (see below) or why it has been difficult for us to make use of medical samples provided as personal evidence (see Chapter 5, paragraph 5.181). We have also been alerted to further scientific references on aluminium, which has enabled us to extend our review of this contaminant (see Chapter 6, paras 6.7 to 6.84). As a result of the consultation exercise, we have extended the recommendation for investigations into the cognitive, behavioural and educational development of children who were under 1 year of age at this time of the incident to include children who were *in utero* at the time of the incident (see Chapter 9, paragraph 9.4).

4. Many of the points raised by the consultation exercise have been dealt with by amendments or further text in the body of the report. However, the responses raised a number of generic issues which it became clear to us had either not been addressed or had not been adequately explained in the draft report. We discuss these below.

<u>Individual medical records</u>

5. Three responses expressed disappointment that we had not asked to see the medical records of those who provided personal evidence to us and who were worried that the incident had adversely affected their health.

6. We discussed the question of individual medical records during the investigation and again in detail after receiving these responses. We considered whether obtaining and reviewing the records of individuals who had been exposed to the contaminated water would provide us with any new information or would be useful *within the remit of our study*. Our terms of reference is "to advise on whether the exposure to chemicals resulting from the 1988 Lowermoor water pollution incident has caused, or is expected to cause, delayed or persistent harm to human health." It is not to discover the reason(s) why individuals are experiencing health complaints nor to develop a treatment protocol. Within the context of our terms of reference, medical records are of limited value. The record of the consultation between the doctor and patient made in a medical record reports the symptoms the patient is experiencing and discusses what is wrong with the patient from the point of view of the doctor and patient. The consultation, and the record of it, is not made from the point of view of whether the patient's symptoms are caused by the contaminants released in the Lowermoor incident. There is no prior hypothesis which we could test in an examination of medical records, as there would be if a scientific study was carried out, such as those we have recommended in Chapter 9.

7. We wish to emphasise that we accepted the information which individuals provided to us about their health at face value and, therefore, it is not clear what further information would be gained from seeing the medical records of these individuals. However, we also wish to emphasise that we recognise, from both the oral evidence and written evidence we received, that some individuals have continuing ill health for which they are concerned to find a cause.

<u>Adequacy of scientific data reviewed by the Subgroup</u>

8. Three respondents were critical of the extent to which we had reviewed the scientific literature on the contaminants whose water concentrations were increased after the incident. Another respondent commented that there were 22 drinking water epidemiology studies statistically linking aluminium to either elderly cognitive impairment or Alzheimer's disease. All four respondents who addressed this issue were asked for further details of missing references which they regarded as important and two replied with these details. Some of the references cited by these respondents were already referenced in the report or in the reviews prepared by the Department of Health Toxicology Unit at Imperial College (see Appendices 21 to 27). Abstracts of any which had not been considered previously were reviewed and relevant papers obtained. Chapters 6 and 7 of the report were updated accordingly.

8. We do not agree that we conducted an inadequate review of the scientific literature on the contaminants. We describe in Chapter 6 the way we went about our review and the data which was used.

9. Another respondent provided a list of 548 hyperlinks to references on aluminium. We obtained and reviewed the abstracts of the papers and determined that some had already been reviewed and some were not relevant to the exposure of individuals from the contaminants in water, for reasons which are described in Chapter 6. Nine references were relevant and we are grateful that these have been brought to our attention. We have referred to these in the revised text on the human and animal toxicity of aluminium.

Adequacy of other information available to the Subgroup

10. Some correspondents considered that we had cited inappropriate information and studies. For example, we were criticised for including a published study of Richmond tests of educational attainment in schoolchildren (see paragraphs 5.116 to 5.124) and data on Special Educational Needs (SEN) (paragraphs 5.150 to 5.159). The data on Richmond tests was included because it was a published study on children in the affected area and, in our report, we discuss all relevant published studies. We discussed the (SEN) data because we were asked to consider these data by a local journalist. We expressed reservations about the suitability of using SEN data to assess effects on health in the draft report (paragraph 5.159).

11. Other correspondents expressed reservations that the report made use of water quality data from SWW plc. These were the only water quality data that were available for the greater part of the period of contamination. It should be noted that these data were not used exclusively and, in our assessment of the implications for health of exposure to the contaminants (Chapter 7), we have also included estimated exposures based on contaminant concentrations in the water samples taken by private individuals.

12. In our investigation, we have attempted to use all the data which is available and we are aware of the limitations of some of these data. We wrote to a number of individuals who responded in the consultation exercise to obtain further information. Where we consider that further studies would be beneficial, we have recommended them in Chapter 9 of the report.

Appendix 7: Drinking water quality – the legislative framework for public drinking water supplies

The situation before 1989

1. Under the Water Act 1945, water undertakers - the Water Authorities, created in 1974, and the statutory water supply companies - were required to "... provide in their mains and communication pipes a supply of wholesome water sufficient for the domestic purposes of all owners and occupiers within the limits of supply...". UK law did not define a quantitative measure of what made water wholesome and there was no requirement to monitor the quality of supplies.

2. General guidance on safe levels of substances that might be permitted in drinking water supplies, and safeguards and best practice to be adopted to ensure production and delivery of a wholesome supply of water were available when WHO published its 1st edition of "International Standards for Drinking Water" in 1958. This was updated in 1964 when the 2nd edition of "International Standards for Drinking Water" were published and the 1st edition of "European Standards for Drinking Water" were also published. Both these were updated in 1970 and 1971 respectively. In 1984 the two editions were combined and published as the WHO "Guidelines for Drinking Water Quality".

3. The 1980 EC Directive on 'Water Intended for Human Consumption' (80/778/EEC) set out standards for drinking water quality. However, this was not enshrined in national law until 1989 (see below). There was no regulatory regime to oversee that water undertakers were carrying out their duties in respect of supplying wholesome water. There was no offence of supplying water unfit for human consumption. There was a formal requirement to notify the appropriate department (usually the then Department of the Environment) of major incidents affecting water supplies. Usually, but not always, the local Medical Officer of Health would be informed if there was a health risk.

4. In the case of the Lowermoor water pollution incident, this lack of suitable water/environment legislation under which investigation and prosecution could take place resulted in the police investigating the incident. A prosecution was initiated by the Director of Public Prosecutions for Public Nuisance by supplying contaminated water. South West Water Authority was fined £1,000 and required to pay costs of £25,000.

The situation since 1989

5. EC Directive 80/778 on 'the Quality of Water Intended for Human Consumption' came into effect on 17 July 1980. It set out Maximum Admissible Concentrations (MACs) (often and usually based on WHO Guideline Values) for various chemical, aesthetic and microbiological quality parameters which tap water was required to meet.

6. In 1989 the water industry was privatised under the water Act 1989 and the Water Authorities became the ten Water and Sewerage Companies of today. The Statutory Water Companies became private water supply only companies. All the water companies were appointed water undertakers under section 6 of the Act.

7. The Water Act 1989, which was consolidated into the Water Industry Act 1991 ("the Act"), made it a legal duty for water undertakers to "... supply only water which is wholesome at the time of supply" (Section 68). The Water Supply (Water Quality) Regulations 1989, made under section 69 of the Act, came fully into force on 1 January 1990. These Regulations for preserving the quality of water reflected the requirements of Directive 80/778 in terms of standards to be met, and also set some nationally derived standards. The 1989 Regulations remained in force until the end of 2003.

8. A new EC 'Drinking Water Directive' came into force on 25 December 1998 and its requirements are incorporated into the new Water Supply (Water Quality) Regulations 2000 (the new Regulations). These new Regulations apply to water companies whose area of supply is wholly or mainly in England. The National Assembly for Wales adopted similar new Regulations at the end of 2001 and these apply to water companies whose area of supply is wholly or mainly in Wales. Whilst some of the requirements of these new Regulations came into force as early as 2001, the majority came into force at the end of December 2003. The new Regulations set some new standards, tightened some existing standards, relaxed some standards, and dispensed with others. There are also changes in the monitoring requirements of supplies.

9. During 2006/7 revisions of the 2000 Regulations were proposed and consulted upon. It is likely that the 2000 Regulations will be amended at the end of 2007 to take into account changes in EU legislation contained in the Surface Water Abstraction Directive and Water Framework Directive. The opportunity has also been taken to incorporate the use of Drinking Water Safety Plans, recommended by WHO, as the most effective means of consistently ensuring the safety of a drinking water supply through the use of a comprehensive risk assessment and risk management approach that encompasses all steps in water supply from catchment to consumer.

10. The standards provide a numerical definition of wholesomeness. Water supplied which contravenes one or more of the standards listed in the Regulations is, by definition, unwholesome.

The old and new Regulations (and the proposed 2007 amendment) set out requirements on:

- monitoring drinking water quality
- water treatment
- the provision of information
- the use of water treatment chemicals
- drinking water system construction products.

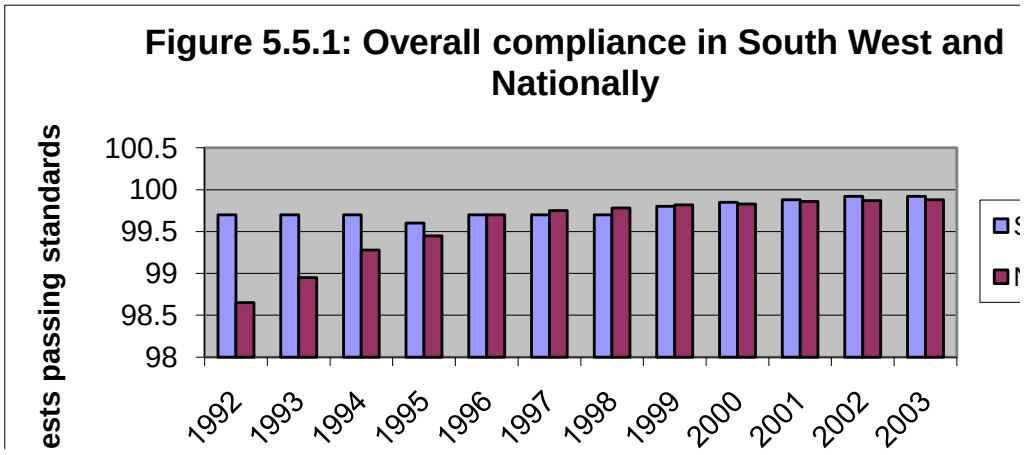
11. Figure 1 shows the number of tests carried out between 1992 and 2003 in the South West and Nationally which met the required standards. From 2004 onwards, when the new Regulations and revised standards came fully into force, the method of

reporting on compliance also changed. It is not possible therefore to compare data from 2004 - 2006 with those from previous years. It was recognised that simply reporting on the number of tests meeting the standards, which indicated that overall compliance was high, could mask localised problems experienced by consumers. The Chief Drinking Water Inspector's Annual Reports on drinking water quality for these years have therefore been issued on a regional basis and more detailed reporting provided on performance by water companies. These reports can be found at www.dwi.gov.uk. For information on water quality in the South West Water area, the Western Regional Reports should be consulted.

12. Section 18 of the 1991 Act requires enforcement action to be taken for any breach of wholesomeness standards, monitoring and treatment, and/or records and information requirements of the Regulations. However, enforcement action is not taken forward if the breach is

- deemed to be trivial or
- unlikely to recur or
- if the water company has taken immediate remedial action to prevent a recurrence or
- if the water company has submitted a legally-binding programme of work to achieve compliance within an acceptable timescale.

Figure 1:



The bars show the proportion of tests which met the required standards.

13. Section 70 of the 1991 Act made it a criminal offence to supply water which is unfit for human consumption. It also provides a defence for the company if it can show that it had no reasonable grounds for suspecting that the water would be used for human consumption; or took all reasonable steps and exercised all due diligence for securing that the water was fit for human consumption on leaving its pipes, or was not used for human consumption. It is for the courts to decide whether water is unfit but, in general, water that causes illness on consumption, or where its appearance, taste or smell is such that people cannot reasonably be expected to drink it, is likely to be deemed unfit. It is important to understand, however, that whilst water which is

unfit is likely to be unwholesome, unwholesome water is not necessarily water unfit for human consumption.

Deterioration of water beyond the point of supply

14. Water companies are not responsible for any deterioration in the quality of the water within a consumer's premises, except in the case of concentrations of copper or lead (the 1989 regulations also included zinc but there is now no longer a standard for this parameter under the new regulations). If the standards for these metals are likely to be exceeded in the water supplied to the cold tap in the kitchen, then the water company must consider further treatment of the water to reduce the risk of the water becoming unwholesome. This measure is intended primarily to reduce exposure of consumers to lead.

The role of the Drinking Water Inspectorate

15. Under the 1991 (and 1989) Act, responsibility for regulating the quality of public drinking water supplies lay with the Secretary of State for the then Department of the Environment. Technical Assessors were appointed under section 86 of the Act to act on their behalf in these matters. Following devolution, this duty also applied to the National Assembly for Wales.

16. The Water Act 2003 amends section 86 of the Act to reflect that such assessors are more generally known as the Drinking Water Inspectorate and to enable the Chief Inspector of Drinking Water to initiate prosecutions in relation to drinking water quality in his/her own name.

17. Water companies are responsible for monitoring the quality of their supplies. This 'self-monitoring' role is subject to checks by local authorities and the Drinking Water Inspectorate. One of the main tasks of the Inspectorate is a rolling programme of continuous technical audit to ensure that water companies are meeting all their regulatory obligations. Water companies must make all results of regulatory sampling available to the general public via their public record.

Drinking Water Quality Incidents

18. The Water Industry (Suppliers' Information) Direction 2009 (and earlier versions) require water companies to notify the Secretary of State or the National Assembly for Wales (in practice, the Inspectorate) of any event, which by reason of its effect on the quality or sufficiency of drinking water, may give rise to a significant risk to consumers' health. The Regulations require that similar notifications are made to health authorities (normally the relevant Consultant in Communicable Disease Control in the Health Protection Agency and Director of Public Health in the relevant Primary Care Trust) and local authorities (normally the relevant Environmental Health Officer). The Inspectorate investigates all such notifications and, in some cases, the investigation could result in the water company being prosecuted for supplying water unfit for human consumption. The results and recommendations arising from the Inspectorate's investigations are made public.

Drinking Water Inspectorate
September 2007 and 2012

Appendices 8 to 11

Appendix 8: Water quality data for the parishes of Camelford, Davidstow, Advent, St Minver Lowlands and St Minver Highlands;

Appendix 9: Water quality data for the parishes of Camelford and Davidstow;

Appendix 10: Water quality data for the parishes of St Teath, Tintagel and Trevalga; and

Appendix 11: Water quality data for the parishes of St Endellion, Forrabury & Minster and St Juliot

These appendices are available on the Subgroup's website (home page: http://cot.food.gov.uk/cotwg/lowermoorsub/)

Appendix 12: Lowermoor water quality modelling report.

Black & Veatch Ltd, August 2004

This report is available on the Subgroup's website (home page: http://cot.food.gov.uk/cotwg/lowermoorsub/)

Appendix 13: Lowermoor water quality modelling report (Phase 2)

Black & Veatch Ltd, August 2006.

This report is available on the Subgroup's website (home page: http://cot.food.gov.uk/cotwg/lowermoorsub/)

Appendix 14: Other water pollution incidents involving aluminium sulphate

A number of other reported incidents in which the water supply has been contaminated with aluminium sulphate are listed below. Little information is available on most of these.

October 1988: The water supply to properties in Hatfield, Hertfordshire was contaminated with aluminium sulphate (Cross, 1990)

March – April 1989: Penwhirn water supply district of Dumfries and Galloway Regional Council: because of a change in raw water quality and subsequent plant failure, water entering the supply contained 'flocculated material' including raised concentrations of aluminium. The maximum concentration of aluminium entering the supply was 3.5 mg/l (Water Research Centre, 1989).

June 1989: The water supply to residents around Newry, Ulster was contaminated with concentrated aluminium sulphate solution (amount unclear, may be up to 30 tonnes) (Cross, 1990).

November 1989: Amlaird, Kilmarnock: a breakdown in treatment led to raised aluminium concentrations in the water supply for at least 4 months (Cross, 1990).

March 2011: Control of the treatment process at Burncrooks water treatment works, Glasgow, was lost for approximately four hours. Concentrations of aluminium exceeded the regulatory standard for a period of 24 hours, with concentrations exceeding 4 mg/l for approximately 6 hours (Drinking Water Quality Regulator for Scotland, 2011).

References

Cross D. Something in the water. Green Magazine, July 1990.

Drinking Water Quality Regulator for Scotland, September 2011. DWQR Investigation into the Burncrooks Incident, North-west Glasgow 17 – 19 March 2011. Ver 2: 26 September 2011. Available at: http://www.dwqr.org.uk/technical/water-quality-incidents/2011-water-quality-incidents

Water Research Centre. Penwhirn district water treatment and distribution: An independent investigation by WRc. Unpublished report, November 1990.

Appendix 15: Report on the estimated consumption of aluminum, sulphate, copper, zinc, lead and pH following the contaimination incident on 6th July 1988. Crowther Clayton Associates. Report no. 91/2737.

Note: during the printing of the Consultation report, it became apparent that the quality of the above report was too poor to be reproduced in a published document. A photocopy of the Crowther Clayton report can be obtained by contacting the Secretariat , whose details can be found at the front of the Consultation report, or it can be viewed as a scanned document on the Subgroup's website (home page: http://cot.food.gov.uk/cotwg/lowermoorsub/)

Appendix 16: Extract from 'The Health of the Population', Department of Public Health Medicine, Cornwall and Isles of Scilly of Health Authority, 1988.

This appendix is available on the Subgroup's website (home page: http://cot.food.gov.uk/cotwg/lowermoorsub/)

Appendix 17: Letter from Department of Health and Social Security to Dr CR Grainger, 'Lowermoor Incident', 24 August 1988

This letter is available on the Subgroup's website (home page: http://cot.food.gov.uk/cotwg/lowermoorsub/)

Appendix 18: Summary and critique of epidemiological studies of the North Cornwall population

Introduction

1. This appendix summarises the studies carried out on the population which was potentially exposed to water that was contaminated by the Lowermoor pollution incident. The studies include investigations of symptomatology, pregnancy outcomes, growth of children, hospital discharges, mortality, cancer incidence, and of leukaemia.

Rowland A, Grainger R, Stanwell Smith R, Hicks N, Hughes A. Water contamination in North Cornwall: A retrospective cohort study into the acute and short-term effects of the aluminium sulphate incident in July 1988. J Royal Soc Health 1990; 5: 166-172

2. This questionnaire study compared symptoms experienced by a cohort of individuals in the Lowermoor water supply area with a cohort in the adjacent Bastreet area.

Study Design

3. Water distribution maps were used to identify the two areas. From the list of households used for water rating purposes, 500 households were selected from each area and a two-part questionnaire was sent to each household. Form A, addressed to the head of household, including general questions on the type of water supply and changes noticed. Form B investigated residence at the time of the incident; symptoms experienced and their severity; visits to GPs, hospitals and chemists; prior or chronic illness; and water consumption both before and after the incident. Several copies of Form B were sent to enable all household members to participate.

Results

4. The response rates were 43.4% and 46% and included 217 households (480 individuals) and 229 households (532 individuals) in the exposed and non-exposed areas, respectively. There were some demographic differences between the respondents from the two areas e.g. in the exposed area there were more households with two or more adult females, fewer individuals aged under 15 and 25-34 and more aged 65-74. About half (49.4%) of respondents in the exposed area reported changing their usual drinking pattern in July, particularly for a duration of up to 7 days. Sixty-three percent of respondents in the exposed area noticed an abnormality in the water (versus 12% in the unexposed group) with taste and colour being most often reported. Forty-nine percent of respondents in the exposed area reported they had experienced definite unusual symptoms since the start of July, compared with 10% of people in the unexposed area. There was a long list of symptoms and the prevalence of all of them was significantly raised in the exposed area relative to the non-exposed area. In the exposed group, 30% of the respondents with symptoms reported that they were still present three weeks after the incident. Few respondents in either group reported that they were unable to undertake normal activities or that they had to take time off work or school. There were no statistically significant differences in hospital admissions,

consulting a GP, or seeking other help between exposed and non-exposed respondents.

Critique

Response Rate

5. The overall response rate was fairly low and the authors report that there were a high number of 'non-resident' addresses such as holiday homes. Of 108 non-respondents contacted, 39 said they had been absent from the area, 11 responded 'old age' as a reason for non-response, 29 were not concerned, 5 said 'poor memory', 4 refused and 20 said their forms had been mislaid, destroyed or not received. The authors do not state whether the 108 people contacted were from within both areas or only the Lowermoor area.

Exposure assessment

6. Water distribution maps and water rating lists were used to identify an area served by the Lowermoor treatment works and a control area. The changes in water consumption patterns reported by respondents from the Lowermoor area offer good evidence that the effects of contaminated water were experienced at the household level.

Demographic and water consumption analyses

7. The authors have produced two-way tables but have erroneously carried out statistical comparisons between the two areas of individual categories within each variable instead of carrying out an overall chi-square test. The latter would probably indicate that there were fewer differences between the respondents from the two areas than are highlighted by the authors.

Interpretation

8. This study found a greatly increased incidence of self-reported symptoms from respondents from the Lowermoor area, compared with those from the Bastreet area. Although the response rate was comparable between the areas, it was low and the investigation of non-response indicates the difficulties of both postal questionnaire studies and, also, carrying these out in a holiday area. There had been many media reports about the incident prior to the study and a letter mentioning most of the symptoms was sent to all residents in the exposed area in August 1988. Thus, it is highly likely that reporting bias occurred. However, it should be noted that a substantial number of exposed respondents reported that their symptoms lasted a long time.

Golding J, Rowland A, Greenwood R and Lunt P (1991). Aluminium sulphate in water in north Cornwall and outcome of pregnancy. British Medical Journal 302: 1175-1175

9. This study was designed to investigate whether the excess aluminium sulphate accidentally added to the water supply in the Lowermoor pollution incident had an adverse effect on the outcome of pregnancies.

Study design

10. The population supplied from the Lowermoor source was identified from information supplied by SWWA and compared with the population from a contiguous area supplied from the Bastreet water treatment works. Information was gathered on pregnancy outcomes for the six months before the incident and up to 42 weeks afterwards. Live births were identified from birth notifications. Miscarriages and terminations were identified by searching hospital records. Stillbirth registrations were examined and the information checked against information provided by family doctors and the family practitioner committee. Social class coding was based on occupation of the mother's partner as recorded in the maternity clinical records. Pregnancy outcomes from three groups were compared: (i) the population receiving Bastreet water, (ii) the population receiving Lowermoor water before the incident, (iii) the population receiving Lowermoor water after the incident. The last group (iii) was defined as the exposed group. Pregnancies resulting in twins were excluded.

Pregnancy outcome results

11. 353 pregnancies were studied, of which 92 were in the exposed group. The mean birth weights were higher in the Lowermoor population than in the Bastreet population (Bastreet 3,280g, Lowermoor pre-incident 3,483g, Lowermoor post-incident 3,330g), with a correspondingly lower percentage of low birthweight babies in the Lowermoor population. There was no difference in the distribution of Apgar scores nor in rates of admission to special care units. There were two perinatal deaths, both in the Bastreet group. It was estimated that there were 88 Lowermoor and 92 Bastreet fetuses *in utero* at the time of the incident, and these resulted in 9 and 7 congenital defects, respectively. Of these, the authors identified those pregnancies where there was a possibility that the incident occurred at the time of gestation when it could have affected the fetus (6 pregnancies from Lowermoor, 2 from Bastreet). All six defects from Lowermoor were defined by the authors as mild. Five were deformations, including four positional talipes.

Critique

Exposure assessment

12. Residence was used as a proxy measure of exposure. No details are given as to how accurately the populations were defined in relation to their water supply source. It is not known whether any misclassification could have occurred, nor how this could have influenced on the results. Comparisons were made between the Lowermoor populations, before and after the incident, but not for comparable groups receiving Bastreet water.

Health outcomes

13. There appears to have been a detailed search of relevant records to obtain health outcome data. However, the authors were not able to collect information for any of the non-resident population who were visiting the areas at the time of the incident.

Control for potential confounders

14. A large amount of data were collected on the mother's reproductive history. These were analysed univariately and showed no major differences between areas. A major difference was found, however, between the social class distribution of the three groups, with the Bastreet population having a higher percentage of the non-manual class (48% versus 34% in both Lowermoor groups) and fewer in social class III manual (30% versus 43% Lowermoor in the pre-incident group, 54% Lowermoor in the post-incident group). Only a small percentage of the Lowermoor post-incident group was in social classes IV and V (12% versus 23% in the Lowermoor pre-incident group, 22% in the Bastreet group). No formal adjustment was made in this paper for these differences. The authors considered that social class does not heavily bias the occurrence of malformations, with the exception of those of the central nervous system.

Interpretations

15. This study found no evidence of a major excess of congenital malformations following the incident, with the exception of an increased rate of talipes. The authors point out that this study only considered defects apparent at birth or shortly after birth. They suggest that talipes can arise if, during pregnancy, there was a period of gross reduction in amniotic fluid or if fetal motor development was affected. There was no indication of the former in the clinical records.

Hawkins N, Greenwood R, Golding J and Harris J (undated). Excess aluminium sulphate in drinking water in North Cornwall and growth of children. Unpublished report.

Introduction

16. This is an unpublished, undated report of a study funded by the Cornwall and Isles of Scilly Health Authority and South West Water Ltd. It was received by the Department of Health in 1999. The aim was to examine the growth of children who were potentially exposed to contaminated drinking water following the Lowermoor incident. Three groups of children were studied: those whose parents were potentially exposed before the child was conceived, and children potentially exposed while *in utero* or during early infancy.

Study design

17. This study appears to be similar to the study of pregnancy outcomes by Golding *et al* (1997) in that the 'exposed population', i.e. that supplied by the Lowermoor water treatment plant, was compared with the population supplied by the Bastreet water treatment plant. Three groups of children were identified in each area:

children who were (i) less than six months old at the time of the incident (infant exposure), (ii) *in utero* at the time of the incident (fetal exposure), and (iii) born between 12 and 48 months after the incident (pre-conception exposure). Live births were identified from birth notifications and height and weight measurements (clustered around 9, 18 and 36 months) were obtained from community health records and linked to the birth data.

Results

18. Statistically significant increases in height for age measurements were seen at 9 months for the exposed fetal and preconception groups compared with the corresponding control groups (approximately 4 cm difference), and at 18 months for all three groups of children (approximately 3.5 cm difference). There were no significant differences in the height for age measurements at 36 months. The only significant difference in the weight for age measurement was at 18 months between the exposed infant group and the control infant group.

Critique

Exposure assessment

19. The problems of using residency as a proxy measure for exposure in this study are the same as those described above for the pregnancy outcome study by Golding *et al* (1997). It is particularly of note that both exposed and non exposed groups of children were identified by the location of the mother at the birth of the child and it was not known where the mothers in the fetal and preconception groups lived during the pollution incident.

Health outcomes

20. The height and weight information was obtained from community health records. However, there appear to be substantially fewer numbers of children for whom these data were available compared with the numbers identified from the live birth records. For example, in the preconception group 594 exposed and 476 non exposed children were identified. However, at the first follow up (9 months), height and weight measurements are presented for only 219 exposed and 221 non exposed children.

21. The numbers of children in each exposure group and at each time period also varies considerably and some comparisons are based on small sample sizes which tend to decrease as the follow up time increases. There is no discussion in the report on the potential impact of loss to follow up, for example, on the representativeness of the sample.

22. The authors comment that there may have been differences in measurement methods between the 2 areas or that there may have been systematic bias due to awareness of children's exposure.

Control for potential confounders

23. Unlike the study by Golding *et al* (1997) there is no mention in the report of whether data were available on the mother's reproductive history. There was also no adjustment for differences in social class distribution between the areas. In the Golding *et al* (1997) study, a smaller percentage of the Lowermoor post incident group was in social classes IV and V compared with the Bastreet group. The effect of this on the results and the potential effects of different methods of infant feeding (e.g. breast or bottle feeding) and nutritional intakes are not discussed in the report.

Interpretation

24. The study found a tendency for exposed children to be, on average, taller, but not heavier, than control children, particularly at 9 and 18 months. There was little difference, however, at 36 months, although these results were based on small numbers. The authors discuss the potential influence of exposure to aluminium, but point out that, in animal toxicity studies, aluminium is generally associated with retarded growth. The study is severely limited by the methods used both for exposure assessment and for ascertainment of the height and weight measurements. There are inherent inaccuracies in the measurement of the height of children below 24 months of age (Stenhouse *et al*, 2004). The limitations are likely to have resulted in major exposure misclassification and an unrepresentative sample of children.

Reference

Stenhouse E, Wright DE, Hattersley AT and Millward BA (2004). Weight differences in Plymouth toddlers compared to British Growth Reference Population. Arch Dis Child 89: 843-44.

Owen PJ and Miles DPB (1995). A review of hospital discharge rates in a population around Camelford in North Cornwall up to the fifth anniversary of an episode of aluminium sulphate absorption. J Pub Health Med 17(2): 200-204.

Introduction

25. This study examined hospital discharge rates during the period 1987-1993 in the area affected by the Lowermoor incident and in the remainder of Cornwall.

Study design

26. The populations studied were derived from the Family Health Services Authority (FHSA) register for the period covered by the financial years 1987 to 1993. The area exposed to the contaminated water from the Lowermoor treatment works was defined by 8 postcode sectors, and this was compared with 23 other localities in Cornwall and with Cornwall as a whole. The number of consultant episodes and of people discharged were obtained from the Patient Administration System. Indirect standardisation was used with all Cornwall rates being used as the standard and adjusted for repeat discharges.

Results

27. The standardised discharge ratio for the Lowermoor population rose steadily from 93.4 in 1987-88 to 111.9 in 1991-1992, with a slight fall to 108.2 in 1992-93. None of the other localities showed this trend. Analyses by cause as a percentage of the total showed similar values for Lowermoor and all Cornwall, for all years, except for complications of pregnancy where Lowermoor had a higher ratio throughout the period. The authors report that analyses of the discharge rates per 1000 population after the incident showed increases in respiratory disease, in diseases of the arteries, and in signs, symptoms and ill-defined conditions. For men, there were also increases in diseases of the digestive system, genito-urinary system, arthropathies and related disorders, diseases of the pulmonary circulation, and other forms of heart disease. The authors do not clearly define to which population these results refer but they make the comment that "the differences were not statistically different". This could refer to a difference between men and women or between Lowermoor and Cornwall. The authors do not appear to have carried out standardisation by cause of discharge.

Critique

28. This study is based on postcode sectors.

Exposure assessment

29. The localities were areas previously set up as an aid to planning; they were created from groups of postcode sectors. The use of 8 sectors to define the potentially exposed population was thus very imprecise. There is no discussion of how these sectors overlap with the actual areas served by the Lowermoor treatment plant, nor how much misclassification might have occurred. The populations were derived from FHSA registers. These record changes of address when an individual moves to a new doctor but may not be completely up-to-date when short distance moves are made. The authors show that there is only a small difference in age distribution between populations defined from the FHSA register and the 1991 census. However, this does not address the potential inaccuracy of the postcode data held by the FHSA and how this might influence classification as exposed or non-exposed.

Hospital discharge data

30. These data need careful handling as an illness in an individual can lead to multiple discharge records, both for genuine re-admission and for transfer between wards and consultants. The authors were obviously aware of the problems but it is not clear from the paper whether they have effectively addressed them all. It can be assumed that they treated the data from all years in the same way but the patterns they have described may partly be due to changes in hospital record keeping practices.

Control for potential confounders

31. No control was carried out for potential confounding factors and these were not discussed.

Interpretation

32. The results appear to indicate a rise in hospital discharges from the Lowermoor area over the years. However, this study is potentially severely limited by a lack of precision in the definition of the exposed area, the potential problems with hospital discharge data, and a complete lack of any confounding data. The authors offer no explanation for the apparent rise in discharges in the Lowermoor area.

Owen PJ, Miles PB, Draper GJ and Vincent IJ (2002). Retrospective study of mortality after a water pollution incident at Lowermoor in North Cornwall. British Medical J 324: 1189

Introduction

33. This short paper reports the result of a study to investigate the mortality occurring in the resident population supplied by the Lowermoor treatment works and compares them with a population from a control area. The summary below includes a discussion of the content of the paper together with additional information about the study given to the committee by the authors.

Study Design

34. The total study population is the same as that used in the earlier study on hospital discharges (Owen and Miles, 1995) and consisted of residents living in 8 North Cornwall postcode sectors. On the basis of advice from South West Water Ltd, and using postcode data, the residents were categorised as exposed (11,114 residents) i.e. receiving water supplied by Lowermoor works or non-exposed (5,359 residents). The names of individuals in these areas were flagged[97] at the Office of National Statistics (ONS) so that details of death certification and cancer registration could be obtained. Flagging at ONS took place in 1991 following the second LIHAG report i.e. two and a half years after the water pollution incident. Mortality in the two areas was compared and age/sex standardisation was also carried out using the whole of Cornwall and the Isles of Scilly, and England and Wales as two comparison populations. Causes of death were obtained from 1988 to 1997.

Results

35. The overall mortality in both the exposed and unexposed populations was lower than that expected using both comparison populations (exposed SMR = 81.6, 95% CI 77.2-86.2; non-exposed SMR= 75.9 95% CI 69.2-83.1; comparison population Cornwall and the Isles of Scilly). SMRs for different causes of deaths

[97] All deaths, and all newly diagnosed cases of cancer, are notified to the Office of National Statistics (ONS) so that national rates of mortality and of cancer incidence can be compiled. The information is also recorded on the National Health Service Central Register. Researchers and organisations such as health authorities can be notified when ONS receives cancer incidence or mortality information on an individual in a group under surveillance if the individual has been "flagged" or marked in the Central Register. This is subject to the researcher or organisation receiving the appropriate approval including, if necessary, permission from a research ethics committee.

have not been published or submitted with the exception of those for circulatory disease (exposed SMR= 89.5, 95% CI 83.5- 95.8; non-exposed SMR= 84.7, 95% CI 75.5- 94.7). SMRs for circulatory disease for each year from 1988 to 2000 fluctuated between 49 and 124, but were based on small numbers of observed deaths. A comparison of the proportion of deaths by major cause between the exposed and non-exposed areas found similar proportions, with the exception of injuries and poisoning (3.2% (41 deaths) exposed, 1.9% (9 deaths) non-exposed). Further investigation showed a slightly greater proportion of road traffic accidents in the Lowermoor affected area.

Critique

Population Definition and Exposure Assessment

36. The population was categorised as exposed or not exposed according to residence within postcode sectors in 1991 and using an unspecified method by South West Water Ltd. to indicate which residents received water from the Lowermoor treatment plant and which received water from a different source. The study did not attempt to include non-residents temporarily present at the time. The authors acknowledge that the register of people flagged at ONS is imperfect, due mainly to the two and a half year gap before flagging took place. During this period, some residents will have moved away from the area and others will have moved in. The health service registration scheme in place in 1991 did not allow a full correction of this to be performed.

Health Outcomes

37. The population was flagged at ONS for deaths. ONS usually give details of any emigrations or losses to follow-up which have occurred. Further communication with the authors has revealed that, by the end of June 1999, 2% of the population had left the district or had been lost to follow-up (2.2% exposed, 1.5% unexposed). The published paper presents deaths up to 1997 only, although some of the submitted information seems to include deaths up to 2000. However, causes of death should now be available for up to 2003.

Analysis

38. Age and sex standardisation was carried out. Although not stated explicitly in the paper, we understand that the standard five-year age and calendar periods were used. SMRs have not been published or submitted for different specific causes of death other than all circulatory diseases although there appear to be large enough numbers for analysis by broad disease grouping.

Interpretation

39. This study indicates that the population resident in the affected area at the time of the incident has similar mortality patterns to the population living in an adjacent control area and that mortality overall is less than that of the population of Cornwall and the Isles of Scilly and the population of England and Wales. However, mortality is a crude indicator of long-term health and it is unlikely that a study of this type,

which has no data on other exposures or lifestyle factors, would be sensitive enough to detect any relationship between a single incident and adverse health.

Owen PJ, Miles DPB, Draper GJ, Vincent TJ and Harling C. A study of cancer incidence and mortality in two cohorts in North Cornwall affected by the Lowermoor pollution incident. Unpublished report.

Introduction

40. This paper reports cancer incidence data from 1988 to 1998 for the population of the area supplied by the Lowermoor treatment works in residence at the time of the pollution incident and also for residents of a comparison area.

Study Design

41. The study populations were the same as those discussed in the paper reporting mortality results (Owen *et al*, 2002). Cancer registrations were obtained from the UK cancer registers. The South West Intelligence Services removed duplicate records and ensured that the correct primary tumour had been recorded. SMRs (i.e. using indirect standardisation) for deaths due to cancer were calculated using England and Wales as the standard population. Direct standardisation was used for cancer incidence. The European population was used as a standard.

Results

42. European age-standardised rates per 100,000 population for all malignant neoplasms for both exposed and non-exposed areas were less than those for Cornwall and the South West (exposed 293.5, non-exposed 298.9, Cornwall 360.5, South West 358.8). The SMRs for all cancers for both areas were also considerably lower than that expected using the England and Wales mortality rate (exposed SMR=85, non-exposed SMR=75). The age-standardised incidence rate per 100,000 population for leukaemia for the exposed area was slightly lower than those of the non-exposed area, Cornwall and the South West (exposed 9.6, non-exposed 10.6, Cornwall 10.8, South West 10.5). However, SMRs for leukaemia for both exposed and non-exposed areas were slightly higher than expected (exposed SMR=120, non-exposed SMR=109).

Critique

Population definition and exposure assessment

43. See comments under Owen *et al* (2002).

Health Outcomes

44. ONS provide both death and cancer registration information. It is assumed that the latter data were used for this analysis although this is not completely clear from the paper.

Analysis

45. Age-sex standardisation was used for the cancer deaths. Direct standardisation was used for the cancer incidence analysis, instead of indirect standardisation, although the age-specific cancer incidence rates for England and Wales are readily available, enabling a standardised incidence rate to be calculated. In addition, the European population was used as a standard instead of the population of England and Wales. Only results for all malignant neoplasms and leukaemia have been presented although the numbers would be sufficient for analyses by cancer subtype.

Interpretation

46. This paper indicates that all cancer mortality and incidence in the Lowermoor area are lower than those of Cornwall and the South West. Leukaemia mortality is slightly raised, however, and the incidence is approximately the same as in Cornwall and the Southwest. This study suffers from similar limitations to the previously reported mortality study. Both papers are also limited in that they do not report standardised cause-specific results.

Foster AM, Prentice AG, Copplestone JA, Cartwright RA and Ricketts C (1997). The distribution of Leukaemia in association with domestic water quality in Southwest England. Eur J Cancer Prev 6: 11-19.

Introduction

47. This ecological study investigated the incidence of haematological malignancies in areas of Devon and Cornwall with differing water supplies, between 1984 and 1988.

Study design

48. Forty-six water supply areas were defined using ordnance survey maps and water supply area maps for the study period 1984-88. The water supply area maps were provided by South West Water plc. The population in each area was identified using electoral ward maps and, where wards were divided by a water supply area boundary, by allocating enumeration district centroid. The haematological malignancy data were obtained from the database held by the Leukaemia Research Fund's Centre for Clinical Epidemiology at Leeds University. The diagnostic groups used were acute myeloblastic leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic myeloid leukaemia (CML), myelodysplastic syndromes (MDS) and myeloproliferative disorder (MPD). Age-standardised incidence ratios were calculated using the whole of Devon and Cornwall as the standard population. An appropriate statistical procedure was used to determine whether there was significant variation in incidence between areas. South West Water provided summary statistics for the period 1970-90 from its water quality control data set for 35 of the areas for pH, nitrate, fluoride, copper, aluminium, lead and trihalomethane (THM)

concentrations. The samples were taken at the point where the treated water enters the supply. The water quality statistics were analysed for their conformation with the WHO guidelines for drinking water quality.

Results

49. There was no evidence of any significant variation in incidence between areas for CML and MDS. The other disease groups all showed some variation but only MPD was statistically significant. AML and ALL taken together, i.e. the acute leukaemias, showed significant variation.

50. pH, nitrates and aluminium did not conform to the WHO guidelines in the period 1984-88. The weighted mean values for aluminium concentration varied between 0.015 and 0.34 mg/l compared with the guideline maximum of 0.20 mg/l. In four areas (not specified in the paper) the weighted mean exceeded the guideline, with the maximum value being 2.44 mg/l. The authors state that this excludes the data relating to the Lowermoor incident. Stepwise multiple linear regression, to investigate the correlation between the water quality indicators and the disease incidence data, showed significant correlations in the following cases: the incidence ratios for AML, MDS, AML+ALL and AML+ MD with aluminium concentrations; the incidence ratio of CML with THM and fluoride concentrations; the standardised incidence rate of MPD and copper concentrations; and the standardised incidence rate of AML+ MDS and THM concentrations.

Critique

Exposure assessment

51. This study made a onsiderable effort to define the water supply areas accurately but the authors acknowledge that their method of division of split wards may have been a source of error. The water quality indicators used were mean values from water quality control testing. Thus, these are a proxy measure of values at the tap and do not indicate actual intake concentrations. A case was defined as one who was resident in the relevant area at the time of diagnosis. The use of concurrent water quality indicators may not be relevant to the occurrence of the disease outcome.

Health outcomes

52. The database was compiled with the collaboration of haematologists and pathologists and therefore case ascertainment was likely to be complete. The diagnoses were also validated by regional review.

Interpretation

53. This study found an apparent correlation between standard incidence ratios for some leukaemic groups and water quality indicators, particularly aluminium and THMs. Although the data are of good quality, apparent associations derived from ecological studies must be treated with caution. One problem is that of latency and relevant exposure window. The authors of the paper pointed out that the water quality indicators may reflect the patterns of other social or environmental factors. It should

be noted that no attempt was made in this study to control for potential confounders such as socioeconomic status. Leukaemia is known to have a higher incidence in the higher social classes.

Alexander F. Childhood health events in relation to the Lowermoor water incident and the Camelford leukaemia cluster. Revised final report to the Department of Health, May 2002.

Introduction

54. This study investigated infectious illnesses recorded in the GP records for two cohorts of children identified following the Lowermoor incident.

Study Design

55. The cohort used in the study had previously been defined by the Department of Public Health Medicine of the Cornwall and Isles of Scilly Health Authority, and had been classified as exposed or not exposed to the water supply from the Lowermoor treatment works. This study restricted the cohort to children who were aged under 10 years at the time of the incident; who had had no diagnosis of leukaemia, lymphoma or cancer; and who were still registered with a local GP when the study was conducted. The study also carried out analyses of three separate subgroups:

- Children in year 9 during 1995/6 at Sir James Smith's Secondary School compared with those in year 9 in adjacent years.
- Children at Camelford Primary School in year 2 during 1988/9 compared with those in year 2 in adjacent years.
- Children in the same tutor group in Sir James Smith's School as three children who had been diagnosed with leukaemia (affected children) compared with other children in the secondary school cohort.

56. Infectious disease episodes recorded in GP notes were identified. The frequency of occurrence of some health outcomes e.g. tonsillitis, was also recorded.

Results

57. The total number of infectious disease events increased in the first year after the Lowermoor incident in the exposed cohort (8.2% versus 7.6% in the previous year) but not in the unexposed cohort (6.9% versus 8.2% in the previous year). There was a large number of all the common childhood infections, and these varied considerably by calendar period. Significantly higher proportions of children in the exposed cohort than in the unexposed cohort were positive for chicken pox and for any herpes virus episode. Higher proportions of the exposed cohort than of the unexposed, and of the affected tutor group than the rest of the secondary school cohort, had chicken pox before the incident. Multivariate regression analysis, adjusted for age at 31/12/88, gender and GP response, showed that there was more infectious illness overall before the incident in the exposed cohort than in the unexposed cohort.

Critique

Exposure Assessment

58. See comments under Golding *et al* (1991).

Health Outcomes

59. This study extracted data from GP notes. Potential incompleteness and inaccuracies may have occurred in these notes and such errors would have been difficult to ascertain. Only those infections actually presented to a GP would be included. Mild or self-limiting episodes may thus not have been reported.

Completeness and non-response

60. The study was restricted to those children who were still registered with a local GP when the study was conducted. Those who moved outside the area would, therefore, have been omitted. No indication of the number of these was given in the paper. In addition, children outside the initial defined cohort attending the schools could not be included. This limited the ability of the study to identify patterns of illness in specific school years and times.

61. Although ethical approval was given to carry out the study on an "opt-out" basis, i.e. patients were only excluded if they actively wrote to refuse consent, some GPs required patients to give positive consent. This led to substantial loss of subjects in some practices. Non-response was greater for older subjects and males.

Interpretation

62. This study does not indicate any association between the Lowermoor incident and subsequent infectious illness in children exposed to the contaminated water. However, the study did find evidence of increased infectious illnesses in 1995 in secondary school year 9 and a similar increase in total infectious illness in the tutor group compared with other secondary school children at similar times. The author considered that these findings are consistent with the hypothesis that the incidence of leukaemia is more likely when exposure to infectious agents is increased.

Appendix 19: Report of the North Cornwall Homeopathic Project

This report is available on the Subgroup's website (home page: http://cot.food.gov.uk/cotwg/lowermoorsub/)

Appendix 20: Summing-up by the West Somerset Coroner

This appendix is available on the Subgroup's website (home page: http://cot.food.gov.uk/cotwg/lowermoorsub/)

Appendix 21: Review of the scientific literature on aluminium (1994 to April 2002) prepared for the Lowermoor subgroup by the Department of Health Toxicology Unit, Imperial College, London

Note: this was a paper prepared for discussion by the Lowermoor subgroup. It does not necessarily represent the views of the subgroup

REPORT ON TOXICITY OF ALUMINIUM:

An update of the 1997 W.H.O. (I.P.C.S) report, with emphasis on neurotoxicity

Prepared for the Committee on Toxicity Subgroup established to consider health effects of the Lowermoor Water Pollution Incident.

Prepared by Department of Health Toxicology Unit, Clinical Pharmacology Department, Division of Medicine, Imperial College of Science and Medicine.

Notes on the preparation and format of this report

This report is essentially an update of the 1997 W.H.O. (IPCS) Environmental Health Criteria 194 report on Aluminium, with particular focus on neurotoxicology. As such, some parts represent *verbatim* sections of that report, where there was nothing to update or to modify, and these parts are italicised and IPCS report page numbers appended. Since these parts were mostly summary text in the IPCS report, they do not contain references. Relevant references to information contained in these parts may be found in the IPCS report. Updated material was sourced from years 1994 to present, although some references appear from before 1994 which were not included in the IPCS report. New references in tables are printed in bold type.

CONTENTS

SUMMARY AND CONCLUSIONS

1. Identity, physical and chemical properties, and analytical methods

Elemental aluminium is a metal, but its high reactivity means that it exists naturally as the ion, Al^{3+}, and forms 8.13% of the earth's crust making it the third most common element. It occurs naturally as Al^{27} with eight radioactive isotopes, the most stable being Al^{26}. Mostly it exists as complexes of aluminium oxide, the species formed when the element reacts with oxygen or water, and aluminium silicate. The metal is light, strong, corrosion-resistant, readily machined and as such is often alloyed with other metals.

Aluminium levels in biological or environmental samples are assayed by a number of methods, the most common being graphite furnace atomic absorption spectroscopy. The method is sensitive to 1.9-4.0µg/litre in biological fluids and 0.005-0.5µg/g dry weight in tissues depending on treatment, separation and concentration methods. Contamination of the samples with aluminium from air, vessels or reagents during sampling and preparation is the main source of error. Fixing and staining can introduce artefactual aluminium into tissue sections to be analysed by microprobe or electron microscopy.

2. Sources, environmental transport, distribution and transformation

Aluminium is released to the environment naturally and by anthropogenic means. Aluminium silicates (clays) are a major component of soils, contribute to the aluminium levels of dusts concentrated from mining and agriculture, and in particulates from coal combustion. Acidity mobilizes aluminium in monomeric forms, increasing bioavailability. However, as it is ubiquitous in the earth, natural processes far exceed anthropogenic contributions to the environment.

At pH values greater than 5.5, aluminium exists naturally mostly in an undissolved form such as gibbsite ($Al(OH)_3$) or as aluminosilicates. However high amounts of dissolved organic material, can bind with aluminium leading to increased concentrations of dissolved aluminium in lakes and waterways. The solubility in nature of aluminium in equilibrium with solid phase $Al(OH)_3$ depends largely on pH and on concentrations of complexing agents such as fluoride, silicate, phosphate and organic matter. When soils are acidified, for instance by acid rain or mine drainage, aluminium can be released into solution and enter waterways.

3. Environmental levels and human exposure

Airborne aluminium levels vary from 0.5 ng/m^3 over Antarctica to more than 1000 ng/m^3 in heavily industrialized areas, where it occurs mainly as soil-derived dusts. A relatively high estimate of urban exposure might be 40µg/day by inhalation, representing perhaps 0.4% of total exposure.

In freshwater, aluminium can be suspended or dissolved, bound with organic and inorganic ligands, monomeric and polymeric, or can exist as a free aluminium ion. Aluminium speciation is determined by pH and the concentrations of dissolved organic carbon (DOC), fluoride, sulphate, phosphate and suspended particulates. Dissolved aluminium concentrations for water around neutral pH are usually low (1.0

- 50 µg/litre). Acidic water can show 500-1000 µg/litre. At the extreme acidity of water affected by acid mine drainage, dissolved aluminium concentrations of up to 90 mg/litre have been measured.

Normal exposure to aluminium is almost totally through food and beverages and water, and food is by far the main contributor. Foods vary widely in their aluminium content and aluminium-containing utensils can increase the content, but a survey across countries indicates that daily intake is less than 15mg/day and 5-10mg/day for an average western diet is probably a reasonable estimate. Drinking water contributes only about 0.2mg/day. A relatively high estimate of urban exposure might be 40µg/day by inhalation, representing perhaps 0.4% of total exposure. Aluminium is absorbed transdermally from antiperspirant. Medically, antacid users may ingest 500mg aluminium in a day. Occupationally, aluminium welders may inhale 20mg aluminium in dust, perhaps more depending on welding technique and workplace setup, and probably welding fume also, the composition of which is unclear; however it is much more bioavailable than food and particulate.

4. Kinetics and metabolism

Aluminium is poorly absorbed in humans. Blood and urine concentrations have been used to measure uptake and estimate absorption, increased urine levels having been observed among aluminium welders and aluminium flake-powder producers, and recently the use of the radioisotope Al^{26} has proved very useful in human and animal biokinetics studies. Gastrointestinal absorption is the most important route of entry for non-occupationally exposed people, however the mechanism is not understood. Variation in absorption results from the aluminium species, pH, presence of other compounds such as citrate which may enhance and silicon which may reduce, and fed or fasting state.

Estimates of uptake from food are 0.28 – 0.64% and from drinking water range from 0.004-1.6%, reasonable values perhaps being 0.1-0.3%. Investigations using Al^{26} indicate that people normally absorb an estimated 0.5-3.0% of their total intestinal Al absorption from drinking water. Absorption, at least from drinking water, may be higher in the elderly. These estimates and modifying factors are similar in the rat, the most commonly studied laboratory organism, in which absorption is estimated at below 1%. Absorption from inhaled aluminium oxide was estimated at 1.9% and from welding and smelting fume probably much higher, perhaps as much as 4%.
Of the Al in blood serum, ~89% (+/- 5%) is bound to to transferrin and ~11% (+/-5%) to citrate. Tissue distribution in normally exposed humans has been measured as: bone – 54%; muscle – 14%; skin – 13%; adipose – 5%; blood and vessels – 4%; connective tissue – 3%; liver – 3%; GI tract – 2%; CNS – 1%. This profile may alter with age. Only bone and liver have significant capacity to concentrate aluminium. Brain is thought to have an active efflux mechanism. Significant inhalation leads to high levels in lung, hilar nodes, spleen and liver. Where load is high, liver levels are high due to accumulation from breakdown of red blood cells. Body burden by exposure level can be estimated from Al^{26} studies and studies in occupationally exposed workers. Normal environmental daily exposure was estimated as 6µg, high occupational 40 µg, and high pharmaceutical 2000 µg.

Aluminium is overwhelmingly excreted by the urinary route and blood aluminium is mostly cleared by excretion. In a tracer study, more than half of the administered Al^{26} had left the blood within 15 min and the decline continued, leaving < 1% in the blood after 2 days. Total excretion up to 13 days was 83% (urine) and 1.8% (faeces), leaving 15% in the body. After 4 months more than 90% was excreted. Bone, especially, acts as a reversible sink for acute high levels of Al. Urinary excretion has excess capacity, perhaps to do with speciation effects in serum at higher levels; with increasing doses in humans and in rats, serum levels stayed roughly constant while urinary excretion increased with dose. Bone and other tissues store aluminium in the chronically (e.g. occupationally) exposed, such that in welders exposed for more than 10 years urinary concentration did not change markedly following cessation of exposure. In these welders, the urine half-life was more than 6 months.

5. Effects on laboratory mammals and in vitro test systems

Acute toxicity of aluminium by the oral route in animals is low, LD_{50} values ranging from about 200mg/kg body weight up to 1000mg/kg. A NOAEL in rats of 52mg/kg for subchronic Al nitrate in drinking water has been documented. In beagle dogs given aluminium phosphate in the diet for 6 months, a NOEL ~ 70 mg Al/kg body weight was observed. Another trial, using sodium aluminium phosphate for 26 weeks, a LOEL = 75 to 80 mg Al/kg body weight per day was recorded.

No obvious fetotoxicity was noted, nor were general reproductive parameters changed after gavage treatment of rats with 13, 26 or 52 mg aluminium/kg body weight per day (as aluminium nitrate). The LOAEL for developmental effects (reduced postnatal growth, bone growth abnormalities and reduced fetal weight) was 13 mg/kg. Maternal toxicity was not examined. These effects were not observed at much higher doses of aluminium hydroxide. Two studies on brain development used dams fed high dose oral aluminium lactate, however renal and gastric damage have been observed in similarly treated dams, so where these effects are not excluded it is impossible to determine the direct cause of any neuropathology in the pup in such a system. A review of 14 studies which included 4 different Al compounds administered by 4 different routes (gavage, feed, intraperitoneal injection, and subcutaneous injection) with total doses ranging from 13.5 to 8,400 mg/kg reported that fetal Al levels were not increased in 6 of 7 studies and pup Al levels were not increased in 4 of 5 studies in which they were measured.There is no indication that aluminium is carcinogenic in animals. It can form complexes with DNA and cross-link chromosomal proteins and DNA, but it has not been shown to be mutagenic in bacteria or induce mutation or transformation in mammalian cells in vitro. Chromosomal aberrations have been observed in bone marrow cells of exposed mice and rats.

Aluminium can cause osteomalacia in larger animals and a similar condition in rodents, at very high levels of bone aluminium load. Aluminium in feed caused lymph node hypertrophy in mice.

Aluminium is neurotoxic in experimental animals, although this varies among species. In susceptible species, toxicity following parenteral administration is characterized by progressive neurological impairment, followed by lethal status. Morphologically, the progressive encephalopathy is associated with neurofibrillary pathology in large and medium size neurons predominantly in the spinal cord, brainstem and selected areas

of the hippocampus. These tangles are morphologically and biochemically different from those that occur in Alzheimer's disease. Oral administration does not produce these effects. Behavioural impairment has been observed in the absence of encephalopathy or neurohistopathology in experimental animals exposed subchronically to soluble aluminium salts (e.g., lactate, chloride) in the diet or drinking-water at doses above 200 mg aluminium/kg body weight per day. Neurophysiologically, *in vivo* studies show orally administered high dose aluminium may affect glutamate metabolism and may alter calcium homeostasis and promote lipid peroxidation. Indeed, most recent studies concentrate on aluminium as a pro-oxidant and/or as an inflammatory agent. Aluminium does not increase reactive oxygen species (ROS) production by itself, but can increase the Fe-induced production of reactive oxygen species. Al may reduce the activity of antioxidant enzymes and promote a pro-oxidant environment. This may increase beta-amyloid aggregation, which may further increase ROS production. Glial cells may be the main target of pathology of aluminium, and may be more sensitive to ROS-induced inflammation than are neurons. Intracisternal aluminium in rabbits produced an inflammatory response, and aluminium may promote inflammation by increasing tumour necrosis factor production. Note that these studies are early stage investigations, often not replicated and generally studies are not yet of the number and quality that a paradigm of Al neurotoxicity due to increased ROS is generally accepted.

6. Effects on humans

No acute pathogenic effects in the general population have been described after oral exposure to aluminium.

In Cornwall, a population of about 20,000 individuals was exposed for at least 5 days to increased levels of aluminium sulphate, accidentally placed in a drinking-water facility. Case reports of nausea, vomiting, diarrhoea, mouth ulcers, skin ulcers, skin rashes and arthritic pain were noted. These symptoms were mostly mild and short-lived. Later, 55 residents reporting poor memory and concentration were investigated. Although aluminium was the major contaminant (and sulphate), the pH dropped significantly and copper and zinc in particular were leached into the water from plumbing. Based on the likely exposure, biokinetics, aluminium intake studies and cognition studies among antacid users, it is unlikely that aluminium was solely responsible for the neurological deficits reported.

Based on neurotoxicity in renal patients and in laboratory animals, aluminium has been identified as a possible environmental contributor to the development or acceleration of Alzheimer's disease as well as impaired cognitive function in the elderly. It has also been suggested that stamped fine aluminium powder and fume may be risk factors for impaired cognitive function and pulmonary disease in certain occupations. Epidemiology has focussed on aluminium in drinking water as a possible risk factor.

Although neurobiological studies in general do not support a link, 13 epidemiological studies of Alzheimer's disease and aluminium in drinking water have been reported. Of 10 which were of sufficient quality to be informative, in terms of outcome and exposure measures, bias and control for confounders, five support an association and five do not. Of those in support, most show relative risks of around 2 with large

confidence intervals, when the total aluminium concentrations in drinking-water was 100 µg/litre or higher. Some show higher risks when aluminium levels are higher and subjects are older. Thirteen studies have examined a possible link between high aluminium exposure from antacids and cognitive decline. No significant positive association was observed.

Scientific interest in aluminium as a primary cause of Alzheimer's disease has waned since 1994. Epidemiology supporting a link between Alzheimer's disease (and other cognitive decline) and aluminium in drinking water cannot be reconciled with biokinetic data which is sufficiently repeatable and robust in its demonstration that humans absorb less than 3% of their normal aluminium load from drinking water, making a biological explanation difficult. The positive results reported in the epidemiological literature might be explained by: a/ chance exacerbated by publication bias; b/ methodological shortcomings; c/ aluminium in drinking water as proxy for other causative or contributory factor(s), which may also be causative as a genetics by environment interaction; d/ aluminium interacting with another environmental factor in causation.

Occupationally exposed workers can have quite elevated levels of serum and urinary aluminium, especially welders and smelters. Although fumes inhaled can also contain several other compounds including manganese which is also a known neurotoxin, some workers feel that data is sufficient to state that this aluminium exposure can contribute to cognitive and motor deficits, and as such have proposed NOAEL- and LOAEL-equivalents using post-shift urinary concentrations.

Exposure in patients with chronic renal failure to aluminium-containing dialysis fluids and pharmaceutical products may cause acute intocxication, encephalopathy, vitamin-D-resistant osteomalacia and microcytic anaemia. These clinical syndromes can be prevented by reduction in exposure to aluminium.

Premature infants, even where kidney impairment is not severe enough to cause raised blood creatinine levels, may develop increased tissue loading of aluminium, particularly in bone, when exposed to iatrogenic sources of aluminium. Where there is kidney failure, seizures and encephalopathy may occur.

Recently macrophagic myofasciitis has been described, a syndrome characterised by diffuse muscle and joint pain and fatigue, and by muscular infiltration of granular macrophages and lymphocytes which contain aluminium hydroxide inclusions. The cause appears to be the Al hydroxide carrier used in vaccines

There is insufficient information to allow for classification of the cancer risk from human exposures to aluminium and its compounds. Animal studies do not indicate that aluminium or aluminium compounds are carcinogenic.

REVIEW

1. Identity, physical and chemical properties, and analytical methods

Aluminium is a silvery-white, ductile and malleable metal. It belongs to group IIIA of the Periodic Table, and in compounds it is usually found as Al^{III}. It forms about 8% of the earth's crust and is one of the most reactive of the common metals. Exposure to water, oxygen or other oxidants leads to the formation of a superficial coating of aluminium oxide, which provides the metal with a high resistance to corrosion. Aluminium oxide is soluble in mineral acids and strong alkalis but insoluble in water, whereas aluminium chloride, nitrate and sulfate are water soluble. Aluminium halogenides, hydride and lower aluminium alkyls react violently with water.

Aluminium possesses high electrical and thermal conductivity, low density and great resistance to corrosion. It is often alloyed with other metals. Aluminium alloys are light, strong and readily machined into shapes.(IPCS p1)

Various analytical methods have been developed to determine aluminium in biological and environmental samples. Graphite furnace-atomic absorption spectrometry (GF-AAS) and inductively coupled plasma-atomic emission spectrometry (ICP-AES) are the most frequently used methods. Contamination of the samples with aluminium from air, vessels or reagents during sampling and preparation is the main source of analytical error. Depending on sample pretreatment, separation and concentration procedures, detection limits are 1.9-4 µg/litre in biological fluids and 0.005-0.5 µg/g dry weight in tissues using GF-AAS depending on treatment, separation and concentration methods, and 5 µg/m^3 in air and 3 µg/litre in water using ICP-AES. (IPCS p1)

Later studies pay much more attention to avoid contamination. Contamination has been a problem with a number of earlier studies due to the ubiquity of Al in the environment and the often low levels of Al in the assayed samples.

Makjanic and co-workers (1997; 1998) describe the technique of nuclear microscopy as applied to Al detection in unfixed tissue sections. Although the sensitivity is only >15ppm (see table 1), the technique avoids the demonstrated contamination of tissue sections by fixing and staining.

The widely used morin stain for tissue samples can detect amounts of Al less than 1ppm (Ahmed and Hossan 1995). A newer stain, lumogallion, may be both more sensitive and more specific than morin (Kataoka *et al.* 1997).

Priest (2001) describes the detection of Al^{26} in very small amounts (10^{-17} g) in biological samples using accelerator mass spectrometry (AMS). This has become a valuable tool in describing and modelling Al biokinetics in man.

Table 1: Methods and sensitivities of Aluminium detection in biological samples

METHOD	DETECTION LIMIT
Instrumental neutron activation analysis (INAA)	1 ppb (µg/kg)
Electrothermal atomic absorption spectroscopy (AA)	1 ppb
Electon energy loss spectroscopy (EELS)	>500 ppm (mg/kg)
Energy dispersive (electron probe) X-ray microanalysis (EDX)	>20 ppm

Proton probe nuclear microscopy	>15 ppm
Secondary ion mass spectrometry (SIMS)	1 ppm
Laser microprobe mass spectroscopy (LMS; LAMMA)	1 ppm
Solachrome azurine stain	20 ppm
Morin stain	? ppb
Lumogallion stain	ppb

From Yokel (2000), updated

2. Sources, environmental transport, distribution and transformation

Aluminium is released to the environment both by natural processes and from anthropogenic sources. It is highly concentrated in soil-derived dusts from such activities as mining and agriculture, and in particulate matter from coal combustion. Aluminium silicates (clays), a major component of soils, contribute to the aluminium levels of dust. Natural processes far outweigh direct anthropogenic contributions to the environment. Mobilization of aluminium through human actions is mostly indirect and occurs as a result of emission of acidifying substances. In general, decreasing pH results in an increase in mobility and bioavailability for monomeric forms of aluminium. The most important raw material for the production of aluminium is bauxite, which contains up to 55% alumina (aluminium oxide). World bauxite production was 106 million tonnes in 1992. Aluminium metal has a wide variety of uses, including structural materials in construction, automobiles and aircraft, and the production of metal alloys. Aluminium compounds and materials also have a wide variety of uses, including production of glass, ceramics, rubber, wood preservatives, pharmaceuticals and waterproofing textiles. Natural aluminium minerals, especially bentonite and zeolite, are used in water purification, sugar refining, brewing and paper industries. (IPCS p1)

Aluminium occurs ubiquitously in the environment in the form of silicates, oxides and hydroxides, combined with other elements such as sodium and fluorine and as complexes with organic matter. It is not found as a free metal because of its reactivity. It has only one oxidation state (+3) in nature; therefore, its transport and distribution in the environment depend only upon its coordination chemistry and the chemical-physical characteristics of the local environmental system. At pH values greater than 5.5, naturally occurring aluminium compounds exist predominantly in an undissolved form such as gibbsite ($Al(OH)_3$) or as aluminosilicates, except in the presence of high amounts of dissolved organic material, which binds with aluminium and can lead to increased concentrations of dissolved aluminium in streams and lakes. Several factors influence aluminium mobility and subsequent transport within the environment. These include chemical speciation, hydrological flow paths, soil-water interactions, and the composition of the underlying geological materials. The solubility of aluminium in equilibrium with solid phase $Al(OH)_3$ is highly dependent on pH and on complexing agents such as fluoride, silicate, phosphate and organic matter. The chemistry of inorganic aluminium in acid soil and stream water can be considered in terms of mineral solubility, ion exchange and water mixing processes. (IPCS p2)

Upon acidification of soils, aluminium can be released into solution for transport to streams. Mobilization of aluminium by acid precipitation results in more aluminium being available for plant uptake.

3. Environmental levels and human exposure

3.1. Environmental levels

3.1.1. Air

Aluminium is a major constituent of a number of atmospheric components particularly in soil-derived dusts (both from natural sources and human activity) and particulates from coal combustion. In urban areas aluminium levels in street dust range from 3.7 to 11.6 µg/kg. Airborne aluminium levels vary from 0.5 ng/m^3 over Antarctica to more than 1000 ng/m^3 in industrialized areas. (IPCS p3)

3.1.2. Freshwater

Surface freshwater and soil water aluminium concentrations can vary substantially, being dependent on physico-chemical and geological factors. Aluminium can be suspended or dissolved. It can be bound with organic or inorganic ligands, or it can exist as a free aluminium ion. In natural waters aluminium exists in both monomeric and polymeric forms. Aluminium speciation is determined by pH and the concentrations of dissolved organic carbon (DOC), fluoride, sulphate, phosphate and suspended particulates. Dissolved aluminium concentrations for water in the circumneutral pH range are usually quite low, ranging from 1.0 to 50 µg/litre. This rises to 500-1000 µg/litre in more acidic water. At the extreme acidity of water affected by acid mine drainage, dissolved aluminium concentrations of up to 90 mg/litre have been measured. (IPCS p3)

3.2. Occupational exposure

Occupational exposures have been reported as total dust or particulate matter: e.g., potroom workers, 1.67 mg/m^3 (Kongerud & Samuelsen, 1991); production of abrasives, 0.2 to 44.6 mg aluminium oxide/m^3 (Jederlinic et al., 1990); MIG welders, 10 mg/m^3; TIG welders, 1 mg/m^3; respirable particles with a mean aluminium content of 39% (Ulfvarson, 1981; Sjögren et al., 1985) and aluminium soldering of aluminium cables, 1.1 mg/m^3 respirable dust decreasing to 0.7 mg/m^3 after installation of a vacuum collection system (Hjortsbert, 1994). (IPCS p74) It is possible that welders and smelters and remelters are exposed to fume –an ultra-fine condensation aerosol- which is not particulate and is more absorbable (Priest 2001).

Workers exposed to solid rocket motor fume, aluminium arc sprayers and welders, and workers within the production industry all show much higher excretion levels than normal (Priest 2001). Smelter workers and Al flake and powder producers show the highest levels in production areas, and Al welders higher still. Bauxite miners tend not to show similar patterns of high exposure (de Kom *et al.* 1997).

Al in air inside welders' respiratory equipment was 0.9mg/m^3 (Bast-Pettersen *et al.* 2000) in contrast with 0.002mg/m^3 in normal urban air, and is likely to be much more bioavailable as it is Al vapour condensation fume rather than small particulates of relatively insoluble oxides and silicates. Compared with past measures in workplaces where monitoring and practice was less stringent, this may be a relatively low figure (see (Doll 1993)).

Several countries including the UK and USA have set an occupational exposure limit of 5mg/m^3 for respirable Al dust. Sweden lowered the limit from 4 to 2mg/m^3 in 1997 (Sjogren 1997)

3.3. General population exposures

3.3.1 Air

Pulmonary exposure to aluminium is determined by air concentration, particulate size and ventilatory volume. Air concentrations vary between low levels in rural settings (20-500 ng/m^3) and higher levels in urban settings (1000-6000 ng/m^3). Particles larger than 5-10 µm diameter tend to be removed from inhaled air and penetrate poorly into the lungs. Humans living in an urban area with ambient aluminium concentrations of about 2000 ng/m^3, particle size < 5 µm and a ventilatory volume of 20 m^3/day would be exposed to 40 µg aluminium/day by inhalation. (IPCS p74)

3.3.2 Drinking water

The WHO recommended maximum level is 200µg/l based on aesthetic considerations such as colour and turbidity rather than any toxicological issues (WHO 1998). In the UK, for example, only 0.7% water company samples exceeded this level in 1993 (WHO 1997). In Germany the number is 2.7%, and some private sources such as wells in areas with low buffering soil and high acid stress have levels up to 10mg/l (in W.H.O. (1997)).

Al salts, typically sulfate (alum) or chlorides, are used as flocculants to remove colour or turbidity from drinking water. Estimates suggest a 40-50% chance that use of these preparations increase the soluble Al concentration of finished water (reviewed in Soni *et al.* (2001)). Broad spatial variation has been documented with a peak reading of 530µg/l and median concentrations up to five times higher associated with alum treatment (Cech and Montera 2000). Treatment will alter the Al species profile; Schintu *et al.* (2000) report that there is a shift following treatment from organic to inorganic Al forms and that treatment did not increase total Al, but results suggest that finished water has more bioavailable Al.

3.3.3. Food and beverages

The only statement on maximum recommended intake is from FAO/WHO (1989). It set the Provisional Tolerable Weekly Intake at 7mg/kg body weight, apparently derived by applying an uncertainty factor of 100 to a NOEL of 110 mg/kg/d in an unpublished 6-month study of acidic sodium Al phosphate in the diet of beagle dogs. However a very similar-looking published study listed in table 9 reports an NOEL for Al in this form of 70mg/kg/day.

In general, aluminium content of frequently consumed food increases in the following order: beverages, food of animal origin, food of plant origin (Muller *et al.* 1998). Some foods have very high Al contents, for instance a single slice of some US processed cheeses may contain as much as 50mg Al due to addition of basic sodium Al phosphate emulsifier (Kasel), such cheeses often being used in fast foods. Otherwise cheese may be high in Al anyway (~290µg/g), as are some herbs and spices (400-600µg/g) (Soni *et al.* 2001) and especially baking powders which contain acidic sodium Al phosphate (SALP), which may contain 23000µg/g such that a single slice of cake or bread could contain 15mg Al (Priest 2001). Tea leaves are high in Al (~1300µg/g), although the infusion contains low levels (2.8µg/ml), and coffee even less. Because food levels are generally relatively low, a healthy individual is not at risk of Al toxicity from normal dietary consumption (Muller *et al.* 1998).

Some factors can increase the Al content of food. Aluminium cookware leaches some Al into cooked food, but generally only significant amounts when the food is acidic, especially tomato sauce (reviewed in (ATSDR 1999)). Eating 10g of tomato sauce which has been cooked in aluminium cookware may provide up to 6mg Al (Soni *et al.* 2001). Grilling flesh imparts more Al to the food when wrapped in foil and when cooked with Al-rich spices (Ranau *et al.* 2001). Otherwise the use of Al foil in cooking contributes little. ICMR (1999) and Neelam *et al.* (2000) provide evidence of generally higher levels when cooking and storing food, especially when using new utensils although this is set in an Indian context regarding food types cooked and levels of use of Al utensils. Neelam *et al.* (2000) point out that although their estimates of exposure levels are higher than others published, they would still not come close to exceeding the WHO recommended level. Although Soni *et al.* (2001) question these data they estimate total addition of Al to foods from cooking is finally about 3.5mg/day, which is not inconsiderable. However this estimate seems to assume exclusive use of Al cookware and food preparation for a family, so perhaps closer to 0.5-1.0mg/day per person. This was supported by a study of dialysis patients who used aluminium kitchen utensils, in whom a greater serum Al decrement was seen following replacement with stainless steel (Lin *et al.* 1997). Surprisingly a storage effect is generally not observed with beer; Al concentration is little greater than in drinking water (Sharpe and Williams 1995). Finally, although tea leaves are very high in Al, little Al is consumed in tea or in coffee (Rajwanshi *et al.* 1997).

3.4 Miscellaneous exposures

Anatacids can supply 840-5000mg (Lione 1985) although this estimate may be more relevant to its time, as current preparations tend to contain less Al. A more recent estimate of 50-1000+ was made by Epstein (1990). Phosphate binders are similar preparations typically given to dialysis patients.

Al-containing antiperspirants can be absorbed transdermally (Flarend *et al.* 2001), uptake of which might be increased in abraded or otherwise wounded skin. The entry of Al into the body through ‘wounds’ includes vaccine injections, prostheses, bone-reconstructive cement and shrapnel.

3.5 Total human intake of aluminium from all environmental pathways

Non-occupational human exposure to aluminium in the environment is primarily through ingestion of food and water. Of these, food is the principal contributor. The daily intake of aluminium from food and beverages in adults ranges between 2.5 and 13 mg. This is between 90 and 95% of total intake. Drinking-water may contribute around 0.4 mg daily at present international guideline values, but is more likely to be around 0.2 mg/day.Pulmonary exposure may contribute up to 0.04 mg/day. In some circumstances, such as occupational exposure and antacid use, the levels of exposure will be much greater. For example, >500 mg of aluminium may be consumed in two average-sized antacid tablets. There are some difficulties in assessing uptake from these exposures because of analytical and sampling difficulties(IPCS p3).

One assumed typical daily intake from all sources is 10mg Al (Priest 2001), although Soni *et al* (2001) estimates a typical U.S. dietary intake as 26.5mg with a range of 20-40. This is given with a breakdown which indicates an 18.4mg contribution from

baking soda added to grain products, which may be unrepresentative, although Greger and Baier (1983) state that the upper level of dietary Al intake in the US is 125mg! A later estimate is about 7.5mg/day (Pennington and Schoen 1995). Using total diet or duplicate diet methodologies, daily intake estimates from food in Finland, Japan, Switzerland and UK were 6.7, 4.5, 4.4 and 3.9mg respectively [summarized in W.H.O.(1997)]. Such an intake can be increased by one to two orders of magnitude easily with the ingestion of Al-containing antacids or buffered analgesics. Occupational exposure, also, can markedly increase intake. People normally absorb an estimated 0.5-3.0% of their total Al absorption from drinking water.

4. Kinetics and metabolism

4.1 Absorption

4.1.1 Animals

4.1.1.1 Oral administration

Absorption via the gastrointestinal tract is usually less than 1%. The main factors influencing absorption are solubility, pH and chemical species. Organic complexing compounds, notably citrate, increase absorption. Aluminium absorption may involve calcium and iron transport systems. Dermal and inhalation absorption have not been studied in detail. Aluminium is distributed in most organs within the body with accumulation occurring mainly in bone at high dose levels. To a limited but as yet undetermined extent, aluminium passes the blood-brain barrier and is also distributed to the fetus. Aluminium is eliminated effectively by urine. Plasma half-life is about 1 h in rodents (IPCS p81).

Estimates of fractional uptake by animal, Al species and oral dose are summarized and referenced in table 2, and serum levels following various treatments are summarized in table 3.

The rat has afforded the opportunity to study bioavailability changes in labile Al (Al^{3+}, monomeric hydroxo and sulfate complexes). To test the hypothesis that labile Al in drinking water is more available for absorption in the gastro-intestinal tract than Al complexed in the rat feed. Glynn *et al.* (1995) fed rats Al-containing feed and Al-free water or Al-containing feed and 4mg/litre Al in acidic water for 10 weeks (98% of the Al was labile). No increase of Al levels in the bone, liver or brain tissue of the rats was observed versus controls. Al speciation in a simulated rat stomach indicated that labile Al in drinking water is rapidly complexed by feed constituents as the water enters the stomach, resulting in a very low concentration of Al-lab (Danielsson *et al.* 1995; Glynn *et al.* 1995). This does not necessarily deny increased absorption, given the efficiency of excretion. Indeed, (Yokel *et al.* 2001), using low doses of Al^{26} in drinking water, showed that presence of food in the stomach and hardness of water did not significantly affect oral bioavailability, which was around 0.3%, suggesting that the presence of food merely delays absorption in the rat. Perhaps 4mg/litre in drinking water is too low a dose to overcome urinary excretion capacity so that higher tissue levels were not observed.

To make the point that body burden of Al in humans cannot be ascertained by measuring Al in drinking water, (Glynn *et al.* 1999) exposed rats to 0, 10, 50, or 500 mg labile Al/litre in acidic drinking water (pH 3) for 9 wk. This resulted in a nondetectable absorption of Al at 10 mg Al/litre but increased absorption of Al at 50 and 500 mg Al/litre, suggesting a saturation of the Al-binding capacity of feed components in the lumen of the stomach, causing the appearance of labile Al. They conclude that the presence of labile Al in drinking water does not necessarily result in a high Al absorption since the bioavailability of labile Al depends on the amount and type of Al-binding components present in the gastrointestinal tract at the time of drinking, in contradiction of the results of Yokel *et al.* (2001).

Fasting increased Al^{26} absorption from drinking water by 10-15 times, but co-ingested silicon had no effect (Drueke *et al.* 1997). In contrast (Belles *et al.* 1998) found that silicon reduced tissue Al levels and urinary excretion, however animals in this study were given very large doses of both Al and of silicon, which may have then dominated the gut environment.

As in humans, some chemical factors alter absorption in rats. The organic acids citrate, malate, tartrate and lactate increase tissue levels (and presumably uptake) of Al (Testolin *et al.* 1996), lactate especially associated with increased levels in the frontal cortex. Certain co-administered polyphenolic acids, present in brewed beverages such as tea and coffee, increased kidney, bone and brain Al levels in rats, as did citrate (Deng *et al.* 2000). Silicon decreased uptake and tissue deposition (Belles *et al.* 1998) but fluoride enhanced Al uptake, this latter contrary to results with humans (Allain *et al.* 1996).

Although citrate is well known to enhance Al uptake, Taylor *et al.* (1998) contest the hypothesis that Al from the gut enters the bloodstream complexed with citrate because the kinetics of the two chemicals' uptake into and loss from blood are different. In rats, (Jouhanneau *et al.* 1997) estimate gut absorption following Al^{26} dosing as 0.05% which is enhanced 2-5 fold by coadministered citrate. Taking 5-hour urinary excretion following gavage with Al^{26}, (Schonholzer *et al.* 1997) estimated 0.1% absorption of Al hydroxide and Al maltolate, 0.7% for Al citrate and 5.1% for Al citrate administered with sodium citrate. This, and the fact that the citrate and Al levels peak in blood at different times strengthens the view that citrate enhances Al absorption by increasing gut permeability to the metal, perhaps by loosening tight junctions between gastric mucosal cells (Taylor *et al.* 1998).

It had been suggested that Al uptake is mediated by iron-specific pathways. A comprehensive study by Ittel *et al.* (1996) negates this view. The negative effect of calcium may be because Ca and Al seem to be absorbed by the same or similar mechanisms (Vandervoet and Dewolff 1998). Ca balance can affect Al absorption in rabbits (Long *et al.* 1994).

The significance to humans of actual absorption levels in animals is uncertain given known inter- and intraspecies differences in bioavailability (WHO 1997).

Table 2. Gastrointestinal absorption of aluminium compounds

Species	Dose	Form	f (%)[a]	Method[b]	Remarks	References
Rat	8.1 mg/kg	$AlCl_3$	27	3		Gupta *et al.* (1986)
Rat	1; 12 mg Al/kg	Lactate	0.18	2		Wilhelm *et al.* (1992)
Rat	1; 12 mg Al/kg	lactate	0.02	3		Wilhelm *et al.* (1992)
Rat	35 mg Al/kg	sucralfate, lactate	0.015	2		Froment *et al.* (1989a)
Rat	35 mg Al/kg	$AlCl_3$	0.037	2		Froment *et al.* (1989a)
Rat	1.20 mmol Al/kg	lactate	0.037	2		Froment *et al.* (1989a)
Rat	3.8 ng 26Al and 63 ng 27Al in citrate		0.02	2		Jouhanneau *et al.* (1993)
	and citrate-free solutions		0.02	2		
Rat	1; 12 mg Al/kg	lactate	0.18	2		Wilhelm *et al.* (1992)
Rat	1; 12 mg Al/kg	lactate	0.02	3		Wilhelm *et al.* (1992)
Rat	35 mg Al/kg	sucralfate	0.015	2		Froment *et al.* (1989a,b)
Rat	35 mg Al/kg	$Al(OH)_3$	0.015	2		Froment *et al.* (1989a,b)
Rat	35 mg Al/kg	$AlCl_3$	0.037	2		Froment *et al.* (1989a,b)
Rats	Al^{26}, single gavage		0.28	3		Yokel *et al.* (2001)

Species	Dose	Form	f (%)[a]	Method[b]	Remarks	References
Rats	Al^{26}, single gavage					
		hydroxide	0.1	1		Schonholzer *et al.* (1997)
		citrate	0.7			
		citrate + Na citrate	5.0			
		maltolate	0.1			
Rabbit	10.8, 540 mg Al/kg	lactate	0.70-1.9	3	no significant influence of dose	Yokel & McNamara (1985)
Rabbit	2.5-10 mmol/kg	various	0.3-2.2	3	absorption: soluble>insoluble; minor differences between best bioavailability, citrate; minor influence of renal Impairment	Yokel & McNamara (1989)
Sheep	1-2 g/day	$Al_2(SO4)_3$; Al-citrate; $AlCl_3$	2-15	1	order of absorption: $Al_2(SO_4)_3$>Al citrate>$AlCl_3$	Allen & Fontenot (1984)

From W.H.O. (1997), updated.

[a] f = mass Al absorbed + mass Al ingested

[b] 1 = balance study; 2 = estimation based on urinary excretion; 3 = comparison of areas under plasma aluminium concentration after oral and intravenous application

Table 3. Blood aluminium concentrations in experimental animals exposed orally to aluminium compounds[a]

Species	Sample	Dose	Duration	Compound	Aluminium concentration (control value)	Reference
Rat (8 Wistar)	blood		24 days	$Al_2(SO_4)_3$	(6.5 mg/kg w.w.)	Ondreicka *et al.* (1966)
		2835 mg Al/kg feed			10.8 mg/kg w.w.	
Rat (male albino)	serum			$Al(OH)_3$	(0.24 mg/litre)	Berlyne *et al.* (1972)
		150 mg Al/kg/d, gavage			0.99 mg/litre	
Rat (male SD, 8/group)	serum			$AlCl_3$	(0.91 mg/litre)	Mayor *et al.* (1977)
		0.1% aluminium in feed			day 10: 1.12 mg/litre	
					day 25: 1.09 mg/litre	
Rat (male SD, 7/group)	blood		11 weeks		(0.005 mg/kg w.w.)	Slanina *et al.* (1985)
		3 d/w, gavage		$Al(OH)_3$	0.009 mg/kg w.w.	
				Al citrate	0.014 mg/kg w.w.	
				$Al(OH)_3$ + citrate	0.039 mg/kg w.w.	
Rat (male SD, 10/group)	blood			$Al(NO_3)_3$	(3.7 mg/kg w.w.)	Gómez *et al.* (1986)
		375 mg/kg/d			3.1 mg/kg w.w.	
		750 mg/kg/d			2.5 mg/kg w.w.	
		1500 mg/kg/d, in water			3.0 mg/kg w.w.	
Rat (female SD, 10/group)	blood		100 days	$Al(NO_3)_3$	(< 0.5 mg/kg)	Domingo *et al.* (1987b)
		360 mg/kg w.w.			< 0.5 mg/kg	
		720 mg/kg w.w.			< 0.5 mg/kg	
		3600 mg/kg w.w., oral			< 0.5 mg/kg	
Rat (18 male, weanling SD)	serum		29 days	$Al(OH)_3$	(0.28 µmol/litre)	Greger & Powers (1992)
		0.39 mmol Al/kg diet			0.98 µmol/litre	

Species	Sample	Dose	Duration	Compound	Aluminium concentration (control value)	Reference
		aluminium + 4% citrate			1.15 µmol/litre	
		100 mmol Al/kg diet				
		+ 4% citrate, in feed			1.09 µmol/litre	
Rat (weanling SD, 4/group)	serum	160 mg Al/kg d, gavage,	10 days		(18.8 µg/litre)	Santos *et al.* (1987)
		1,25-(OH)2-D3			24.3 µg/litre	
		1,25-(OH)2-D3 + Al(OH)3			29.5 µg/litre	
		1,25-(OH)2-D3 + Al citrate			16.3 µg/litre	
Rats	serum		105 days		(10.8 µg/litre)	Garbossa *et al.* (1998)
		27mg/kg/d, gavage		Al citrate	76 µg/litre	
		2700mg/l in drinking water			130 µg/litre	
Rabbit (male NZ, 3-4/group)	serum		1 month		(5 µg/litre)	Thornton *et al.* (1983)
		50 g/kg in feed		AlCl3	14 µg/litre	
				Al+ethanol	24 µg/litre	
Cattle (steer, 6/group)	blood		84 days	AlCl3	(0.103 mg/litre)	Valdivia *et al.* (1978)
		300 mg/kg			0.118 mg/litre	
		600 mg/kg			0.100 mg/litre	
		1200 mg/kg, in feed			0.120 mg/litre	

From (W.H.O. 1997)

[a] 1,25-$(OH)_2$-D_3 = 1,25-dihydroxy-vitamin D_3; d = day; NZ = New Zealand; SD = Sprague-Dawley; w = week; w.w. = wet weight

4.1.1.2 Inhalation

(Rollin *et al.* 1991) examined the effect of dust as Al oxide at 0.56mg/m^3 for 5 months on New Zealand white rabbits. They found that this level, one twentieth of the recommended level at the time, resulted in an increased brain level about 2.5 times normal, whereas serum levels were only slightly raised.

No systematic studies of inhalation of Al in animals have been reported.

4.2.1 Humans

4.2.1.1 Oral administration

Aluminium and its compounds appear to be poorly absorbed in humans, although the rate and extent of absorption have not been adequately studied. Concentrations of aluminium in blood and urine have been used as a readily available measure of aluminium uptake, increased urine levels having been observed among aluminium welders and aluminium flake-powder producers.

The mechanism of gastrointestinal absorption of aluminium has not yet been fully elucidated. Variability results from the chemical properties of the element and the formation of various chemical species, which is dependent upon the pH, ionic strength, presence of competing elements (silicon), and the presence of complexing agents within the gastrointestinal tract (e.g., citrate).

The biological behaviour and gastrointestinal absorption of aluminium in humans ingesting aluminium compounds has been studied by using the radioactive isotope Al^{26}. Significant intersubject variability has been demonstrated. Measured fractional uptakes of 5×10^{-3} for aluminium as citrate, 1.04×10^{-4} for aluminium hydroxide and 1.36×10^{-3} for the hydroxide given with citrate were reported. A study of the fractional uptake of aluminium from drinking-water showed an uptake fraction of 2.35×10^{-3}. It was concluded that members of the general population consuming 1.5 litres/day of drinking-water containing 100 µg aluminium/litre would absorb about 3% of their total daily intake of aluminium from this source depending upon the levels found in food and the frequency of antacid use (IPCS p4).

Priest (2001) reviews the biological behaviour and bioavailability of Al in man. Most Al enters the body via the gut for the majority of people. Occupationally, inhalation is a significant route and medically, direct contact with bloodstream has been particularly important in haemodialysis of renal failure patients, when the dialysate was made from water containing too much Al.

The mechanisms of aluminum absorption are not known, but both passive and active transcellular processes and paracellular transport are believed to occur (Greger and Sutherland 1997). Comparison with other trivalent metal ions suggest that only 0.01% of insoluble species such as the oxides and silicates will be absorbed. But the aqueous chemistry of Al is complex which makes precise understanding of absorption difficult, as both insoluble species and bioavailable labile Al are formed in varying amounts depending on pH and initial concentration (Kiss 1995; Corain *et al.* 1996) and presence of complexing anions.

Priest *et al.* (1995) shows a 50 fold increase in uptake of Al citrate compared with Al hydroxide, and when the hydroxide was administered with citrate, uptake was increased 14 times. Lactate produces a similar effect (reviewed in (Priest 2001)), and it is likely that other dietary organic acids such as malate, oxalate, tartrate, malonate and gluconate produce similar effects (Testolin *et al.* 1996; Priest 2001). This is supported by studies in rats (Testolin *et al.* 1996). On the other hand, co-ingested silicon can reduce Al bioavailability by up to 85% (Edwardson *et al.* 1993; Jugdaohsingh *et al.* 2000), by formation of insoluble precipitates, as can fluoride and phosphate anions (Priest 2001).

Based on long term excretion of administered Al^{26}, Priest (1993) estimated a 2% lifetime retention. Estimates of rates of absorption can then be calculated by two methods (Priest 2001). Firstly, using their own estimated terminal body burden (Priest *et al.* 1995), a dietary Al intake of 10mg/day, estimated 98% excretion (or 2% retention) an absorbed fraction of 0.14% is estimated. Based on other estimates of terminal body burden we get a high estimate of 1.6% and central estimates of 0.5-0.8% absorption. Talbot *et al.* (1995) agrees, suggesting large intersubject variation in long-term Al retention, based on measures after 6 days following Al^{26} injection. Estimates for food are 0.28 – 0.64% (Stauber *et al.* 1999).

Using their own biokinetic data based on daily excretion studies, an estimate of 0.08% absorption is obtained, or 0.15% if a higher measure of excretion is used (Priest 2001). In a similar approach, Stauber *et al.* (1999) studied 29 healthy volunteers who drank alum-treated drinking water (ATW) or pure water while on an Al-controlled diet during two-day periods. 1-2% of the daily intake of Al came from ATW and an estimated 0.3-0.4% of the Al in ATW was absorbed; the same percentage as absorbed from food. Drinking 1.6 litres/day of ATW containing 140 mu g/L Al would contribute an estimated 0.4-1.1% of the lifetime body burden of Al. Priest *et al.* (1998) estimates less than 0.2% of the absorbed Al comes from drinking water.

Because measurement of small increases over background levels of the common isotope of Al (Al^{27}) can be difficult and contamination is a problem, Al^{26} is employed. However Al^{26} cannot be compounded with anions to form all the species typically ingested in food and water, which is a limitation of this work.

Roberts *et al.* (1998) report a significant 2-3 fold increased serum Al level in Alzheimer's dementia (AD) patients and in those on Al hydroxide (antacid) therapy compared with controls. Urine Al output was increased even more so. There were 114 controls aged 30-65, 8 AD patients aged 65-86 and 8 peptic ulcer/dyspepsia patients aged 39-70. The antacid result is valid because the samples are roughly age matched but the AD-control comparison is invalid because the age ranges barely overlap, especially in light of Taylor *et al.* (1992) who showed that Al uptake increases with age.

Moore and co-workers (1997; 2000) report significantly increased Al uptake in Downs Syndrome patients (who develop AD early) and in AD patients. Although this former study repeats the work and results of Day *et al.* (1994), it also repeats their methodological errors of failing to observe plateau levels. If this is not done, because the time course of absorption can vary and be protracted over many hours, an accurate estimate of absorption is impossible (Priest 2001). Edwardson *et al.* (1993) demonstrate the variability of plasma concentrations at early times post ingestion, and

Priest (Priest *et al.* 1996; Priest *et al.* 1998) demonstrates variation between individuals in absorption and excretion over time, largely due to differences in gut transit. However comparison of uptake levels at single time points is still useful data and is suggestive of an effect of Downs Syndrome and AD on Al absorption. Reiber *et al.* (1995) reject the possibility that Al in drinking water is more readily assimilated than other forms of Al based on issues of solubility and the likely chemical transformations that take place in human gut.

Table 4 shows results of studies to determine, variously, the effect of Al ingestion and renal function on serum and urinary Al levels.

Table 4: Blood and urine aluminium concentrations in humans after oral ingestion of aluminium compounds[a]

Subjects and treatment	Aluminium concentration in blood (µg/litre)	Aluminium concentration in urine (µg/litre)	Remarks	Reference
5 normal subjects, 2 patients with CRF; $Al(OH)_3$ antacids, 86-91 mmol/day	not specified	not specified	Al absorption normal: 0.3-3.6 mmol/day CRF: 3.3-9.1 mmol/day	(Cam *et al.* 1976)
Normal subjects, $Al(OH)_3$, oral, 3.8 g Al/day for 3 days	not detected	(85.8 µg/day) increased by 4-10 times		(Recker *et al.* 1977)
Normal subjects, 2.2 g Al for 3 days $Al(OH)_3$ $Al2(CO_3)_3$ $Al(OH)_2$-aminoacetate $AlPO_4$	plasma: (6-7) 17 14 17 9	 (8-16) 176-325 51-355 243-726 52-60	cumulative increase in excretion (µg) 730 ± 487 567 ± 437 1430 ± 1157 123 ± 77	(Kaehny *et al.* 1977)
Normal subjects CRF CRF + Al	6.2 (serum) 13.4 (serum) 34.2	not detected		(Marsden *et al.* 1979)
Normal subjects, antacids taken orally, 23-313 mg/day for 18-30 days	plasma Al: 2-fold increase	urinary Al excretion: 2- to 6-fold increase	Al balance positive during Al administration	(Gorsky *et al.* 1979)

Subjects and treatment	Aluminium concentration in blood (µg/litre)	Aluminium concentration in urine (µg/litre)	Remarks	Reference
Al-hydrocarbonate (Lithiagel), oral, 1.84 g Al/day; 5 days	(before Al: 8.35) 3-day Al: 15.9 5-day Al: 14.8 after 1 week Al: 8.0	(before Al: 6.35) 3-day Al: 430.8 5-day Al: 262.5 after 1 week Al: 12.2	serum aluminium in dialysed patients treated with Aludrox: 6-254 µg/litre	(Mauras *et al.* 1983)
Al-supplemented diet control: 4.6 mg Al/day test: 125 mg Al/day	serum (before: 4) control: 4 test: 7	urinary excretion: control: 35-36 µg/day test: 105-129 µg/day	normalized to creatinine control: 20 mg/kg test: 57-72 mg/kg	(Greger and Baier 1983)
12 subjects (normal young) given 280 nM Mg + 190 nM Al/day for 4 weeks	serum Al placebo: 0.3-0.9 test: 0.8-1.1	placebo: 1.0-3.0 test: 3.6-20.2		(Herzog and Holtermuller 1982)
CRF, on home dialysis on CAPD	(3.4 plasma) 37.7-68.7 33.9-45.0		no correlation with Al concentration in hair	(Wilhelm *et al.* 1989)
Sucralfate (sucrose, Al hydroxide, sulfate) 2g twice/day	serum Al doubled from basal (single measure only)			(Schutze *et al.* 1995)

From (W.H.O. 1997), updated.

[a] control values are given in parentheses

CAPD = continuous ambulatory peritoneal dialysis; CRF = chronic renal failure

4.2.1.2 Inhalation

Al in inhaled particulates is not very soluble and particulate size affects bioavailability. Assuming an average urban non-occupational inhalation exposure to be 40µg Al/day and the estimated uptake of 0.05% (Priest 2001), normal daily intake by inhalation would be 0.02µg/day, an insignificant amount in comparison with intake from food.

Absorption from inhalation of an 'industrial-type' aerosol of Al oxides was estimated using Al^{26} and found to be 1.9%, much higher than by ingestion. Most inhaled Al was mechanically cleared from the body although some would have been expectorated and swallowed. (Priest 2001) concludes that, given estimates of exposure, Al oxide is too insoluble to contribute significantly to body burden and that Al workers with high urine levels must be inhaling more soluble forms.

Gitelman *et al.* (1995) took serum and urine samples before and after a 3- to 5-day work shift of Al workers and controls. Median exposure values were 25 and 100 $\mu g/m^3$, respectively. Significant differences were seen between exposed and controls for the urinary aluminium/creatinine ratios [incremental difference 5.67 mg/kg ($P < 0.01$) pre-shift; 8.01 mg/kg ($P < 0.01$) post-shift]. Urinary aluminium/creatinine ratios were greater in workers from plants with higher aluminium exposures. These results are consistent with the systemic absorption of aluminium from occupational exposure and suggest the presence of a sensitive uptake process for airway aluminium. Thus inhalational exposure assuming 4 days X 8 hour work shifts only and $20m^3$ air inspired/day is 2.5mg, raised urinary output by ~40%. Four days' ingestion of 125mg Al/day produced a ~200% increase in urinary Al output (Greger and Baier 1983). Comparing these two studies, an inhalational exposure 200 times less than a dietary exposure caused a urinary output increase only 5 times less, perhaps suggesting that inhalational exposure of this type (i.e. Al fume) could be 40 times more bioavailable than dietary exposure. Thus the ratio of uptake:exposure is markedly greater by inhalation compared with ingestion but the mechanism is unknown (Gitelman 1995).

Noting that manganese can be taken up via the olfactory pathways and pass transneuronally to other parts of the brain, Tjalve and Henriksson (1999) hypothesize that Al might possess similar properties, although this has not been investigated nor high concentrations in the olfactory bulbs noted.

4.2.2 Dermal – human and animal

Using Al^{26} in humans, Flarend *et al.* (2001) showed that transdermal absorption of Al from a roll-on antiperspirant is equivalent to about 2.5% of the daily intake from the gut assuming 0.1% absorption of a 10mg/day Al intake. This is usually Al chlorhydrate.

Transdermal uptake of Al has been demonstrated in shaved adult mice (Anane *et al.* 1995).

4.2 Distribution

4.2.1 Animal Studies

4.2.1.1 Distribution in plasma

Although Al-citrate is the predominant small molecular weight Al species in plasma, it represents only ~11% of the total Al, the remaining ~89% being bound to transferrin (Ohman and Martin 1994). It is likely that most Al enters the brain via transferrin-mediated endocytosis although the exact mechanism is not known and it has not been conclusively demonstrated. However brain entry of Fe and Mn by this method have been shown.

While previous work suggests that up to 10% of Al in serum may be bound to albumin (W.H.O. 1997), Harris and co-workers find no epirical or theoretical evidence for any significant binding of Al in serum to albumin (1996; 1996).

(Zafar *et al.* 1997) showed that orally administered Al^{26} in rats accumulated in tissues in the order: bone > spleen > kidney similar liver > brain, and that about 1% was absorbed.

Table 5 summarizes studies which have measured brain and bone Al in animals.

Orally administered Al^{26} enters the brains of rats (Walton *et al.* 1995; Yumoto *et al.* 1997). Yokel *et al.* (1999) consider Al uptake and retention in the rat brain, reviewing their own and others' work. Since brain Al concentration is considerably less than normal blood Al, it is likely that Al is sequestered in some brain compartment(s). But the brain is not a "one way sink" for Al. *In vivo* microdialysis is a sensitive method for determining levels of unbound substances from extracellular spaces on both sides of the blood-brain barrier. In rats, (Ackley and Yokel 1997) demonstrate that the brain:blood Al-citrate ratio is normally less than 1 (~0.19) and that the monocarboxylic acid transporter may represent the active process removing Al from the brain. Equally though, Al-citrate enters the brain more quickly than expected based on simple diffusion predicted by lipophilicity, therefore it is thought that this transporter may actively move Al-citrate into the brain as well as out.

In brain, normal diffusion of the citrate form may be the most important route of entry, and certainly normal levels of functional transferrin are not necessary for normal levels of uptake into brain and other tissues, except for spleen, muscle and bone (Barker *et al.* 1997).

Administration of an intravenous bolus of Al^{26} with coadministered Al^{27} resulted in persistent brain levels of Al^{26}, mainly associated with the nuclear fraction and in particular the chromatin fraction (Yumoto *et al.* 1997). A similar administration resulted in a peak brain level of 0.005% of administered dose, which had a half life of about 150 days (Yokel *et al.* 2001).

Chronic administration resulted in higher brain levels in young rats compared with adult and old (Domingo *et al.* 1996; Gomez *et al.* 1997; Gomez *et al.* 1997) but no activity or learning deficits at any age.

Longer exposure and reduced renal function both increased tissue Al levels in rats, but those factors explained only 35% and 19% of the variance so that factors other than inter-individual variation may have a significant effect upon body burden (Ecelbarger *et al.* 1994). Work by (Liu *et al.* 1996) supports this result, adding that calcium deficiency potentiates the renal effect. They suggest that, as renal tubular function is known to decline with age, Al may accumulate more with age.

Hypotransferrinmaemia increased only bone uptake of Al^{26}, by three times in mice (Radunovic *et al.* 1997), suggesting the importance of complexing of Al to smaller molecular weight species, probably mostly citrate, in bone uptake.

Transdermal uptake of Al has been demonstrated in shaved adult mice, and appeared to result in preferential uptake in the hippocampus (Anane *et al.* 1995).

Table 5. Tissue aluminium concentrations in experimental animals administered aluminium compounds orally[a]

Species	Treatment	Bone	Brain	Reference
Mouse (BALB/c, 5-10/group)	$AlCl_3$, gavage 200 mg/kg per day 300 mg/kg per day	n.d.	n.d.	Cranmer *et al.* (1986)
Mouse (Swiss, 6/group)	Al lactate, 25 mg Al/kg (= control), 500 mg Al/kg diet 1000 mg Al/kg diet	(5.3 mg/kg w.w.) 5.0 mg/kg w.w. 6.5 mg/kg w.w.	35.3 mg/kg w.w. 38.3 mg/kg w.w. 108.7 mg/kg w.w.	Golub *et al.* (1989)
Rat (8 Wistar)	2835 mg Al/kg in feed, (as $Al_2(SO_4)_3$), 24 days	femur (702 mg/kg w.w.) 912 mg/kg w.w.	(7.1 mg/kg w.w.) 10.8 mg/kg w.w.	Ondreicka *et al.* (1966)
Rat (juvenile, male SD, 8/group)	aluminium in water (1) control (2) 0.32 g Al/litre, 29 days (3) low Ca2+ + Al	n.d.	n.d.	Cann *et al.* (1979)
Rat (male SD, 8/group)	100 mg Al/kg b.w. 6 d/w; by gavage $Al(OH)_3$ (9 weeks); Al citrate (4 weeks); citric acid (4 weeks)	 (0.36 mg/kg w.w.) 0.41 mg/kg w.w. x 40 increased x 20 increased	cortex: (0.013 mg/kg w.w.) 0.013 mg/kg w.w. 0.057 mg/kg w.w. 0.028 mg/kg w.w.	Slanina *et al.* (1984)
Rat (male SD, 7/group)	gavage; 3 d/w; 11 week $Al(OH)_3$ Al citrate $Al(OH)_3$ + citrate	(0.22 mg/kg w.w.) 0.89 mg/kg w.w. 10.7 mg/kg w.w. 26.6 mg/kg w.w.	(0.016 mg/kg w.w.) 0.012 mg/kg w.w. 0.048 mg/kg w.w. 0.092 mg/kg w.w.	Slanina *et al.* (1985)
Rat (weanling, male	270 mg Al/kg diet, 18 days	tibia: (1.9 mg/kg w.w.)	(0.0 mg/kg w.w.)	Greger *et al.* (1985a)

Species	Treatment	Bone	Brain	Reference
SD, 6/group)	$Al(OH)_3$	15.6 mg/kg w.w.	2.2 mg/kg w.w.	
	Al palmitate	15.0 mg/kg w.w.	0.6 mg/kg w.w.	
	Al lactate	13.0 mg/kg w.w.	1.6 mg/kg w.w.	
	$AlPO_4$	14.5 mg/kg w.w.	1.3 mg/kg w.w.	
Rat (weanling, male SD, 9/group)	$Al(OH)_3$ in diet, 67 days	tibia: (4.04 mg/kg)	n.d.	Greger *et al.* (1986)
	257 mg Al/kg diet	11.3 mg/kg (3.13 mg/kg)		
	1075 mg Al/kg diet	10.4 mg/kg		
Rat (male SD, 10/group)	$Al(NO_3)_3$, in water, 4 w	(5.75 mg/kg w.w.)	(1.4 mg/kg w.w.)	Gómez *et al.* (1986)
	375 mg/kg/d	11.4 mg/kg w.w.	7.7 mg/kg w.w.	
	750 mg/kg/d	8.5 mg/kg w.w.	10.1 mg/kg w.w.	
	1500 mg/kg/d	17.7 mg/kg w.w.	7.9 mg/kg w.w.	
Rat (female SD, 10/group)	$Al(NO_3)_3$, oral, 100 d	(17.15 mg/kg w.w.)	(< 0.5 mg/kg w.w.)	Domingo *et al.* (1987b)
	360 mg/kg w.w.	75.08 mg/kg w.w.	4.93 mg/kg w.w.	
	720 mg/kg w.w.	79.18 mg/kg w.w.	2.09 mg/kg w.w.	
	3600 mg/kg w.w.	56.39 mg/kg w.w.	4.28 mg/kg w.w.	
Rat (SD, weanling 6/group)	$Al(OH)_3$, in feed, 10 d	femur: (6.8 mg/kg d.w.)	n.d.	Chan *et al.* (1988)
	50-60 mg/kg b.w.	8.4 mg/kg d.w.		
Rat (male, weanling SD)	$Al(OH)_3$, 28 d	tibia:	n.d.	Ecelbarger & Greger (1991)
	13 mg Al/kg diet	36 mmol/kg w.w.		
	+ 5 mmol/kg citrate	36 mmol/kg w.w.		
	41 mg Al/kg diet	50 mmol/kg w.w.		
	+ 5 mmol/kg citrate	69 mmol/kg w.w.		
Rat (18 male, weanling SD)	$Al(OH)_3$ in feed, 29 days	tibia: (28.9 mmol/kg w.w.)	n.d.	Greger & Powers (1992)
	0.39 µmol Al/g diet	52.6 mmol/kg w.w.		
	aluminium + 4% citrate	74.4 mmol/kg w.w.		
	100 µmol Al/g diet	79.6 mmol/kg w.w.		
	+ 4% citrate			

Species	Treatment	Bone	Brain	Reference
Rat	Al citrate	(1.59 mg/kg d.w.)		(Garbossa *et al.* 1998)
	27mg/kg/day gavage	(1.85 mg/kg d.w.)	not different from control	
	2700mg/litre drinking water	3.33 mg/kg d.w.	not different from control	
Rabbit (female NZ, 8/group)	inhalation exposure 0.56 mg Al/m^3 as Al_2O_3 8 h/d; 5 d/w; 5 months	(18.2 mg/kg d.w.) 22.2 mg/kg d.w.	(4.1 mg/kg d.w.) 10.1 mg/kg d.w.	Röllin *et al.* (1991a)
Rabbit (male NZ, 3-4/group)	50 g/kg $AlCl_3$, in feed 1 month Ethanol aluminium + ethanol	(n.d.)	cortex, gray matter: (n.d.) 3.1 mg/kg d.w. 1.3 mg/kg d.w. 3.0 mg/kg d.w.	Thornton *et al.* (1983)
Dog	$Al(OH)_3$ in feed, 3 g/d; 5 months	n.d.	cerebral cortex: 0.77 mg/kg d.w. 2.4 mg/kg d.w.	Arieff *et al.* (1979)
Cattle (steer, 6/group)	$AlCl_3$ in feed, 84 d 300 mg/kg 600 mg/kg 1200 mg/kg	(n.d.)	(6.4 mg/kg w.w.) 7.6 mg/kg w.w. 5.5 mg/kg w.w. 7.7 mg/kg w.w.	Valdivia *et al.* (1978)

From (W.H.O. 1997), updated

Values in parentheses are normal control values in unexposed animals; b.w. = body weight; d = day; d.w. = dry weight; n.d. = not detected; NZ = New Zealand; SD = Sprague-Dawley; w = week; w.w. = wet weight

4.2.2 Human Studies

4.2.2.1 In plasma

Generally 85-90% of serum Al is bound to the protein transferrin, dropping to around 80% in uraemic serum and no convincing evidence exists for a significant role of serum albumin (Harris 1996). The rest is mostly bound by citrate (Yokel 2000). On the basis of stability constants, Ohman and Martin (1994) agree that, of the Al in blood serum, ~89% (+/- 5%) binds to transferrin and ~11% (+/-5%) to citrate.

Table 4 indicates some normal values, although high values for normal subjects may be due to systematic sampling errors.

4.2.2.2 Distribution in tissues and body burden

Table 6 shows distribution among tissues in humans from a variety of exposures. Note that Al distribution within tissues may not be homogeneous because of known differences due to route of absorption, and many measures are based on small samples so that unusually high values should be interpreted with caution in the absence of an obvious biological explanation.

(Priest 2001) reviews literature on body burden. The highest levels are found in the lungs and lymph nodes which are undissolved particulate deposits and are not regarded as part of the systemic body burden of Al. An ICRP report (1975)suggests the following tissue distributions in 'Reference Man': bone – 54%; muscle – 14%; skin – 13%; adipose – 5%; blood and vessels – 4%; connective tissue – 3%; liver – 3%; GI tract – 2%; CNS – 1%. Only liver, skeleton, connective tissues and skin concentrate more Al than the average for the whole body. Note that contamination may easily have affected the reading for skin. If so, only bone significantly concentrates Al. Inhalation exposure of insoluble aerosol Al seems to lead to unusually high levels in lung, hilar lymph nodes, spleen and liver, with a lower fraction being found in bone. Where the load is very high e.g. dialysis encephalopathy patients, the liver often contains abnormally high proportion due to red blood cell breakdown releasing Al in renal failure, and kidneys also show high levels.

It is possible that age alters this profile. Hongve *et al.* (1996) examined 84 samples of head of femur and 95 liver samples from deceased elderly Norwegians. Two cases had high Al levels in bone (16.8 and 18.0 mg/kg ash weight) and liver (10 and 22.7 mg/kg dry weight) tissues. The remaining cases showed about ten to fifteen-fold variation of the Al level in both liver (0.4-5.7 mg/kg) and bone (0.5-5.8 mg/kg). There was no correlation between the level in liver and bone when the two cases with the highest levels were excluded.

Long-term high exposure combined with renal insufficiency will cause Al buildup in organs including brain. Reusche *et al.* (1996) showed significant correlations of both intake of Al-containing drugs and duration of haemodialysis with the degree of deposition of Al-containing proteinaceous inclusions in the brain.

(Yokel 2000), reviewing, indicates that brain Al entry from blood may involve transferrin-receptor mediated endocytosis and a more rapid process transporting small molecular weight Al species. The major species in brain extracellular fluid is likely to be Al-citrate and there probably exists active Al efflux from the brain as Al citrate.

Table 6: Tissue aluminium concentrations (mg/kg) in humans exposed to aluminium compounds[a]

Subjects and treatment	Bone	Muscle	Kidney	Liver	Lung	Brain	Remarks	Reference
Normal adult	n.d.	1.55 d.w.	2.02 d.w.	2.4 d.w.	122.5 d.w.	1.4 d.w.	adrenal: 4.8 d.w. spleen: 3.7 d.w. duod.: 4.56 d.w. jejun.: 2.84 d.w. ileum: 9.86 d.w.	Tipton & Cook (1963)
Healthy human controls	hard water area: 73.4 w.w. soft water area: 60 w.w.	0.5 w.w.	whole kidney: 0.4 w.w. cortex: 0.4 w.w. medulla: 0.3 w.w.	2.6 w.w.	18.2 w.w.	whole brain: 0.5 w.w. frontal lobe: 0.05 w.w. basal ganglia: 0.07 w.w.		Hamilton *et al.* (1973)
Normal males Stonemason	< 15 d.w. n.d.	n.d. n.d.	11 d.w. 16 d.w.	19 d.w. 130 d.w.	230 d.w. 2000 d.w.	n.d.	spleen: (22 d.w.) 520 d.w. heart: (11 d.w.) 2.0 d.w. adrenal: (37 d.w.) n.d.	Teraoka (1981)
Ball-mill room worker in aluminium powder factory	30 w.w.	n.d.	n.d.	90 w.w.	upper lobe: 430 w.w. lower lobe: 340 w.w.	5 w.w.		McLaughlin *et al.* (1962)

Subjects and treatment	Bone	Muscle	Kidney	Liver	Lung	Brain	Remarks	Reference
Surgical and autopsy specimen (hyperparathyroidism)	n.d.	no Al intake: 2.0 d.w. Al intake: 7.6 d.w.	n.d.	n.d.	n.d.	n.d.	no Al intake: PT: 13 d.w. thy: 3.5 d.w. Al intake: PT: 78 d.w. thy: 8.8 d.w.	Cann *et al.* (1979)
Normal controls:	10.6	23.6	17.5	15.8	97.2	11.9	spleen: 17.2	Flendrig *et al.* (1976)
uraemia, non-dial:	6.4	24.7	33.8	19.7	142.3	n.d.	25.1	
uraemia, dial:	23.5	39.6	44.1	32.9	127.1	12.1	37.9	
DES:	272.7	13.8	156.5	610.2	99.6	66.1	454.5	
DES normal control uraemia/dial uraemia/non-dial	cortical bone: (3.88) 46.83 8.4 trabecular bone: (2.39) 98.48 37.4	(1.22) DES: 23.6 non-DES:10.24	n.d.	n.d.	n.d.	grey matter: (2.18) non-DES: 6.5 DES: 24.98 brain white matter: (2.00) non-DES: 3.81 DES: 5.59		Alfrey *et al.* (1976)
Iliac bone (biopsy or autopsy spec.) control uraemia, non-dial dial dial + transpl	5.7 ash 13.6 ash 151.8 ash 92 ash	n.d.	n.d.	n.d.	n.d.	n.d.	correlation of duration of dialysis and bone Al	Ellis *et al.* (1979)
Patients			n.d.			grey matter:	spleen:	Alfrey (1980)

Subjects and treatment	Bone	Muscle	Kidney	Liver	Lung	Brain	Remarks	Reference
healthy controls	3.3 d.w.	1.2 d.w.		4.0 d.w.	56 d.w.	2.2 d.w.	3.8 d.w.	
uraemia, non-dial	27 d.w.	2.6 d.w.		25.5 d.w.	75 d.w.	4.1 d.w.	35 d.w.	
uraemia, dial	115 d.w.	9.1 d.w.		160 d.w.	89 d.w.	8.5 d.w.	243 d.w.	
DES	281 d.w.	15 d.w.		301 d.w.	215 d.w.	24.5 d.w.	493 d.w.	
Uraemia + dial		n.d.	n.d.	n.d.	n.d.	n.d.		Hodsman *et al.* (1982)
normal control	2.4 d.w.							
osteomalacia	175 d.w.							
osteitis fibrosa	46 d.w.							
mixed lesions	81 d.w.							
mild lesions	67 d.w.							
Normal, necropsy	n.d.	n.d.	n.d.	n.d.	n.d.	cortex: 0.23-2.7 d.w. white matter: 0.6-1.1 d.w.		Crapper *et al.* (1973)
Normal adult	n.d.	n.d.	n.d.	n.d.	n.d.	1.9 d.w.		Crapper *et al.* (1976)
infant						0.7 d.w.		
fetus						0.7 d.w.		
Normal controls	n.d.	n.d.	n.d.	n.d.	n.d.	2.5 d.w.	whole brain	McDermott *et al.* (1979)
						5.6 d.w.	hippocampus	
						2.4 d.w.	frontal cortex	
						1.4 d.w.	temporal cortex	
						2.9 d.w.	parietal cortex	
						2.9 d.w.	occipital cortex	
						2.6 d.w.	cerebellum	
						1.5 d.w.	corpus callosum	
						4.1 d.w.	mininges	
						1.3 d.w.	isolated neurons	
Normal adult	n.d.	n.d.	n.d.	n.d.	n.d.	0.467 w.w.		Markesbery *et al.*

Subjects and treatment	Bone	Muscle	Kidney	Liver	Lung	Brain	Remarks	Reference
normal infant						0.298 d.w.		(1981)
Al welders (2) welding fumes	(0.6-5 d.w.) 18-29 d.w.	n.d.	n.d.	n.d.	n.d.	n.d.	also increased: blood and urinary Al concentration	Elinder *et al.* (1991)
CRF, cumulative oral Al intake:	(median values)						no correlation with Al concentration in hair: control: 2.6 dial: 1.6-5.5	Wilhelm *et al.* (1989)
0 kg	5.3							
< 0.25 kg	47.5							
0.25 to 0.5 kg	56.7							
0.5 to 1.0 kg	62.6							
1.0 to 5.0 kg	133.4							
Controls (surgical specimens)	18.8 w.w.	n.d.	n.d.	n.d.	n.d.	n.d.	no differences between cortical and medullary bone; no correlation with age	Burnel *et al.* (1982)
CRF (biopsies; intake of variable amounts of Al)	6-130 w.w.							
Normal elderly	0.5-5.8 ash wt.			0.4-5.7 d.w.			no correlation between subjects	Hongve *et al.* (1996)

Subjects and treatment	Bone	Muscle	Kidney	Liver	Lung	Brain	Remarks	Reference
surgical specimens trabecular bone								
Controls	18.2 +/- 7.37 d.w.							O'Mahony *et al.* (1995)
Alzheimer's	11.9 +/- 4.04 d.w							

From (W.H.O. 1997), updated

[a] Normal control values are given in parentheses

DES = dialysis encephalopathy syndrome; dial= on haemodialysis;
w.w. = wet weight; non-dial= not on haemodialysis;
d.w. = dry weight; transpl= transplantation;
n.d. = no data; PT= parathyroid gland;
ARF = acute renal failure; thy= thyroid gland
CRF = chronic renal failure;

[b] All concentrations expressed as mg Al/kg fat-free solid

(Priest 2001) summarizes expected terminal body burdens given various levels of exposure (table 7)

Table 7: Predicted Terminal Body Burdens of Aluminium after 30 Years Continuous Exposure. Upper and Lower Estimates based on Results of Al^{26} Retention studies (Priest *et al.* 1995; Talbot *et al.* 1995)

	Body Burden at 50 years		
Intake source	Assumed daily uptake µg	Low Estimate	High Estimate
Low Environmental	1	85µg	880µg
Environmental	6	510µg	5.3mg
Occupational	40	3.4mg	35mg
High Occupational	220	19mg	200mg
High Pharmaceutical	2000	170mg	1.76g

From Priest 2001

4.3 Excretion

4.3.1 Studies in animals

In animals aluminium is eliminated effectively by urine. Following single intravenous doses of up to 100 µg/kg body weight in rats, aluminium was quantitatively recovered from urine (Wilhelm et al., 1992). It is difficult to obtain an accurate half-life for low oral doses, since the rate of aluminium absorption is low. Data on plasma half-life and on renal clearance have been mainly obtained from parenteral administration generally using high doses of aluminium (Wilhelm et al., 1990). It seems that at doses comparable with human exposure the plasma half-life is less than 1 h. (IPCS p106)

Jouhanneau *et al.* (1997) found that urinary excretion and skeletal retention each accounted for about 0.05% of a single ingested dose of Al^{26} in Wistar rats after 30 days, brain and liver retention 4×10^{-8} and 2×10^{-6} respectively. Co-administration of citrate increased these values 2-5 fold, showing significant variation between individuals. 90% of that excreted in the urine was excreted within the first 48 hours.

4.3.2 Studies in humans

The biokinetics of aluminium in man have been evaluated by Priest and his co-workers (Priest et al., 1991, 1995b, 1996; Talbot et al., 1995) using Al^{26} injected into human volunteers. These authors described the pattern of urinary excretion of the isotope following its intravenous injection as citrate, the effect of excretion on body retention and the relationship between aluminium levels in blood and in urine/faeces. In a first study using a single volunteer (Priest et al., 1991, 1995b, 1996), the authors confirmed that aluminium is overwhelmingly excreted by the urinary route and that most blood aluminium is cleared to excretion. More than half of the Al^{26} had left the blood within 15 min and the decline continued, leaving < 1% in the blood after 2 days. Total excretion up to 13 days was 83% (urine) and 1.8% (faeces), leaving 15% in the body. After 4 months more than 90% was excreted. With increasing time the rate of urinary excretion, as indicated by the fraction of retained aluminium (Rt), decreased with time (t) according to the power function:

$Rt = 35.4\ t^{-0.32} (t > 1)$

At 1178 days after injection about 4% remained in the body; an estimated 94% had been excreted by the urinary route and 2% in the faeces. Faecal excretion most likely represented aluminium that had entered the gastrointestinal tract in bile. The power function calculated for the fraction of aluminium excreted by the urinary route (Ut) at time (t) after intake was:

$Ut = 0.47\ t^{-1.36}$

The excretory clearance rate (ECR) from whole blood (in kg/day) during the first two weeks after injection was expressed as:

$ECR = 42\ t^{-0.14}$

In a second study (Talbot et al., 1995) of shorter duration, but using six male volunteers, inter-subject variability was examined. This showed significant inter-subject variation in the pattern of aluminium excretion. For example, after 5 days an average of 71.8% ± 7.3% (SD) of the injected activity had been excreted in urine (range 62.4-82.9%). Of this total, an average of 59.1% was excreted in the first day, 7.2% in day two, 2.6% in day three, 1.7% in day four and 1.1% in the fifth day. In the same period an average of 1.2% was excreted in the faeces. With respect to blood clearance to urine, the study showed a gradual decrease in the fraction of blood aluminium excreted per unit time, indicating a changing speciation of aluminium in the blood. Overall, the results of the study were wholly consistent with those generated in the single volunteer study, with the first volunteer showing aluminium biokinetics in the middle of the range of results generated by the multi-volunteer study.

Sjögren et al. (1985) studied previously unexposed volunteers and individuals previously exposed to welding fumes containing aluminium at their workplaces for different periods of time. All subjects were exposed to welding fumes containing aluminium during a working day for about 8 h. In previously unexposed individuals urinary aluminium concentration after exposure was increased but decreased to pre- exposure levels after a few days. The half-life of the first phase of excretion was approximately 8 h. In welders exposed for less than 2 years the aluminium concentration decreased during the weekend, the half-life being about 9 days. In welders exposed for more than 10 years urinary concentration did not change despite cessation of exposure. In these welders, the urine half-life was more than 6 months (Sjögren et al., 1988). (IPCS p106-7). This is due to slow release of the previously accumulated levels in tissues, especially bone and liver.

Priest (2001) suggests that biliary (faecal) excretion of trace amounts of Al may exceed urinary excretion in the long term, based on an observed low level plateau after 4 days post ingestion. If true, this would imply an active ability of the biliary system to take up and concentrate Al.

Urinary excretion seems efficient. A short term high exposure will not result in persistently high serum Al, in fact peak Al in serum occurs within about 60 minutes and falls quickly following ingestion as it distributes through tissues and is excreted. In most studies, increases in urinary excretion with dose are proportionally greater than those for serum Al, thus single doses of Al can show very high urine levels accompanied by only modest increases in serum Al (Gitelman 1995). Nagy and Jobst (1994) noted that while urinary Al levels increased in parallel to increasing dose of a single antacid administration, serum levels did not, although they admit that serum Al levels are

considerably influenced by time of sampling, a critical point noted by Priest (2001). Table 2 suggests that serum Al doubles during longer-term antacid use across a range of doses, again suggesting excess urinary capacity. This may be because of a different serum speciation profile at higher serum levels involving greater binding to smaller molecular weight compounds. Serum levels are very high only in cases of renal insufficiency or moderately high with chronic high exposure i.e. inhalational.

As an example, Riihimaki *et al.* (2000), examined serum and urinary Al in welders, dividing them into three groups: referents (mild steel welders), low exposure and high exposure. Respective group median serum Al levels were: 0.08, 0.14, and 0.46 umol/l, and the corresponding urinary levels were 0.4, 1.8, and 7.1 µmol/l. So the serum Al levels increased from referents by factors of approximately 2 and 6 respectively, and in urine by factors of 4 and 18. Relationships between serum and urinary Al levels can be seen in table 2.

5. Effects on laboratory mammals and in vitro test systems

5.1 Single exposure

The acute toxicity of metallic aluminium and aluminium compounds is low, the reported oral LD_{50} values being in the range of several hundred to 1000 mg aluminium/kg body weight per day. LC_{50} values for inhalation have not been identified. (IPCS p5)

Table 8 shows variation in LD_{50} values by Al compound, animal speciaes and route of administration. Especially notable is the difference between intraperitoneal doses and oral doses.

Table 8: LD_{50} values for various aluminium compounds

Compound	Species	Route of administration	LD_{50} (mg Al/kg b.w.)	Reference
$AlCl_3$	mouse (male	oral (gavage)	770	Ondreicka
$Al_2(SO_4)_3$	Dobrá Voda)		980	*et al*. (1966)
$Al(NO_3)_3$	mouse (Swiss;	oral (gavage)	286	Llobet *et al*.
	20/sex)	i.p.	133	(1987)
$AlCl_3$		oral (gavage)	222	
		i.p.	105	
$Al_2(SO_4)_3$		oral (gavage)	> 730	
		i.p.	40	
$AlBr_3$		oral (gavage)	164	
		i.p.	108	
$Al(NO_3)_3$	rat (Sprague-	oral (gavage)	261	Llobet *et al*.
	Dawley, 20/sex)	i.p.	65	(1987)
$AlCl_3$		oral (gavage)	370	
		i.p.	81	
$Al_2(SO_4)_3$		oral (gavage)	> 730	
		i.p.	25	
$AlBr_3$		oral (gavage)	162	
		i.p.	82	

5.2 Short-term studies

In short-term studies in which an adequate range of end-points was examined following exposure of rats, mice or dogs to various aluminium compounds (sodium aluminium phosphate, aluminium hydroxide, aluminium nitrate) in the diet or drinking-water, only minimal effects (decreases in body weight gain generally associated with decreases in food consumption or mild histopathological effects) have been observed at the highest administered doses (70 to 300 mg aluminium/kg body weight per day). Systemic effects following parenteral administration also included kidney dysfunction.

There have been several repeated dose toxicity studies in which a wide range of end-points, including clinical signs, food and water consumption, growth, haematological and serum analyses, tissue and plasma concentrations of aluminium, histopathology, have been examined following oral exposure to various aluminium compounds. There were no treatment-related effects in rats fed up to 288 mg Al/kg body weight per day as sodium aluminium phosphate or 302 mg Al/kg body weight per day as aluminium hydroxide in the diet for 28 days (Hicks et al., 1987). In a subchronic study in which aluminium nitrate was administered in drinking-water to rats, the only effect observed was a significant decrease in body weight gain associated with a decrease in food consumption at 261 mg Al/kg body weight per day. (NOEL = 52 mg Al/kg body weight per day) (Domingo et al., 1987b).

When small groups of Beagle dogs were given sodium aluminium phosphate for 6 months in the diet, there were no treatment-related effects except for a decrease in food consumption not associated with a decrease in body weight (NOEL = approximately 70 mg Al/kg body weight) (Katz et al., 1984). Similarly, in small groups of Beagle dogs administered up to 80 mg Al/kg body weight per day as sodium aluminium phosphate for 26 weeks, the only treatment-related effect was a sharp, transient decrease in food consumption and concomitant decrease in body weight in males (LOEL = 75 to 80 mg Al/kg body weight per day; Pettersen et al., 1990). (IPCS p111)

Basic Al toxicological data in terms of NOAELs and LOAELs has not increased since the W.H.O. report.

Adequate inhalation studies were not identified. Following intratracheal administration of aluminium oxide, particle-associated fibrosis was observed, similar to that found in other studies on silica and coal dust. (IPCS p6)

Table 9 details results of short term oral administration studies in animals. No new studies have been reported since the W.H.O report.

Table 9: Toxicity of aluminium compounds after repeated oral administration

Protocol description[a]	End-points examined	Results	Reference
5-10 male rats (Weizman strain) per group; $Al_2(SO_4)_3$ (200 or 350 mg Al/kg body weight per day in drinking water), $AlC1_3$ (250 mg Al/kg body weight per day in drinking water), $Al(OH_3)$ (150 mg Al/kg body weight per day by gavage) for an unspecified period; groups of animals that were 5/6 nephrectomized similarly exposed	clinical signs, histopathology (appears to have been limited to animals that died during study), tissue concentrations	periorbital bleeding in 3 of 5 animals at 350 mg/kg body weight per day $Al_2(SO_4)$; tissue and serum levels highest in nephrectomized animals; clinical signs of toxicity and death in all groups of nephrectomized animals; comments: protocol and results poorly documented; inadequate for establishment of effect levels	Berlyne *et al*. -1972
Controls: 56 male Sprague-Dawley rats 10.5 mg Al/kg exposed groups 16 animals, ingesting: aluminium hydroxide, 1079 mg Al/kg diet (29 days) or 1012 mg Al/kg diet plus 4% citrate (29 days), 2688 mg/kg and 4% citrate (12 or 29 days); 24 h prior to sacrifice, all animals injected i.p. with desferrioxamine (DFO) or buffer	aluminium concentrations in tibia, liver, kidney and serum; serum aluminium concentrations after DFO; urinary aluminium excretion with and without DFO treatment; body and organ weight gain and haematological status	five of these measures (concentrations in tibia, liver, and serum and urinary excretion with and without DFO treatment); were highly correlated with oral exposure; changes induced by DFO were very small; ingestion of citrate had small but significant effects on aluminium retention; rats fed citrate weighed less (not associated with differences in intake of feed) and had significantly enlarged kidneys and livers and significantly smaller tibias; haematocrits were inversely correlated to tissue concentrations of aluminium - more evident with oral than parenteral exposure; hepatic iron was elevated with the citrate-containing diets but was only weakly correlated with hepatic aluminium concentrations; comments: comparisons of aluminium exposure in tibias and sera of rats exposed parenterally and orally indicated that 0.01 to 0.04% of dietary aluminium was absorbed; inadequate for establishment of effect levels owing to limited range of end-points examined; primarily an investigation to monitor aluminium body burdens	Greger & Powers -1992

Protocol description[a]	End-points examined	Results	Reference
Administration to groups of 6 rats exposed in a 2x2x2x2 factorial design of diets containing 13 or 1112 mg Al/kg as aluminium hydroxide, citrate (0 or 5.2 mmol/kg diet) and calcium (2.7 or 10.0 g/kg diet) for 30 days; groups of 6 rats exposed in a 4x2 factorial design to 14 or 904 mg Al/kg diet and one of 4 levels of citrate (0, 10, 21 or 31 mmol/kg diet) for 28 days; groups of 7 rats exposed in 2x2x2 factorial design to 9 or 1044 mg Al/kg diet and citrate (0 or 21 mmole/kg diet) sham-operated or with one kidney removed for 28 days	tissue concentrations of aluminium; body and organ weight changes	ingestion of citrate increased retention of aluminium in bone of rats fed 1000 mg Al/kg diet and increased apparent absorption of zinc; when dietary calcium intake was increased from 67 to 250 mmol/kg diet, aluminium concentrations in bone were reduced without a change in growth of rats; reduction in kidney function (by removal of one kidney), which was insufficient to alter growth, increased aluminium retention in bone by 13% in rats fed aluminium; rats fed aluminium retained only 0.01 to 0.5% as much as those injected; comments:authors concluded that tissue concentrations and, presumably, toxicity can be altered by moderate changes in diet and kidney function even though overall retention of orally administered aluminium is low, inadequate for establishment of effect levels owing to limited range of end-points examined; designed primarily to investigate effect of dietary citrate, calcium and decreases in kidney function on absorption of aluminium	Ecelbarger & Greger -1991
Groups of 10 female Sprague- Dawley receiving 1, 26, 52 or 104 mg Al/kg body weight per day as $Al(NO_3)_3$ in drinking water for 28 days	clinical signs, food and water consumption, growth, haematological and serum analyses, tissue and plasma concentrations of aluminium, histopathology	no effects on any end-points examined except for mild histopathological changes in the spleen and liver of high dose group (hyperaemia in the red pulp of the spleen and liver; periportal lymphomonocytic infiltrate in the liver); dose-dependent accumulation of aluminium in spleen, heart and gastrointestinal tract; comments: well-conducted repeated dose toxicity in which a wide range of end-points was examined, though short term; NOEL = 52 mg Al/kg body weight per day; LOEL = 104 mg Al/kg body weight per day (aluminium nitrate)	Gómez *et al*. -1986

Protocol description[a]	End-points examined	Results	Reference
Groups of female Sprague-Dawley rats receiving 0, 26, 52 or 261 mg Al/kg body weight per day as $Al(NO_3)_3$ in drinking-water for 100 days	clinical signs, food and water consumption, organ and body weights, haematological and serum analyses, tissue and plasma concentrations of aluminium, histopathology	significant decrease in body weight gain at highest dose associated with decrease in food consumption; no dose-dependent accumulation of aluminium in tissues; comments: well-conducted repeated dose toxicity in which a wide range of end-points; LOEL = 261 mg Al/kg body weight per day; NOEL = 52 mg Al/kg body weight per day for subchronic period of exposure	Domingo *et al*. (1987b)
Groups of Beagle dogs (4/sex) administered 0, 0.3, 1.0 or 3.0% sodium aluminium phosphate in the diet for 6 months (118, 317 and 1034 mg/kg body weight per day in males and 112, 361 and 1087 mg/kg body weight per day in females	clinical signs, food and water consumption, organ and body weights, haematological and serum analyses, urinalysis, ophthalmological examinations, tissue and plasma concentrations of aluminium, histopathology	statistically significant decreases in food consumption in females but no associated decrease in body weight; no other treatment-related effects; comments: range of end-points examined; subchronic period of exposure for dogs; small group sizes; NOEL = 1087 mg/kg body weight per day (approximately 70 mg Al/kg body weight per day)	Katz *et al*. -1984
Groups of Beagle dogs (4/sex) administered 0, 10, 22 to 27 or 75 to 80 mg Al/kg body weight per day as sodium aluminium phosphate in the diet for 26 weeks	clinical signs, food and water consumption, organ and body weights, haematological and serum analyses, urinalysis, ophthalmological examinations, tissue and plasma concentrations of aluminium, histopathology	sharp, transient decrease in food consumption and concomitant decrease in body weight in high-dose males; in same group, decrease in testes weight and histopathological changes in the liver and kidney considered to be secondary to decreased food consumption; slight increase in concentration of aluminium in the brain in high-dose females but not males; comments: wide range of end-points examined; subchronic period of exposure for dogs; small group sizes; minimal toxicity at the highest dose; LOEL = 75 to 80 mg Al/kg body weight per day	Pettersen *et al*. -1990

Protocol description[a]	End-points examined	Results	Reference
Groups of 25 male Sprague-Dawley rats fed control diets or 30 000 mg/kg KASAL I (6% aluminium-sodium aluminium phosphate), 7000 or 30 000 mg/kg KASAL II (13% aluminium-sodium aluminium phosphate) or 14 470 mg/kg aluminium hydroxide for 28 days (5, 141, 67, 288, 302 mg Al/kg body weight per day, respectively)	clinical signs, food and water consumption, organ and body weights, haematology and clinical chemistry urinalysis, ophthalmological examinations, concentrations of aluminium in the femur, histopathology	no treatment-related effects or significant deposition of aluminium in bone; comments: wide range of end-points examined; short-term exposure; no effects at 141 mg Al/kg body weight per day KASAL I; NOEL for KASAL II = 288 mg Al/kg body weight per day; no effects at 302 mg Al/kg body weight per day aluminium hydroxide	Hicks *et al*. -1987
Groups of 15 albino male rats administered aluminium sulfate (0, 17, 22, 29, 43, 86 and 172 mg Al/kg body weight) and potassium aluminium sulfate (43 mg Al/kg body weight, 29 mg Al/kg body weight) in deionized water for 21 days; 5 rats killed weekly	histopathological examination of heart, liver, kidney, brain, testes, stomach and femur	dose-related cytotoxic effect in the liver - cytoplasmic degeneration at 17 to 29 mg Al/kg body weight with multifocal degeneration and fibrous tissue proliferation at higher doses. Dose-related effects in the kidney at 17 mg Al/kg body weight per day as aluminium sulfate, slight swelling of the tubules. With increased dose, increased swelling and degeneration of the cortical tubules. Degeneration of the nerve cell at 29 and 43 mg Al/kg body weight per day aluminium sulfate and potassium aluminium sulfate, respectively, which was more severe at higher doses. Some evidence of spermatological cell decrease at doses of 43 mg Al/kg body weight per day and above. Multifocal degeneration and decalcification at 43 mg Al/kg body weight per day and above for both salts, which increased with increasing dose; degeneration of calcified bone and irregularity of osteoblasts in animals exposed to 86 and 171 mg Al/kg body weight as aluminium sulfate. Hyperplasia and ulceration of stomach at highest doses. Comments: difficult to verify reported effect levels based on limited information presented in paper.	Roy *et al*. (1991b)

From (W.H.O. 1997),

[a] Strain, number of animals/group and vehicle specified, where available; doses reported as mg/kg body weight, unless specified

5.3 Reproductive and developmental toxicity

Studies are inedequate to allow useful reporting of reproductive toxicity of Al.

A review of 14 studies which included 4 different Al compounds administered by 4 different routes (gavage, feed, intraperitoneal injection, and subcutaneous injection) with total doses ranging from 13.5 to 8,400 mg/kg reported that fetal Al levels were not increased in 6 of 7 studies and pup Al levels were not increased in 4 of 5 studies in which they were measured.

No overt fetotoxicity was noted, nor were general reproductive parameters changed after gavage treatment of rats with 13, 26 or 52 mg aluminium/kg body weight per day (as aluminium nitrate). However, a dose-dependent delay in fetal growth was noted with LOAEL for females at 13 mg/kg and in male offspring at 26 mg/kg. The lowest-observed-adverse-effect level (LOAEL) for developmental effects (decreased ossification, increased incidence of vertebral and sternebrae terata and reduced fetal weight) was 13 mg/kg (aluminium nitrate). These effects were not observed at much higher doses of aluminium hydroxide. There were reductions in postnatal growth at 13 mg/kg (aluminium nitrate), although maternal toxicity was not examined. In studies on brain development, grip strength was impaired in offspring of dams fed 100 mg aluminium/kg body weight as aluminium lactate in the diet, in the absence of maternal toxicity. (IPCS p6)

Oral Al lactate (400mg/kg/day) administered orally to pregnant rats during the second and third weeks of gestation resulted in reduced locomotor coordination and the operant conditioning test performance in the pups, in the absence of any effect on litter size, mortality rate, and weight gain (Muller *et al.* 1990). Subcutaneous Al administered to dams can reach the brains of fetuses and of sucklings (Yumoto *et al.* 2001) but no similar observations from orally administered Al^{26} have been reported. Borak and Wise (1998) reviewed 14 similar studies of maternal –fetal/neonatal Al transfer which included 4 different Al compounds (hydroxide, chloride, lactate, and citrate) administered by 4 different routes (gavage, feed, intraperitoneal injection, and subcutaneous injection) with total doses ranging from 13.5 to 8,400 mg/kg. Fetal Al levels were not increased in 6 of 7 studies and pup Al levels were not increased in 4 of 5 studies in which they were measured. Poulos *et al.* (1996) observed renal and gastric damage in Al-treated dams, pointing out that "it is impossible to determine the cause of any neuropathology in the pup in a system where Al delivery overlies a background of multisystem defect and altered maternal homeostasis", and underlining the importance of controlling for background pathology which may secondarily promote neurotoxicity. In this study, though, the rats were fed Al as lactate at 3.2g/litre in drinking water, a very high dose of Al and presumably quite acidic water.

5.4 Other effects

There is no indication that aluminium is carcinogenic. It can form complexes with DNA and cross-link chromosomal proteins and DNA, but it has not been shown to be mutagenic in bacteria or induce mutation or transformation in mammalian cells in vitro. *Chromosomal aberrations have been observed in bone marrow cells of exposed mice and rats. (IPCS p6).* No studies examining carcinogenicity of Al were found, and no incidental reports of tumorigenesis in other toxicity studies have been noted.

Osteomalacia, as it presents in man, is observed consistently in larger species (e.g., dogs and pigs) exposed to aluminium; a similar condition is observed in rodents. These effects appear to occur in all species, including humans, at aluminium levels of 100 to 200 µg/g bone ash. (IPCS p7). Effects are only observed with intraperitoneal or intravenous administration and seem to occur at doses of 1-10mg/kg/day (W.H.O. 1997). Al is taken up by parathyroid cells complexed with transferrin and inhibits PTH secretion but not production (Smans *et al.* 2000).

"Pharmacological doses" of Al chronically fed to mice caused lymph node hypertrophy, a finding supported in vitro, although spleen cell cultures were unaffected (Lauricella *et al.* 2001). This inconsistent picture nonetheless suggests the possibility of immunological effects of chronic large doses of Al taken orally.

5.5 Neurotoxicity

There is considerable evidence that aluminium is neurotoxic in experimental animals, although there is considerable variation among species. In susceptible species, toxicity following parenteral administration is characterized by progressive neurological impairment, resulting in death with status epilepticus (LC_{50} = 6 µg Al/g dry weight of brain). Morphologically, the progressive encephalopathy is associated with neurofibrillary pathology in large and medium size neurons predominantly in the spinal cord, brainstem and selected areas of the hippocampus. These tangles are morphologically and biochemically different from those that occur in Alzheimer disease. Behavioural impairment has been observed in the absence of overt encephalopathy or neurohistopathology in experimental animals exposed to soluble aluminium salts (e.g., lactate, chloride) in the diet or drinking-water at doses of 200 mg aluminium/kg body weight per day or more. (IPCS p6)

5.5.1 Neurobehavioural effects

(Bowdler *et al.* 1979) found that repeated oral gavage of Al leading to high brain Al was associated with rapid general activity, decreased ability to maintain roto-rod activity, and increased sensitivity to flicker. In general, the lowest dose causing an observable effect was 400mg $AlCl_3$.$6H_20$/kg/day, which is about 45mg Al/kg body weight/day. No effect was observed at 200mg AlCl3 .6H20/kg/day.

Several authors have documented neurobehavioural effects of chronic Al ingestion in rats, though at levels above 200mg/kg body weight, in particular learning deficits. Effects involved impairment of performance on passive (Thorne *et al.* 1986; Connor *et al.* 1988; Wu *et al.* 1998) and conditioned avoidance responses (Yen-Koo 1992; Bilkei-Gorzo 1993; Lal *et al.* 1993; Gonda and Lehotzky 1996). Varner *et al.* (1994) found no similar effect of 50ppm Al fluoride in drinking water for 45 weeks.

Evidence regarding the role of the cholinergic system in Al-induced learning effects is conflicting (Connor *et al.* 1988; Bilkei-Gorzo 1993; Wu *et al.* 1998). While cholinergic activity was reduced following 100mg/kg Al/day from day 5-14 postnatally in rats, measures of learning ability tested at days 50 and 100 were not diminished (Cherroret *et al.* 1992)

(Yokel 1989) found that a conditioned avoidance response in rabbits was reduced more in older than younger rabbits following repeated intravenous Al lactate.

Golub and co-workers have extensively studied the effects of high Al in diet, from conception, on growth, neurobiochemical and neurobehavioural parameters in Swiss Webster mice. The dose was generally 1000 ppm (compared with a high estimated average of 10ppm in human foods). A dose response in reduced brain weight and grip strength was observed when high Al was administered to pubertal mice (Golub and Keen 1999). It is likely these associations would disappear if correctly analysed with body weight as covariate, as occurred in (Golub and Germann 2001). In any case, differences disappeared into young adulthood despite continued administration. Lifetime high exposure (1mg Al/g food) did not provide a useful model for Al-induced neurodegeneration in ageing; no notable consistent neurobehavioural differences were observed in treated and control groups, in fact brain Al levels were lower in the treated group as was a measure of susceptibility to oxidative damage (Golub *et al.* 2000). Al enhanced performance of a food-motivated operant task that emphasized motor learning and ability in mice, confirming results of previous studies (Golub and Germann 1998). Other responses are equivocal. High dietary exposure (1mg/gram) from conception to 35 days old on a background of normal but suboptimal nutrition produced retarded growth and subtle deficits in several neurobehavioural parameters when tested in >90 day-old female adults but these effects were not seen at 0.5mg/.gram (Golub and Germann 2001). Following 3 months of intraperitoneal Al gluconate, rats' learning performance was unaffected but the total time to finish a trial and the latency to make the first choice were lengthened in Al-intoxicated rats (Struysponsar *et al.* 1997).

Studying rat dams during gestation, (Poulos *et al.* 1996) substituted 120 mM Al lactate (pH 6.5) for drinking water (3.24gAl/litre) and observed progressive cachexia associated with stomach ulceration, decreased renal cortical thickness and stone formation. They caution that high Al in water may cause adverse gastric effects and reduced feeding or absorption, confounding results in studies where high Al levels are administered orally. Similarly, in the neurobehavioural studies cited, the possible role of organ damage was not evaluated sufficiently to be eliminated as a confounding effect (W.H.O. 1997).

5.5.2 Neurophysiological effects

The only primate sudies are those of Sarin and co-workers (1997; 1997), who administered high oral Al (25mg/kg body wt.) chronically to monkeys. They observed a decreased brain lipid content, increased lipid peroxidation and other indices of decreased membrane integrity including some membrane-bound enzymed activities, and results suggest modifications in intracellular calcium homeostasis. No behavioural parameters were measured.

Using in vitro methods, (Gandolfi *et al.* 1998) report that Al modifies calcium uptake in the endoplasmic reticulum (ER), accelerates calcium release from mitochondria and strongly inhibits calcium-ATPase activity with a consequent high-level calcium accumulation inside the cell and suggest that Al neurotoxicity may be related to an alteration of the intracellular calcium regulatory system. The lowest concentration to show an effect was about 25μM. However (Anghileri *et al.* 1994) found no disturbances in calcium metabolism on an organ level in rats fed high Al diets for 6 months. Al-induced toxicity in rat hippocampal neurons is independent of calcium receptor activation (Brenner and Yoon 1994).

Long term high levels of Al in drinking water may depress dopamine sysnthesis in rat hypothalamus (Tsunoda and Sharma 1999). However no dose-response was evident; the lowest dose, 5mg/litre, showed the strongest effect.

The neurotransmitter glutamate is recognized as a neuronal excitotoxin when present in excess in the extracellular space. Disturbances of glutamate levels were observed in cultured rat astrocytes treated with Al chloride (Struys-Ponsar *et al.* 2000) and Al enhanced glutamate-induced degenerative changes in rat hippocampal neurons in vitro (Matyja 2000). Intraperitoneal Al in rats regionally altered levels of glutamate and gamma-amino-butyrate, an inhibitory amino acid, and activities of several related enzymes (Navak and Chatterjee 2001). However in vitro work by (Jones *et al.* 1998) suggests that Al and glutamate do not promote the formation of paired helical filaments, which largely comprise one of the two major histopathological features of Alzheimer's disease.

In studies of Al-induced neuropathology, most attention now focuses on Al as a pro-oxidant and/or as an inflammatory agent. (Christen 2000) reviews persuasive although early evidence that AD and other neurodegeneration may be contributed to by lipid peroxidation. Al does not generally undergo redox reactions *in vivo* and does not alone produce an increase in oxidative damage (Bondy and Kirstein 1996). But it can increase the Fe-induced production of reactive oxygen species (ROS) (Xie *et al.* 1996; Mundy *et al.* 1997; Campbell *et al.* 1999) and Fe-induced peroxidation of membranes in vitro (Xie and Yokel 1996), perhaps by directly altering membrane structure (Gutteridge *et al.* 1985). These two findings have been replicated *in vivo* (Fraga *et al.* 1990; Bondy and Kirstein 1996). However Al has been shown to act as both pro- and antioxidant when added to rat brain homogenates, presumably depending on the integrity of the membranes (Oteiza *et al.* 1993), and did not increase Fe-mediated hydroxyradical production *in vivo* (Xie *et al.* 1995). Large oral doses of Al also decreased cerebral and hepatic catalase and superoxide dismutatse activity in young chicks but did not cause increased lipid peroxidation (Swain and Chainy 1998). Chronic (6wk) feeding of high Al in rats resulted in a decrease of thiols, glutathione reductase and ATPase in brain homogenate, an environment which can be considered deficient in anti-oxidants.

In vitro studies suggest a possibly vicious circle; ROS increased beta-amyloid aggregation (Dyrks *et al.* 1992) and beta-amyloid and fragments can produce increased ROS (Hensley *et al.* 1994), and beta-amyloid-induced ROS formation was increased by Fe and Al (Bondy *et al.* 1998). Although it should be borne in mind that Al levels used in these studies are far higher than physiological levels, it is not yet certain that artefact is behind studies showing Al and Fe associated with the neurofibrillary tangles (NFTs) and senile plaques (SPs) seen in AD brains. Lipid peroxidation of rat synaptosomes in vitro resulted in accumulation of Al (Amador *et al.* 1999).

(Campbell *et al.* 2001) hypothesize that the Al sulphate-induced increase in ROS generation is due to a glial response to extracellular colloidal Al particles. Previously it was demonstrated in vitro that glioma cells are much more sensitive to Al-induced ROS increase than are neuroblastoma (Campbell *et al.* 1999). Glial cells also seemed to be the major targets of Al action in a study by (Platt *et al.* 2001), who observed a greater inflammatory response in Al-injected rats compared to controls and a degeneration of cholinergic terminals in the cortex and hippocampus. They suggest that these features may represent a link between Al and AD, although the review of (Lukiw and Bazan 2000) omits any discussion of Al and inflammation in AD pathogenesis.

In rabbits, Al enhanced frontal cortical expression of glial fibrillary acidic protein (GFAP) which has been shown to be associated with gliosis, a generic response of the CNS to neural injury (Yokel and Ocallaghan 1998). This increased expression was moderated by injection of trivalent cation chelators. However Neill *et al.* (1996) found no evidence for any effect of aluminium on amyloid precursor protein expression or processing in rats.

(Tsunoda and Sharma 1999) fed Al sulphate in water to mice and noted that expression of mRNA for tumour necrosis factor-alpha in cerebrum was significantly increased among treated groups in a dose-dependent manner. This factor is a cytokine involved in the response to neuronal damage and may reflect microglial cell activation as part of the inflammatory response. The lowest doses were 5 and 25 ppm for one month.

6. Effects on humans

6.1 Acute toxicity

It is unlikely that Al is acutely toxic to man, given the high oral doses sometimes taken medically. Woodson (1998) reports the case of a patient with normal renal function who took, on average, 6.3g/day elemental Al as antacid over 8 years, presenting with vitamin D-resistant osteomalacia. This is one of the highest documented human intakes, both acutely and chronically.

6.2 Neurological effects

6.2.1 Acute effects

In non-medically exposed people with normal renal function, no acute pathogenic effects have been described after exposure to aluminium.

The closest we have to descriptions of acute toxicity of aluminium are those of acute intoxication associated with dialysis and renal insufficiency. Cumming *et al.* (1982) report an episode of patients on continuous ambulatory peritoneal dialysis in which a batch of dialysate with high Al had been used. Plasma Al exceeded 484µg/litre and patients reported anorexia, nausea, vomiting, cramp-like abdominal pain, weight loss and general malaise. Neurological symptoms were not a feature here but may be seen when plasma Al exceeds 500µg/litre and tend to a very rapid onset of features including agitation, confusion, myoclonic jerks and grand mal seizures. Speech disturbance is sometimes an early sign. In children, regression of motor and verbal skills are the main features (Schrier and Gottschalk 1997). Recovery appears to be complete following reduction in Al levels, and there have been no consistent reports of subsequent symptomatology, neurological or otherwise.

Rarely, perfusion of the bladder with alum is used to stop persistent haematuria. Little is absorbed but where renal function is compromised it has caused reversible encephalopathy in a 4 year old with acute renal failure (Moreno *et al.* 1991) and intoxication and death in an elderly man (Shoskes *et al.* 1992). It is unlikely that this treatment is used any longer, except in error, in renal patients.

6.2.2 Subchronic effects

Six weeks after surgery to reconstruct bone in the skull using cement containing Al, a patient exhibited signs typical of dialysis dementia. Postmortem analysis showed elevated Al levels in brain tissue, the episode apparently the result of direct contact of the cement with a cerebrospinal fluid leakage (Reusche *et al.* 2001) although this was not the eventual cause of death. Two similar non-fatal cases were described by Leveque *et al.* (1996)

The only report of Al levels and nuerobehavioural parameters in normal subjects is that of (Bowdler *et al.* 1979). They tested elderly subjects and found that higher serum Al levels were associated with impaired visuo-motor coordination, poor long-term memory, and increased sensitivity to flicker. However blood was taken once only, immediately following testing, but more worryingly Al levels in serum appear to be between 2 and 3 orders of magnitude higher than those typically reported (see table 4). Not all subjects were included in analysis and no response gradient was reported.

In England, a population of about 20,000 individuals was exposed for at least 5 days to increased levels of aluminium sulphate, accidentally placed in a drinking-water facility. The highest measured level of Al in tap water was 620mg/litre, although concentrations dropped rapidly as the polluted water ran through the system. Case reports of nausea, vomiting, diarrhoea, mouth ulcers, skin ulcers, skin rashes and arthritic pain were noted. Three years after the incident, Altmann and colleagues (1999) (previously circulated to Lowermoor subgroup as paper L24) were asked to investigate 55 residents who claimed to have suffered cerebral damage. In 1999, their report concluded that "people who were exposed to the contaminated water at Camelford suffered considerable damage to cerebral function". There is no scientific description of a similar effect of short term high exposure to Al, and the conclusion was widely criticized mainly because exposure was not known, controls were inadequate and the study cohort was self-selected. But in this case the water chemistry was complex. There was low pH, high copper, zinc and lead as well as Al and sulphate, and doubtless other perturbations of the normal water chemistry.

6.2.3 Chronic neurological effects – intoxication and dialysis encephalopathy

Aluminium intoxication developed over weeks or months in patients with chronic renal failure when dialysis fluids or parenteral solutions contained aluminium (Alfrey et al., 1972; Klein, 1991), or when the main source was aluminium-containing oral phosphate binders. In patients suffering from renal failure, increases in serum and tissue aluminium concentration were observed. The increased aluminium content in brains of patients with renal failure seems to be the major etiological factor in the development of the neurological syndrome termed either dialysis encephalopathy or dialysis dementia. Aluminium intoxication is caused by using haemodialysis fluids made from tap water without removal of the aluminium (Elliot et al., 1978). After the introduction of water treatment with a combination of filtration, softening, carbon absorption, reverse osmosis and de-ionization, these clinical syndromes were prevented. Nephrologists limit the exposure to aluminium from dialysis fluids and drugs. This follows the introduction of guidelines in the USA, Canada, Japan and the EEC. As a consequence, in most dialysis centres the dialysis fluids are monitored and the aluminium level is kept below 0.4 µmol/litre (10 µg/litre). Aluminium-free phosphate-binding agents such as calcium carbonate are preferably used for oral medication. The same clinical syndromes have been described in patients with renal impairments, including premature infants who have not been dialyzed, and are a consequence of aluminium accumulation from aluminium-containing pharmaceutical products and parenteral solutions (Finberg et al., 1986).

Dialysis encephalopathy is a complication of prolonged haemodialysis first described in 1972 (Alfrey et al., 1972). The main symptoms are speech disorder followed by the development of dementia, convulsions and myoclonus. The mean duration of dialysis was 48 months and the dialysis fluids were made with untreated tap water. Elevated aluminium contents were found in the brain, muscle and bone tissues of the affected patients. The same findings were reported from other dialysis centres in Europe and the USA. Many outbreaks of encephalopathy have been described in association with the use of dialysis fluids containing a high concentration of aluminium, usually above 200 µg/litre (Flendrig et al., 1976; McDermott et al., 1978; Alfrey, 1978).

In a study with 55 patients suffering from dialysis encephalopathy in six dialysis centres using a uniform clinical classification, the incidence of dialysis encephalopathy rose significantly with increasing cumulative exposure to aluminium via the dialysate (Schreeder et al., 1983).

Epidemiological studies of dialysis centres in England showed that encephalopathy was almost non-existent in those centres using water with aluminium concentrations less than 50 µg/litre to prepare dialysis fluids. The incidence of encephalopathy rose progressively with higher water concentrations of aluminium. The Registration Committee of the European Dialysis and Transplant Association made a European survey, which showed clusters of encephalopathy in certain areas of Britain, Spain, Greece and Scandinavia. In Britain, 92% of the patients in these areas had been treated with dialysis fluids made from softened tap water (Kerr & Ward, 1988). No signs of overt aluminium toxicity were observed in 27 long-term haemodialysis patients on dialysis fluids containing low aluminium concentrations (Altmann et al., 1989) and these subjects had only mildly elevated serum aluminium levels. However, defects in several tests of psychomotor function, including digit coding, were found. (IPCS p155-6)

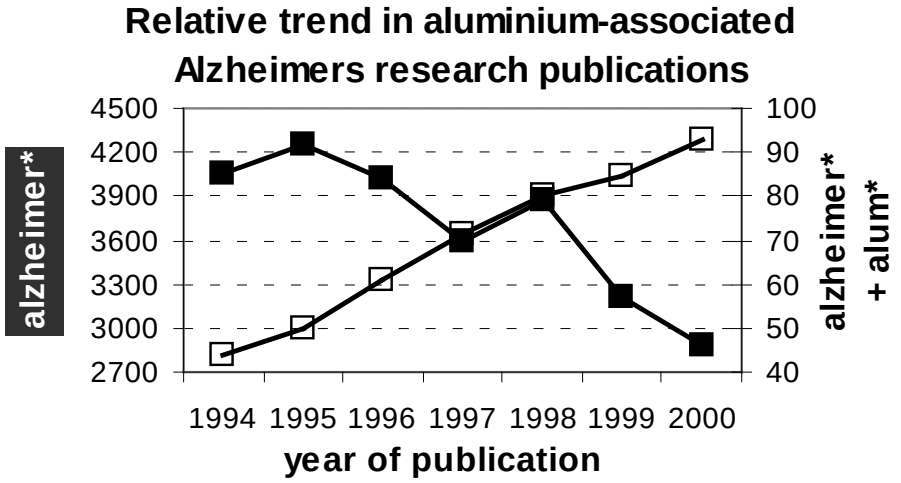
6.2.4 Chronic neurological effects - Aluminium and Alzheimer's disease

It has been hypothesized that aluminium in the drinking-water is a risk factor for the development or acceleration of Alzheimer disease as well as for impaired cognitive function in the elderly. It has also been suggested that stamped fine aluminium powder and fume may be risk factors for impaired cognitive function and pulmonary disease in certain occupations. (IPCS p7)

6.2.4.1 Scientific trends in research

Based on a yearly search of Current Contents, scientific interest in Al as a primary cause of AD is waning, especially relative to general Alzheimer's research (see fig 1). Most effort is being directed at Fe^{2+} mediated oxidative stress and damage as the most proximate causes of AD neurodegeneration (Christen 2000), and most pathophysiological studies of Al now focus on a possible role in augmenting this process.

Figure 1



The WHO report describes six points (summarized, in bold type) on which an association between AD and aluminium is based. Relevant research updates follow each of these summaries.

6.2.4.2 Neuropathological changes on Al administration in animals

1/ Parenteral administration of Al salts in some species of animals results in neurofibrillary changes in neurons and a unique progressive neurological impairment, although the changes differ from those seen in AD ultrastructurally and biochemically.

In Alzheimer's disease (AD) the microtubule-associated protein tau is redistributed abnormally into paired helical filaments (PHFs) forming neurofibrillary tangles (NFT) within cells, which correlate with neuronal destruction and dementia.

Many studies use aluminium *in vivo* and in vitro to induce neurofibrillary changes or major components of AD neurofibrillary tangles, although never using orally administered Al, and no contemporary studies claim their system to be a model for AD development. Rabbits seem most responsive, rats somewhat less so.

Most recent contributions are from Savory and co-workers (Savory *et al.* 1995; Huang *et al.* 1997; Singer *et al.* 1997; Savory and Garruto 1998; Savory *et al.* 1998). Intracisternal administration of Al-maltolate to rabbits resulted in neurodegeneration which displayed a number of immunochemical similarities to NFTs in AD, representing the major components of NFTs in humans. This is probably a result of Al-induced post-translational hyperphosphorylation of neurofilament protein, and this is an action of Al. Strong *et al.* (1996), summarizing, state that this is probably the source of Al-induced neurofilamentous aggregates characteristically seen in cats, rabbits, ferrets and non-human primates.

Rats show neurobehavioural effects of oral Al administration which are associated with disturbed acetylcholine metabolism, which is also seen in AD (Julka *et al.* 1995), but do not show cytoskeletal pathology. They do show many other changes including free radical-mediated cytotoxicity, lipid peroxidation, impairments in glucose utilization, agonist-stimulated inositol phosphate accumulation, reduced cholinergic function, and altered protein phosphorylation (reviewed in Strong *et al.* 1996). Astrocytic function may be a mechanistic target of Al-induced neurotoxicity in the rat (Guo-Ross *et al.* 1999).

6.2.4.3 Aluminium in AD brains and lesions

2/ Elevated Al levels were reported in bulk grey matter from AD-affected brains. However there have also been negative results reported.

3/ Al has been detected in the two histopathological features of AD: intracellular neurofibrillary tangles (NFT) and extracellular senile plaques (SP), as well as in neuronal nuclei affected by neurofibrillary pathology in AD. Again, negative results have also been reported.

At the time of writing the IPCS report, the situation regarding Al content in bulk tissue from AD brains was unresolved and therefore largely uninformative. Methodological issues were at the root of the argument. Bjertness and colleagues (1996) avoided methodological deficiencies such as poor neuropathological assessment, failure to age-match the control samples, geographical heterogeneity in the AD and control populations, failure to control for age and sex, small sample sizes lacking statistical power. They showed no elevation of Al in either frontal or temporal cortex of brains from AD subjects using graphite furnace atomic absorption spectrometry, a very sensitive technique. Neither did they demonstrate correlation between bulk aluminum concentration and the density of SPs and NFTs in frontal and temporal cortices.

Watt (1996) and Makjanic (1997; 1998) used a novel technique to examine Al levels in NFT- and SP-containing microsections, and highlight the confounding issue of staining of AD brain sections. Nuclear microscopy can detect elemental composition of flash-frozen freeze-dried (otherwise unfixed and unstained) tissue sections, down to 15ppm in the case of Al. They detected no levels above this in AD neurons with and without NFTs, AD supporting tissue (presumably containing SPs), control neurons and control supporting tissue.The technique enabled detection of significantly elevated levels of Mn, P, S, Cl, Fe and Zn in AD neurons and surrounding tissue. Notably they also demonstrated that fixing, staining, and especially osmication for electron microscopy, introduces significant Al into the tissue sample. This level of sensitivity is still too low, however, and the results of Andrasi *et al.* (1995), who found consistently higher Al levels across ten gross areas of AD brains vs. controls, would not have been detectable with this method.

Kasa *et al.* (1995), in a careful study, showed that Al was localised in some SP but not others in AD brains, suggesting that Al is not primarily involved in the pathogenesis of SPs. Finally, elevated levels of cations not similarly implicated in pathogenesis have also been detected in SPs at microprobe levels; Zn (Lovell *et al.* 1998) and Fe (Good *et al.* 1992).

Using desferrioxamine to chelate Al in AD brain sections, Murayama *et al.* (1999) suggest that Al binds to NFTs. It is not clear whether this bound Al was the result of contamination of the sections, although exposure of sections to Al resulted in increased Al staining of NFTs.

Although evidence now indicates otherwise, if AD brains or sections truly do contain more Al than controls, the observation is still more than one step away from indicating causation. If Al is truly causative of AD, it must be present in elevated levels in all AD brains, not just some (Savory *et al.* 1996). It may represent an epiphenomenon due to tissue staining or a secondary phenomenon associated with altered permeability of the blood-brain barrier due to amyloid angiopathy in AD or increased uptake from the gut, rather than a primary etiology. Indeed, serum Al was higher in probable-AD-diagnosed patients compared with age- and sex-matched demented and non-demented controls (Zapatero *et al.* 1995), and AD patients absorbed more radiolabelled Al from orange juice than matched controls (Moore *et al.* 2000).

6.2.4.4 Epidemiology

4/ Epidemiological studies have shown an association between aluminium levels in drinking water and prevalence of AD.

Some 20 epidemiological studies have been carried out to test the hypothesis that aluminium in drinking-water is a risk factor for Alzheimer disease, and two studies have evaluated the association between aluminium in drinking-water and impaired cognitive function. Study designs ranged from ecological to case control. Eight studies in populations in Norway, Canada, France, Switzerland and England were considered of sufficiently high quality to meet the general criteria for exposure and outcome assessment and the adjustment for at least some confounding variables. Of the six studies that examined the relationship between aluminium in drinking-water and dementia or Alzheimer disease, three found a positive relationship but three did not. However, each of the studies had some deficiencies in the study design (e.g., ecological exposure assessment, failure to consider aluminium exposure from all sources and to control for important confounders such as education, socioeconomic status and family history, the use of surrogate outcome measures for Alzheimer disease, and selection bias). In general, the relative risks determined were less than 2, with large confidence intervals, when the total aluminium concentrations in drinking-water was 100 µg/litre or higher. (IPCS p7)

Since 1994 there have been five further studies published which examine the relationship between Al in drinking water and dementia or AD. McLachlan *et al.* (1996) was mentioned by the EHC report but it will be useful in the current context to review it here.

Table 10 summarizes epidemiological studies of AD and Al in drinking water.

Table 10: Summary of epidemiological studies of aluminium in drinking-water and dementia or Alzheimer's disease (AD)

Type of study	Exposure measure of aluminum intake	Outcome measure/data source	Results	Reference
Ecological	aluminum in drinking-water (concurrent) 4 seasonal samples	mention of dementia ICD9 290, 290.1 (dementia) 342.0 (Parkinson's disease) 348.0 (ALS); sex-adjusted death certificate	AD only Al Males Females < 0.05 1.00 1.00 0.05-0.2 1.15 1.19 > 0.2 1.32 1.42 PD and ALS - no gradient	Flaten (1990)
Morbidity prevalence case control	aluminum in finished drinking- water; historical	dementia by diagnostic category (not standard) CT scan center records age-sex-adjusted	all males and females RR 1.3-1.5, no dose-response < 65 males and females 1.4-1.7, dose response	Martyn *et al.* (1989)
Morbidity prevalence case control	finished drinking-water aluminum; historical	"cases" were hospital discharges with Dx of AD (ICD9 331.0), presenile dementia (ICD9 290). age/sex/residence-matched controls with other Dx HMRI data base - Ontario	RR from OR, gradient for AD Al RR from OR < 0.01 1.00 0.01-0.099 1.13 0.10-0.199 1.26 > 0.2 1.46	Neri & Hewitt (1991)
Morbidity prevalence	aluminum in finished drinking- water; residence >15 years urinary aluminum and serum aluminum; historical and concurrent	mnemic skills in octogenerarians, urinary and serum Al sample of 800 residents in high & low aluminum areas, 10 AD patients & controls in each area age, sex, education population based	no difference in mean scores of tests for cognitive function, slightly higher serum aluminium in AD in low aluminium areas; similar urinary excretion in AD and controls hypothesis of association not supported	Wettstein *et al.* (1991)
Morbidity prevalence	aluminum in drinking-water; historical	cognitive function in sample of > 65 years by test battery (DSM III) population-based (2792); age, sex, education, ses, Al in water - many sources for the data	probable AD - gradient-adjusted for age, education, residence RR 4.53/100 µg/litre aluminium (NSS); RR corrected to NS with current aluminium measurement	Michel *et al.* (1991)

Type of study	Exposure measure of aluminum intake	Outcome measure/data source	Results	Reference
Morbidity prevalence case control	aluminum in water, pH, calcium	cognitive function	calcium protective RR = 1.2 with pH < 7.3 NS /all other pH values	Jacqmin *et al.* (1994)
Case control	aluminium in drinking-water; residence-weighted historical	pathological; confirmation of diagnosis in all cases and controls no age-sex-education adjustment	RR 1.7 aluminium > 100 µg/litre RR 2.5 aluminium > 100 µg/litre based adjustment for 10-year weighted exposure history	McLachlan *et al.* (1996)
morbidity prevalence	aluminium in drinking water	Males, mention of AD or presenile dementia (ICD-9), death certificate. Controls bronchopneumonia (ICD-9) cause of death. No age-education adjustments. Controlled for pH, SiO2, F in water	RR 2.42 all ages AD - >336µg/litre RR 3.15 aged 75+ AD - >336µg/litre No dose response (J-shaped response curve)	Forbes *et al.* (1995)
morbidity incidence	aluminium in drinking water, exposure as years before diagnosis	106 males clinical diagnosis AD, controls = other dementia, brain cancer, other neurodegeneration, all aged 45-75. Adjusted for age, SiO2.	no increased risk, highest Al (>109µg/litre) vs. lowest Al (<16µg/litre)	Martyn *et al.* (1997)
case control	Al in drinking water, estimates (historical) of long term exposure, variety of Al species	68 elderly clinically diagnosed, age and sex-matched controls. Adjusted for education, ApoE ε4 allele, AD or dementia history	NS for all 16 Al measures except monomeric organic Al at time of diagnosis, OR = 2.67	Gauthier *et al.* (2000)
prospective cohort	Al in drinking-water, time-weighted historical	2658 males and females aged >65 at baseline, 8 year followup Dementia (DSM-IIIR, Mini-Mental State Examination) AD (NINCDS-ARDRA) population-based (3401), adjusted for age, sex, education, place of residence, wine consumption	RR dementia 1.99 for Al>0.1mg/litre RR AD 2.20 for Al>0.1mg/litre high silica levels may be protective	(Rondeau *et al.* 2000)

From (W.H.O. 1997), updated

The Paquid cohort of 2698 men and women in southwestern France, aged >65 at baseline, were tested for probable or possible AD using an internationally accepted set of diagnostic criteria (NINCS-ARDRA) 8 years after recruitment (Rondeau *et al.* 2000). Exposure was based on two recent surveys and a 10 year prior history for as much of the water networks as possible, calculating weighted means based on length of residence and contribution of the relevent water source. Relative risk of AD for subjects exposed to Al concentration greater than 0.1 mg/litre (exposure weighted by length of use of water supply) was 2.20 (1.24-3.84), adjusted for age, sex, educational level, urban vs. rural residence, drinking water silica levels and wine consumption. They found no association of AD with areas using surface water, much of which is often treated with alum, nor did they find an association with use of Al cooking utensils.

This is certainly the most sophisticated and rigorous statistical analysis in any study yet performed, and the sample size is quite large. In fact most of the deficiencies of past studies were avoided here. Obviously post-mortem diagnosis is the gold standard and this cohort may eventually provide such data. As a measure of its quality, note that this paper appeared in American Journal of Epidemiology, the highest impact general epidemiology journal.

However, using stratified groups of Al levels they found no dose response. And the cohort had very few (n=63) subjects in the high Al group (>0.1mg/litre), all living in just 4 of the 70 parishes studied, which is where all (8) of the excess AD cases came from. An important potential confounder not controlled for is family history of dementia. Gauthier *et al.* (2000) showed an odds ratio (OR) of 6.15 associated with having one or more first degree relatives with dementia. When most excess cases come from a small area, such effects may become important. The authors tried to detect such an effect by assessing relative variation of a random “frailty” factor between and within parishes, although with 70 parishes and so few with high Al, any positive result in this study was unlikely. Interestingly, a later study of cognitive decline on the same cohort found a significant interparish correlation (Rondeau *et al.* 2001).

Gauthier *et al.* (2000) conducted a case control study involving 68 AD-diagnosed elderly patients and age- and sex-matched controls, and gathered data on levels of a variety of Al species and parameters in drinking water at onset of disease and estimates of long-term exposure (1945-onset). Tests of association with AD were made for exposure levels of five Al parameters/species determined both at time of onset of disease and from 1945–onset. Of the ten tests, all were non-significant except that for levels of monomeric organic Al measured at disease onset (OR=2.67, 1.04-6.90). There was no significant association with long term exposure to this species, which might have been expected. This suggests the possibility of a positive result due to chance because of multiple comparisons. In general, though, ORs for the more bioavailable Al species were elevated but not significantly so. Analyses were controlled for education level, ApoE epsilon4 allele and AD or dementia among first degree relatives. This appears to be a relatively well carried out study whose conclusions are weakened by small sample size. Were the sample larger, this study might usefully have assessed interactions of Al levels with other factors controlled for, i.e. the genetic ones: family history and ApoE genotype, and environmental ones: education level and socioeconomic status.

In Ontario, McLachlan *et al.* (1996) compared autopsy-verified AD brain material from 385 patients with controls comprising 125 with no histopathology and 170 with non-AD neurodegenerative diseases, so the outcome measure was as precise as possible. The exposure measure was Al concentration in drinking water at last residence and this was improved by including 10-year weighted residential histories. A significant odds ratio of 1.7 was reported for Al concentrations >0.100mg/litre which increased as the cutoff increased, reaching a maximum of 7.6 at >0.175mg/litre, providing evidence for a dose-response relationship. Although the study did not control for age, sex, education, or socioeconomic status and so for reasons given above must be regarded with caution, the precision of the outcome and exposure data and the magnitude of the ORs make this one of the most persuasive studies yet reported.

Again in Ontario, an interaction of age and Al was suggested in studies using death certificates (Forbes *et al.* 1995) on which AD or presenile dementia (ICD-9) was recorded as the underlying cause (n=3161), using as controls death certificates where bronchopneumonia was the underlying cause. The exposure measure is probably made on the water supply for the residence at time of death, but this is not clear. When analysis was restricted to individuals of increasing age groups, the odds ratios increased markedly, retaining statistical significance, such that the OR for AD for all ages was 2.42 (1.42-4.11) for high Al levels (>0.336mg/litre) vs. low (<0.067mg/litre) In individuals over 75 the figure was 3.15 (1.85-5.36), and for people over 85 was 7.07 for high Al levels (>0.250mg/litre) vs. low after adjustment for other water quality variables.

The Al-level data collection in this study is well done, but the study is deficient in that factors such as age, sex, education, socioeconomic status were not included in the analysis, which is important partly because there were not many individuals in the high Al group and they may have been residing in the same general area. Death certificate data with regard to AD is an imprecise outcome measure because it fails to exclude dementia from other causes, the most common being cerebrovascular degeneration. The reporting might also be criticised on the grounds of selective assignment of Al-level cutoffs. The most populous category (by a factor of 4) was 0.068-0.200mg/litre, which almost showed a protective effect (OR=0.92, 0.84-1.01). If they had used the cutoff in the study cited in support of their findings, which was 0.100mg/litre (McLachlan *et al.* 1996), their results for 0.100-0.200mg/litre would almost certainly have been negative, contradicting the results of that study.

The World Health OrganizationWorld Health Organization maximum recommended level of Al in drinking water is 0.200mg/litre, a level arrived at for aesthetic reasons such as colour and turbidity. Al levels above the WHO recommended levels may be associated with poor water quality. It is possible that in some areas this may be a proxy for low education or socioeconomic status, hence the importance of controlling for these factors. These Al levels are probably uncommon; such consistent high levels have not been reported anywhere else in the epidemiological literature.

One of the most cited studies is that of Martyn *et al.* (1989) which found an OR of 1.5 associated with Al levels >0.110mg/litre compared with levels <0.010mg/litre. However in 1997, Martyn *et al.* (1997) found no evidence of increased risk of AD from aluminum in drinking water at concentrations above 0.110 mg/litre. The study compared 106 men aged 42-75 with clinically diagnosed AD against controls diagnosed with other dementia, brain cancer or other neurodegeneration, and exposure

was ascertained in terms of years before diagnosis. So, although exposure was quite well documented, education and socioeconomic status were not controlled for and the diagnostic criteria for AD could not have been uniform.

The study of 109 presenile (<65 years old) AD-diagnosed patients and matched controls by Forster *et al.* (1995) found no association with Al intake from medicines or drinking water. Although controlled for family history, it lacked power and involved drinking water Al levels too low to be likely to show an effect, as few concentrations exceeded 0.050mg/litre. It. Flaten (2001) suggests that the effects of Al on AD may be greater in senile rather than presenile patients, and it is true that genetic factors are more important in presenile AD, so that environmental factors predominate in senile AD (Rondeau *et al.* 2000).

Rondeau *et al.* (2000) hypothesize a threshold effect of Al to explain their results. This is not supported biologically and in their case is unnecessary because their data is insufficient to show a dose response, in contrast with that of McLachlan *et al.* (1996). But the possibility of a threshold effect is supported perhaps by Forbes *et al.* (1995).

In a test of the proposition that increased Al exposure is necessary for the development of AD, O'Mahony *et al.* (1995) used a sensitive index of exposure, examining Al content of trabecular bone in clinically diagnosed AD patients (n=7) versus age matched controls, and found significantly lower levels in the AD patients.

Given what is known about Al biokinetics in man, the issue of AD and Al in drinking water should be settled by an examination of AD incidence in antacid users. Although today most antacid preparations contain little or no aluminium hydroxide, probably as a result of the concern over AD, prior to about 1990 most contained principally Al hydroxide and a heavy user may ingest 1000mg per day or more Lione (1985). Flaten (2001) reviews 13 studies relating to AD and known or surmised (gastroduodenal ulcer patients) antacid use, mostly done before 1992 and mostly case control studies. Invariably they indicate no significant increased incidence of AD associated with antacid use, although most lack power. However, some, described below, have large sample sizes.

Colin-Jones *et al.* (1989) examined death certificates of peptic ulcer or dyspepsia sufferers originally recruited to test the effects of cimetidine. 55% were aged over 50 years old at recruitment. It is presumed that most took aluminium-containing antacids, some in large amounts for long periods, especially compared with normal Al intake. After 9 years of follow-up, over 2000 had died. Of these, no cause was listed as presenile dementia and only one was AD, which matches the number expected from national rates. Although the study is uncontrolled and the inadequacy of death certificates in recognising AD is acknowledged, were Al to play any significant role in AD pathology, one would expect a group with Al exposure often 10-200 times normal daily intake to show a marked number of excess deaths with AD (or other dementia) as the cause, especially in light of reports of dose-dependence in the epidemiological literature.

Similarly the Scottish hospital record linkage study by Ryan (1994) showed no significant relative risk greater than 1 of a subsequent hospital diagnosis of dementia given peptic ulcer diagnosis at index admission. 101,104 patients from 1968 to 1977 (approximately 1 in 25) were divided among 10 putative dementia-risk groups, one of which was “peptic ulcer”, and one reference control group.

Finally, The Canadian Study of Health and Aging (Anonymous 1994) compared 258 diagnosed AD cases with controls matched for age, study center and residence in community or institution and controlled for family history, education level, head injury, anti-inflammatory drµg use and arthritis histories, and found no significantly increased relative risk of AD associated with antacid use, nor did they find that peptic ulcer was over-represented among AD cases.

6.2.4.5 Desferrioxamine

5/ (McLachlan *et al.* 1991) showed that progression of AD may be slowed by treatment with a trivalent metal cation chelator, desferrioxamine. However this compound also chelates iron which has been linked to free radical damage in AD, or it may have acted through an anti-inflammatory mechanism, or the results may have been biased because the researchers were not blind to treatment vs. placebo groupings.

Since then, several groups have investigated the effects of desferrioxamine in animals, but none has resolved the question of whether the effect was due to its action on Al or otherwise.

Desferrioxamine markedly slowed and probably partially reversed Al-induced neurofibrillary degeneration in rabbits (Savory *et al.* 1994). This reversal finding was confirmed using the same *in vivo* system by demonstrating reduced staining with four monoclonal antibodies to tau protein aggregates (all of which stain NFTs in AD brains) following desferrioxamne treatment (Savory *et al.* 1998).

Gomez *et al.* (1999) administered several chelators of trivalent cations to rats following oral Al loading and showed that oral 1,2-dimethyl-3-hydroxypyrid-4-one (L1) was the most effective in enhancing urinary Al excretion. These types of chelators were also most effective in reducing brain Al in Al-loaded rats (Florence *et al.* 1995). This is useful since the initial clinical trial administered desferrioxamine twice daily intramuscularly for two years.

Repeated intramuscular desferrioxamine can modestly reduce the half life of Al in rat brain (Yokel *et al.* 2001).

6.2.4.6 In vitro *studies*

6/ Al promotes aggregation of beta-amyloid protein (major component of SPs) in vitro and interacts with purified paired helical filament tau-protein (microtubule-associated protein, major component of NFTs) and induces formation of epitopes (antibody recognition sites) found in NFTs but fails to induce filament formation in vitro.

More recently, the possible role of Al in plaque formation has been investigated. Al induced conformational changes in beta-amyloid protein and enhanced its aggregation in vitro (Fasman *et al.* 1995; Vyas and Duffy 1995; Laczko *et al.* 1996; Bondy and Truong 1999), and its deposition on cell surfaces (Kawahara *et al.* 1994). These aggregations were dissolved by desferrioxamine which chelates Al (Kawahara *et al.* 2001). However Fe and Zn, never similarly implicated in AD pathogenesis, also enhance beta-amyloid aggregation (Esler *et al.* 1996). Al may inhibit degradation of beta-amyloid protein in the brain (Banks *et al.* 1996).

In vitro, Abreo *et al.* (1999) report increased uptake of Fe, expression of NFT protein (tau) and inhibition of cell growth after plating human neuroblastoma cells in medium containing Al transferrin (Al-Tf) and Al citrate. Abnormally hyperphosphorylated tau forms aggregated insoluble paired helical filaments (PHF) in AD, which persist and appear in NFTs. Al-EDTA promoted phosphorylation of tau in neuroblastoma cells (Guy *et al.* 1991) but Al chloride failed to do this in cultured neurons (Mattson *et al.* 1993). Shea and co-workers (Shea and Beermann 1994; Shea *et al.* 1995; Shea and Husain 1995; Shea *et al.* 1997) suggest that Al affects several aspects of neurofilament biochemistry: inhibiting the incorporation of newly synthesized subunits into the cytoskeleton of axonal neurites, their degradation and dephosphorylation, their translocation into axonal neurites, and fostering the accumulation of phosphorylated NFs within perikarya. Phosphorylated tau is much more sensitive to Al-induced aggregation (Li *et al.* 1998).

Harrington *et al.* (1994) observed an increase in hyperphosphorylated tau associated with increased brain Al in renal dialysis patients.

Incubation of rat cerebral explant culture with Al increased Al staining inside neurons and immunoreactivity with antibodies which recognizes NFT epitopes including Alz-50, PHF-1 and Tau-2 (Jones and Oorschot 1998; Savory *et al.* 1998). But, using electron microscopy to study the same cell culture, no significant increase in formation of paired helical filaments was found (Jones *et al.* 1998) so Al perhaps only increased exposure of protein to antibody.

Al perturbs neurofilament protein in rabbits *in vivo* (Muma and Singer 1996). Rabbits are the most sensitive to the neurodegenerative properties of Al, but these effects never occur through oral administration. This neurofibrillary pathology differs in several ways from the PHFs seen in AD (Singer *et al.* 1997). Although classical NFTs do not appear in Al-treated rabbit brain Huang *et al.* (1997) examined such brain sections and showed neurofibrillary degeneration which stained positive for amyloid precursor protein (APP), A beta protein, alpha(1)-antichymotrypsin (ACT) and ubiquitin, all of which appear in NFTs of AD brains.

Reusche *et al.* (2001) examined histopathology in brains from people with a history of long-term haemodialysis, a group of people whose intake of Al is necessarily very high to combat hyperphosphataemia and gastric hyperacidity. While both Al intake levels and duration of haemodialysis were associated with degree of dialysis-associated encephalopathy, there was no association with degree of AD morphology. It should be noted that AD changes were only seen in tissue from patients aged over 60 (n=29) and that perhaps other forms of mortality supervene before AD can develop, so the study may have lacked power regarding the question of ingested Al and AD causation. However the result perhaps weakens links between Al-induced neuropathy *in vivo* or in vitro and AD neuropathology in humans, at least in non-elderly patients.

Those with the highest consistent serum Al are dialysis patients, who showed no neurofibrillary tangle formation postmortem, and while more senile plaques and antibody staining against the beta/A4 amyloid precursor protein were seen in dialysis patients, their appearance did not correlate with Al levels in frontal cortex (Candy *et al.* 1992; Edwardson *et al.* 1992; Wisniewski 1994). Brain levels of Al were not higher in renal patients but focal accumulation of aluminium was observed in neurons with high densities of transferrin receptors, indicating transferrin-mediated uptake, in regions such as cortex and hippocampus which are selectively vulnerable in AD

(Edwardson *et al.* 1992). The authors suggest that any role of Al in senile plaque formation is likely to be only part of a complex cascade of changes and that if Al is involved in the pathogenesis of AD, it must be indirectly.

Studies of Al levels in brain tissue and of Al biokinetics, especially with regard to those who have very high intake of Al for medical reasons, indicate that, in general, Al is neither necessary nor sufficient to cause AD. Conclusions from biokinetics data are in complete opposition to those from epidemiology. These are difficult to reconcile. However, because one cannot ignore the studies which find a positive association between Al levels in drinking water and AD, some caveats are added. High levels of brain Al may accelerate the course of pre-existing pathology, although there is still no clear eveidence for this. Al may be involved in a gene X environment interaction whereby some human genotypes are predisposed to a pathogenesis of AD which is promoted by high Al. This possibility is suggested by significant differences in frequencies of N-acetyltransferase 2 genotypes between AD patients and a control population sample. Variation in this enzyme correlates with variation in the cytotoxic and genotoxic responses to a wide diversity of environmental chemicals (Rocha *et al.* 1999). Interestingly also in this vein, Salahudeen *et al.* (2000) suggests that whites undergoing haemodialysis may have greater serum aluminium levels than blacks, which might contribute to the whites' greater rate of mortality. A G X E interaction with drinking water Al might produce the varied epidemiological picture we see. Or high Al in drinking water may play a role in pathogenesis of AD via an environment X environment interaction; Al in drinking water may interact with another component of drinking water, or high Al levels in drinking water may reflect general water quality and thus be a proxy for some other known risk factor, such as education level or socioeconomic status. Again, no evidence exists for or against these hypotheses, but generally the modest increased risks observed by most studies suggest that Al is highly unlikely to be a primary aetiological factor in all cases of sporadic AD. On a more cautionary note, the epidemiological literature in this area may suffer from publication bias (Doll 1993), whereby negative results are perceived as uninteresting and the study either curtailed early and/or not published.

6.2.5 Chronic neurological effects - Aluminium and cognitive function

6.2.5.1 Drinking water

In addition to the epidemiological studies that examined the relationship between Alzheimer’s disease and aluminium in drinking-water, two studies examined cognitive dysfunction and Alzheimer’s disease in elderly populations in relation to the levels of aluminium in drinking-water. The results were again conflicting. One powerful study of 800 male octogenarians consuming drinking-water with aluminium concentrations up to 98 µg/litre found no relationship. The second study used "any evidence of mental impairment" as an outcome measure and found a relative risk of 1.72 at aluminium concentrations greater than 85 µg/litre in 250 males. (IPCS p8).

The Paquid cohort in France has generated a number of reports. Jacqmin *et al.* (1994), first found that cognitive impairment was weakly positively associated with Al at pH < 7.3 but negatively at pH above that, after adjusting for fluoride, calcium, age, sex, educational level, and occupation of the participants. However Rondeau *et al.* (2001), reporting on the same cohort, applied the Mini-Mental State Examination to gauge cognitive decline in the elderly over an average of 5.9 years, finding that simply living in an area with drinking water Al > 0.1mg/litre was not associated with cognitive

decrements. But cognitive decline with time was greater in subjects exposed to high Al and in those exposed to low silica. Analyses were controlled for age at cohort inception, gender, education level but not family history, which might have been important as a significant intraparish correlation was observed.

In the study by (Emsley *et al.* 2000) on trace elements in drinking water and cognitive decline in elderly Chinese, the highest Al level was 0.025mg/litre, making it uninformative in this context.

6.2.5.2 Occupational exposure

Reports of impaired cognitive function related to aluminium exposure are conflicting. Most studies are on small populations, and the methodology used in these studies is open to question with respect to magnitude of effect reported, exposure assessment and confounding factors. In a comparative study of cognitive impairment in miners exposed to a powder containing 85% finely ground aluminium and 15% aluminium oxide (as prophylaxis against silica) and unexposed miners, the cognitive test scores and the proportion impaired in at least one test indicated a disadvantage for the exposed miners. A positive exposure-related trend of increased risk was noted. (IPCS p8)

Neurological syndromes including impairment of cognitive function, motor dysfunction and peripheral neuropathy have been reported in limited studies of workers exposed to aluminium fume. A small population of aluminium welders who were compared with iron welders were reported to show a small decrement in repetitive motor function. When a questionnaire methodology was used in another study, an increase in neuropsychiatric symptoms was reported. (IPCS p9)

Based on occupational exposure, the implication being that exposure is not acute, Riihimaki *et al.* (2000) suggest a threshold level for adverse effect of 6.75-9.45µg/litre in serum, and a urinary level of 108-162µg/litre from a study of Al welders compared with mild steel welders. Sjogren (1997) is more cautious, proposing a tentative dose-response relationship between approximate post-shift urine levels and neurological effects. He suggests a post-shift urinary concentration of 40µg/litre as being a NOAEL, having found no disturbances of motor function, memory or attention in workers below this level, subtle disturbances in motor function and a subclinical tremor at 50-60µg/litre and effects on short-term memory, learning and attention at 100-200µg/litre. However he notes a German study which found no neurological test differences between Al powder producers (median urinary concentration 113µg/litre) and controls

(Kilburn 1998) found significant deficits in a range of neurological test scores (in areas of memory, cognitive, reaction time and balance among workers from an Al remelting plant compared with local and distant controls, and more neurobehavioral, rheumatic, and respiratory symptomatology. This was attributed to higher exposure to aluminum, manganese, vinyl chloride monomer, and other chemicals although levels were not measured. The same author (Kilburn 1999) reviews the occupational Al exposure literature and highlights the confounding factors present in all studies so far. If the workers are in potrooms they may be exposed to coal tar pitch volatiles from electrodes or fluorine, chlorine and cryolite fluxes from refining, or manganese if welding and organochlorines if remelting scrap. Of these, manganese exposure has been linked to neurological signs, including slower visual reaction, reduced eye-hand

coordination and impaired short term memory, making it an obvious confounder. Kilburn states that a discriminating test is that of balance; sway speed is higher in those affected by Al, but does not reference the assertion. We might assume it is because balance deficits were not observed in manganese neurotoxicity but were observed among Al resmelting workers (Kilburn 1998).

Five men with diagnoses of pulmonary aluminosis were followed up 40 years later. Two had died from their lung disease, one after 34 years from heart disease, one was still alive and healthy with normal blood Al levels and the last had developed a dementia with motor disturbances, unlike AD, and had very high Al levels in cerebrospinal fluid (Sjogren *et al.* 1996). Interestingly, this resembles more the Parkinsonism and dementia complexes of Guam and the amyotrophic lateral sclerosis complex of the Kii peninsula, although at least in the latter case the most recent aetiology suggested has been long exposure to high Al and manganese combined with low calcium and magnesium in the soil (Yase *et al.* 2001).

(Sjogren *et al.* 1996) used the same subjects from a previous study (38 Al welders, 39 mild steel welders) which had found slightly slower repetitive motor functions among Al welders and extended the study, finding again decreased motor function in five tests, two of which showed a dose-response with blood and urinary Al levels, but no cognitive deficits. The Al welders had urine levels seven times the controls and a median exposure of 7065 hours. Manganese levels in urine did not differ from controls.

A follow-up of the same groups, but now including smelters and flake powder producers showed no significant deficits in the welders group this time. The smelters had nearly normal Al levels and showed no signinficant neurological decrements. Neither did the flake producers, despite high levels of Al in blood and urine (9µg/litre in blood, c.f. 1µg/litre in controls) but this may have been partly due to different statistical methodology aand low sample size (n=16) and, hence, power (Iregren *et al.* 2001). No cognitive deficits were noted in any group.

(Sim *et al.* 1997) found no change in tremor in both upper and lower limbs, postural stability, reaction time, or vocabulary, but significant ORs for incoordination and buttoning difficulty associated with >10 years potroom work history (smelting).

(Akila *et al.* 1999) conducted a comprehensive study of 79 male Al welders and age matched controls who were mild steel welders from within each workplace. Serum and urinary Al levels were measured and subjects allocated to low and high exposure and referent groups based on urinary Al. The conclusion is that chronic Al exposure of this sort is associated with cognitive deficits in areas demanding time-limited processing and where working memory performance is demanding, and that these effects were generally greater in those with higher exposure. The authors also point out that because changes are often marginal or subclinical, indicating the early stages or neurological dysfunction, choice of tests should be such that component analysis can indicate the underlying cognitive processes which are effecting poor performance.

The neuropsychological testing of Riihimaki *et al* (2000), in agreement with Akila *et al.* (1999), revealed a “circumscribed effect of aluminum, mainly in tasks demanding complex attention and the processing of information in the working memory system and in the analysis and recall of abstract visual patterns”. Subjective reporting of psychological symptoms indicated increases in memory and concentration problems,

fatigue and mild depression which were exposure-related, as were some EEG abnormalities.

A longitudinal cross-sectional study over 5 years on workers from an Al powder manufacturing plant in Germany found no neurophysiological decrements associated with Al exposure at the beginning or at the end of the time period (Letzel *et al.* 2000). Whether or not there was a difference to find, this study was unlikely to find it because the exposed group had relatively low exposure measure (median urinary Al=110µg/litre initially, 24µg/litre at 5 years, see (Riihimaki *et al.* 2000)), the sample sizes were too small to allow adequate power and there were problems with responder bias at 5 years.

The study of (Bast-Pettersen *et al.* 2000) also found no neurological differences between welders and controls, also had low sample size and relatively low exposure indices, but produced a correlation between years of exposure and performance in hand steadiness and reaction time tests.

6.3 Other effects

6.3 Iatrogenic exposure

Iatrogenic exposure in patients with chronic renal failure, exposed to aluminium-containing dialysis fluids and pharmaceutical products, may cause encephalopathy, vitamin-D-resistant osteomalacia and microcytic anaemia. These clinical syndromes can be prevented by reduction in exposure to aluminium. (IPCS p9)

Woodson (1998) reports the case of a 39-year-old pharmacist who self-medicated for peptic ulcer disease with high doses of a potent antacid containing aluminum and magnesium hydroxide. The patient consumed over 18 kg of elemental aluminum and 15 kg of elemental magnesium over 8 years of antacid use, resulting in severe osteomalacia due to profound phosphate depletion. Cessation of this intake, 6.3 grams of Al/day, resulted in marked and striking improvement.

Premature infants, even where kidney impairment is not severe enough to cause raised blood creatinine levels, may develop increased tissue loading of aluminium, particularly in bone, when exposed to iatrogenic sources of aluminium. Where there is kidney failure, seizures and encephalopathy may occur.

Although human exposure to aluminium is widespread, in only a few cases has hypersensitivity been reported following exposure to some aluminium compounds after dermal application or parenteral administration. (IPCS p9)

Recently, however, a syndrome called macrophagic myofasciitis has been described, characterised by diffuse muscle and joint pain and fatigue, and by muscular infiltration of granular macrophages and lymphocytes which contain Al hydroxide inclusions. The cause appears to be the Al hydroxide carrier used in vaccines (Gherardi *et al.* 2001). It is not yet clear how common this condition is.

Pulmonary fibrosis was reported in some workers exposed to very fine stamped aluminium powder in the manufacture of explosives and fireworks. Nearly all cases involved exposure to aluminium particles coated with mineral oil. That process is no longer used. Other cases of pulmonary fibrosis have related to mineral exposures to other agents such as silica and asbestos and cannot be attributed solely to aluminium.

Irritant-induced asthma has been associated with inhalation of aluminium sulfate, aluminium fluoride, potassium aluminium tetrafluoride and with the complex environment of the potrooms during aluminium production. (IPCS p9)

6.3.2. Carcinogenicity

There is insufficient information to allow for classification of the cancer risk from human exposures to aluminium and its compounds. Animal studies do not indicate that aluminium or aluminium compounds are carcinogenic. (IPCS p9)

6.3.3 Genotoxicity

In an abstract, Haugen et al. (1983) reported no increase in the number of sister chromatid exchanges in peripheral blood lymphocytes of workers employed in an aluminium factory. There have been no reports concerning genetic effects of aluminium in humans following oral exposure to aluminium.

6.3.4 Reproductive toxicity

There is no information regarding reproductive toxicity in humans following exposure to aluminium. (IPCS p155)

Reference List to Appendix 21

Abreo, K., F. Abreo, M. Sella and S. Jain (1999). "Aluminum enhances iron uptake and expression of neurofibrillary tangle protein in neuroblastoma cells." Journal of Neurochemistry **72**(5): 2059-2064.

Ackley, D. C. and R. A. Yokel (1997). "Aluminum citrate is transported from brain into blood via the monocarboxylic acid transporter located at the blood-brain barrier." Toxicology **120**(2): 89-97.

Ahmed, M. J. and J. Hossan (1995). "Spectrophotometric determination of aluminium by morin." Talanta **42**(8): 1135-1142.

Akila, R., B. T. Stollery and V. Riihimaki (1999). "Decrements in cognitive performance in metal inert gas welders exposed to aluminium." Occupational & Environmental Medicine **56**(9): 632-639.

Allain, P., F. Gauchard and N. Krari (1996). "Enhancement of aluminum digestive absorption by fluoride in rats." Research Communications in Molecular Pathology & Pharmacology **91**(2): 225-231.

Altmann, P., J. Cunningham, U. Dhanesha, M. Ballard, J. Thompson and F. Marsh (1999). "Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident." Bmj **319**(7213): 807-+.

Amador, F. C., M. S. Santos and C. R. Oliveira (1999). "Lipid peroxidation facilitates aluminum accumulation in rat brain synaptosomes." Journal of Toxicology & Environmental Health **Part A. 58**(7): 427-435.

Anane, R., M. Bonini, J. M. Grafeille and E. E. Creppy (1995). "Bioaccumulation of water soluble aluminium chloride in the hippocampus after transdermal uptake in mice." Archives of Toxicology **69**(8): 568-571.

Andrasi, E., E. Farkas, H. Scheibler, A. Reffy and L. Bezur (1995). "Al, zn, cu, mn and fe levels in brain in alzheimers disease." Archives of Gerontology & Geriatrics **21**(1): 89-97.

Anghileri, L. J., P. Maincent and P. Thouvenot (1994). "Long-term oral administration of aluminum in mice. Aluminum distribution in tissues and effects on calcium metabolism." Annals of Clinical & Laboratory Science **24**(1): 22-6.

Anonymous (1994). "The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada." Neurology **44**(11): 2073-80.

ATSDR (1999). Toxicological Profile for Aluminium (update), Agency for Toxic Substances and Disease Registry.

Banks, W. A., L. M. Maness, M. F. Banks and A. J. Kastin (1996). "Aluminum-sensitive degradation of amyloid beta-protein(1-40) by murine and human intracellular enzymes." Neurotoxicology & Teratology **18**(6): 671-677.

Barker, J., J. Templar, S. J. King, J. P. Day, M. W. B. Bradbury, A. Radunovic, F. Ueda, K. Raja, J. S. Lilley and P. V. Drumm (1997). "Ams measurements to study uptake and distribution of al-26 in mice and the role of the transferrin receptor in aluminium absorption mechanisms." Nuclear Instruments & Methods in Physics Research Section B Beam Interactions with Materials & Atoms **123**(1-4): 275-278.

Bast-Pettersen, R., V. Skaug, D. Ellingsen and Y. Thomassen (2000). "Neurobehavioral performance in aluminum welders." American Journal of Industrial Medicine **37**(2): 184-192.

Belles, M., D. J. Sanchez, M. Gomez, J. Corbiella and J. L. Domingo (1998). "Silicon reduces aluminum accumulation in rats: Relevance to the aluminum hypothesis of Alzheimer disease." Alzheimer Disease & Associated Disorders **12**(2): 83-87.

Bilkei-Gorzo, A. (1993). "Neurotoxic effect of enteral aluminium." Food & Chemical Toxicology **31**(5): 357-61.

Bjertness, E., J. M. Candy, A. Torvik, P. Ince, F. McArthur, G. A. Taylor, S. W. Johansen, J. Alexander, J. K. Gronnesby, L. S. Bakketeig and J. A. Edwardson (1996). "Content of brain aluminum is not elevated in alzheimer disease." Alzheimer Disease & Associated Disorders **10**(3): 171-174.

Bondy, S. C., S. X. Guoross and A. T. Truong (1998). "Promotion of transition metal-induced reactive oxygen species formation by beta-amyloid." Brain Research **799**(1): 91-96.

Bondy, S. C. and S. Kirstein (1996). "The promotion of iron-induced generation of reactive oxygen species in nerve tissue by aluminum." Molecular & Chemical Neuropathology **27**(2): 185-194.

Bondy, S. C. and A. Truong (1999). "Potentiation of beta-folding of beta-amyloid peptide 25-35 by aluminum salts." Neuroscience Letters **267**(1): 25-28.

Borak, J. and J. P. Wise (1998). "Does aluminum exposure of pregnant animals lead to accumulation in mothers or their offspring." Teratology **57**(3): 127-139.

Bowdler, N. C., D. S. Beasley, E. C. Fritze, A. M. Goulette, J. D. Hatton, J. Hession, D. L. Ostman, D. J. Rugg and C. J. Schmittdiel (1979). "Behavioral effects of aluminum ingestion on animal and human subjects." Pharmacology, Biochemistry & Behavior **10**(4): 505-12.

Brenner, S. R. and K. W. Yoon (1994). "Aluminum toxicity in rat hippocampal neurons." Neuroscience Letters **178**(2): 260-262.

Cam, J. M., V. A. Luck, J. B. Eastwood and H. E. de Wardener (1976). "The effect of aluminium hydroxide orally on calcium, phosphorus and aluminium metabolism in normal subjects." Clinical Science & Molecular Medicine **51**(4): 407-14.

Campbell, A., K. N. Prasad and S. C. Bondy (1999). "Aluminum-induced oxidative events in cell lines: Glioma are more responsive than neuroblastoma." Free Radical Biology & Medicine **26**(9-10): 1166-1171.

Campbell, A., M. A. Smith, L. M. Sayre, S. C. Bondy and G. Perry (2001). "Mechanisms by which metals promote events connected to neurodegenerative diseases." Brain Research Bulletin **55**(2): 125-132.

Candy, J. M., F. K. McArthur, A. E. Oakley, G. A. Taylor, C. Chen, S. A. Mountfort, J. E. Thompson, P. R. Chalker, H. E. Bishop, K. Beyreuther, G. Perry, M. K. Ward, C. N. Martyn and J. A. Edwardson (1992). "Aluminum Accumulation in Relation to Senile Plaque and Neurofibrillary Tangle Formation in the Brains of Patients with Renal-Failure." Journal of the Neurological Sciences **107**(2): 210-218.

Cech, I. and J. Montera (2000). "Spatial variations in total aluminum concentrations in drinking water supplies studied by geographic information system (GIS) methods." Water Research **34**(10): 2703-2712.

Cherroret, G., V. Bernuzzi, D. Desor, M. F. Hutin, D. Burnel and P. R. Lehr (1992). "Effects of postnatal aluminum exposure on choline acetyltransferase activity and learning abilities in the rat." Neurotoxicology & Teratology **14**(4): 259-64.

Christen, Y. (2000). "Oxidative stress and Alzheimer disease." American Journal of Clinical Nutrition **71**(2): 621S-629S.

Colin-Jones, D., M. J. Langman, D. H. Lawson and M. P. Vessey (1989). "Alzheimer's disease in antacid users." Lancet **1**(8652).

Connor, D. J., R. S. Jope and L. E. Harrell (1988). "Chronic, oral aluminum administration to rats: cognition and cholinergic parameters." Pharmacology, Biochemistry & Behavior **31**(2): 467-74.

Corain, B., G. G. Bombi, A. Tapparo, M. Perazzolo and P. Zatta (1996). "Aluminium toxicity and metal speciation - established data and open questions." Coordination Chemistry Reviews **149**: 11-22.

Cumming, A. D., G. Simpson, D. Bell, J. Cowie and R. J. Winney (1982). "Acute aluminium intoxication in patients on continuous ambulatory peritoneal dialysis." Lancet **1**(8263): 103-4.

Danielsson, L. G., A. Sparen and A. W. Glynn (1995). "Aluminium fractionation in a simulated rat stomach - an in vitro study." Analyst **120**(3): 713-720.

Day, J. P., J. Barker, S. J. King, R. V. Miller, J. Templar, J. S. Lilley, P. V. Drumm, G. W. A. Newton, L. K. Fifield, J. O. H. Stone, G. L. Allan, J. A. Edwardson, P. B. Moore, I. N. Ferrier, N. D. Priest, D. Newton, R. J. Talbot, J. H. Brock, L. Sanchez, C. B. Dobson, R. F. Itzhaki, A. Radunovic and M. W. B. Bradbury (1994). "Biological chemistry of aluminium studied using al-26 and accelerator mass spectrometry." Nuclear Instruments & Methods in Physics Research Section B Beam Interactions with Materials & Atoms **92**(1-4): 463-468.

de Kom, J. F., H. M. Dissels, G. B. van der Voet and F. A. de Wolff (1997). "Serum aluminium levels of workers in the bauxite mines." Journal of Toxicology - Clinical Toxicology **35**(6): 645-51.

Deng, Z. Y., C. Coudray, L. Gouzoux, A. Mazur, Y. Rayssiguier and D. Pepin (2000). "Effects of acute and chronic coingestion of AlCl3 with citrate or polyphenolic acids on tissue retention and distribution of aluminum in rats." Biological Trace Element Research **76**(3): 245-256.

Doll, R. (1993). "Alzheimers-Disease and Environmental Aluminum." Age and Ageing **22**(2): 138-153.

Domingo, J. L., J. Llorens, D. J. Sanchez, M. Gomez, J. M. Llobet and J. Corbella (1996). "Age-related effects of aluminum ingestion on brain aluminum accumulation and behavior in rats." Life Sciences **58**(17): 1387-1395.

Drueke, T. B., P. Jouhanneau, H. Bande, B. Lacour, F. Yiou and G. Raisbeck (1997). "Effects of silicon, citrate and the fasting state on the intestinal absorption of aluminium in rats." Clinical Science **92**(1): 63-67.

Dyrks, T., E. Dyrks, T. Hartmann, C. Masters and K. Beyreuther (1992). "Amyloidogenicity of beta A4 and beta A4-bearing amyloid protein precursor fragments by metal-catalyzed oxidation." Journal of Biological Chemistry **267**(25): 18210-7.

Ecelbarger, C. A., G. G. Macneil and J. L. Greger (1994). "Importance of kidney function and duration of exposure on aluminum accumulation in mature rats." Nutrition Research **14**(4): 577-586.

Edwardson, J. A., J. M. Candy, P. G. Ince, F. K. McArthur, C. M. Morris, A. E. Oakley, G. A. Taylor and E. Bjertness (1992). "Aluminium accumulation, beta-amyloid deposition and neurofibrillary changes in the central nervous system." Ciba Foundation Symposium **169**: 165-79.

Edwardson, J. A., P. B. Moore, I. N. Ferrier, J. S. Lilley, G. W. A. Newton, J. Barker, J. Templar and J. P. Day (1993). "Effect of silicon on gastrointestinal absorption of aluminium." Lancet **342**(8865): 211-212.

Emsley, C. L., S. Gao, Y. M. Li, C. Liang, R. D. Ji, K. S. Hall, J. X. Cao, F. Ma, Y. P. Wu, P. Ying, Y. Zhang, S. H. Sun, F. W. Unverzagt, C. W. Slemenda and H. C. Hendrie (2000). "Trace element levels in drinking water and cognitive function among elderly Chinese." American Journal of Epidemiology **151**(9): 913-920.

Epstein, S. G. (1990). "Human Exposure to Aluminum." Environmental Geochemistry and Health **12**(1-2): 65-70.

Esler, W. P., E. R. Stimson, J. M. Jennings, J. R. Ghilardi, P. W. Mantyh and J. E. Maggio (1996). "Zinc-induced aggregation of human and rat beta-amyloid peptides in vitro." Journal of Neurochemistry **66**(2): 723-732.

FAO/WHO (1989). Aluminium. In: Evaluation of certain food additives and contaminants. Thirty-third report of the Joint FAO/WHO Expert Committee on Food Additives. (WHO Technical Report Series No. 776). Geneva, World Health Organization**:** 28-31.

Fasman, G. D., A. Perczel and C. D. Moore (1995). "Solubilization of beta-amyloid-(1-42)-peptide: reversing the beta-sheet conformation induced by aluminum with silicates." Proceedings of the National Academy of Sciences of the United States of America **92**(2): 369-71.

Flarend, R., T. Bin, D. Elmore and S. L. Hem (2001). "A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminium-26." Food & Chemical Toxicology **39**(2): 163-168.

Flaten, T. P. (2001). "Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water." Brain Research Bulletin **55**(2): 187-196.

Florence, A. L., A. Gauthier, R. J. Ward and R. R. Crichton (1995). "Influence of hydroxypyridones and desferrioxamine on the mobilization of aluminium from tissues of aluminium-loaded rats." Neurodegeneration **4**(4): 449-455.

Forbes, W. F., S. Lessard and J. F. Gentleman (1995). "Geochemical risk factors for mental functioning, based on the ontario longitudinal study of aging (lsa) .5. comparisons of the results, relevant to aluminum water concentrations, obtained from the lsa and from death certificates mentioning dementia." Canadian Journal on Aging **14**(4): 642-656.

Forster, D. P., A. J. Newens, D. W. K. Kay and J. A. Edwardson (1995). "Risk factors in clinically diagnosed presenile dementia of the alzheimer type - a case-control study in northern england." Journal of Epidemiology & Community Health **49**(3): 253-258.

Fraga, C. G., P. I. Oteiza, M. S. Golub, M. E. Gershwin and C. L. Keen (1990). "Effects of aluminum on brain lipid peroxidation." Toxicology Letters **51**(2): 213-9.
Gandolfi, L., M. P. Stella, P. Zambenedetti and P. Zatta (1998). "Aluminum alters intracellular calcium homeostasis in vitro." Biochimica et Biophysica Acta Molecular Basis of Disease **28**(3): 315-320.
Garbossa, G., G. Galvez, G. Perez, J. Stripeikis, M. Tudino and A. Nesse (1998). "Oral aluminum administration to rats with normal renal function. 2. Body distribution." Human & Experimental Toxicology **17**(6): 318-22.
Gauthier, E., I. Fortier, F. Courchesne, P. Pepin, J. Mortimer and D. Gauvreau (2000). "Aluminum forms in drinking water and risk of Alzheimer's disease." Environmental Research **84**(3): 232-246.
Gherardi, R. K., M. Coquet, P. Cherin, L. Belec, P. Moretto, P. A. Dreyfus, J. F. Pellissier, P. Chariot and F. J. Authier (2001). "Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle." Brain **124**(Pt 9): 1821-31.
Gitelman, H. J. (1995). "Aluminum exposure and excretion." Science of the Total Environment **163**(1-3): 129-35.
Gitelman, H. J., F. R. Alderman, M. Kurs-Lasky and H. E. Rockette (1995). "Serum and urinary aluminium levels of workers in the aluminium industry." Annals of Occupational Hygiene **39**(2): 181-91.
Glynn, A. W., A. Sparen, L. G. Danielsson, G. Haegglund and L. Jorhem (1995). "Bioavailability of labile aluminium in acidic drinking water - a study in the rat." Food & Chemical Toxicology **33**(5): 403-408.
Glynn, A. W., A. Sparen, L. G. Danielsson, B. Sundstrom and L. Jorhem (1999). "Concentration-dependent absorption of aluminum in rats exposed to labile aluminum in drinking water." Journal of Toxicology & Environmental Health **56**(7): 501-512.
Golub, M. S. and S. L. Germann (1998). "Aluminum effects on operant performance and food motivation of mice." Neurotoxicology and Teratology **20**(4): 421-427.
Golub, M. S. and S. L. Germann (2001). "Long-term consequences of developmental exposure to aluminum in a suboptimal diet for growth and behavior of Swiss Webster mice." Neurotoxicology & Teratology **23**(4): 365-372.
Golub, M. S., S. L. Germann, B. Han and C. L. Keen (2000). "Lifelong feeding of a high aluminum diet to mice." Toxicology **150**(1-3): 107-117.
Golub, M. S. and C. L. Keen (1999). "Effects of dietary aluminum on pubertal mice." Neurotoxicology & Teratology **21**(5): 595-602.
Gomez, M., J. L. Esparza, J. L. Domingo, P. K. Singh and M. M. Jones (1999). "Chelation therapy in aluminum-loaded rats: influence of age." Toxicology **137**(3): 161-168.
Gomez, M., D. J. Sanchez, J. M. Llobet, J. Corbella and J. L. Domingo (1997). "Concentrations of some essential elements in the brain of aluminum-exposed rats in relation to the age of exposure." Archives of Gerontology & Geriatrics **24**(3): 287-294.
Gomez, M., D. J. Sanchez, J. M. Llobet, J. Corbella and J. L. Domingo (1997). "The effect of age on aluminum retention in rats." Toxicology **116**(1-3): 1-8.
Gonda, Z. and K. Lehotzky (1996). "Effect of prenatal aluminium lactate exposure on conditioned taste aversion and passive avoidance task in the rat." Journal of Applied Toxicology **16**(6): 529-32.
Good, P. F., D. P. Perl, L. M. Bierer and J. Schmeidler (1992). "Selective Accumulation of Aluminum and Iron in the Neurofibrillary Tangles of Alzheimers-Disease - a Laser Microprobe (Lamma) Study." Annals of Neurology **31**(3): 286-292.
Gorsky, J. E., A. A. Dietz, H. Spencer and D. Osis (1979). "Metabolic balance of aluminum studied in six men." Clinical Chemistry **25**(10): 1739-43.
Greger, J. L. and M. J. Baier (1983). "Effect of dietary aluminum on mineral metabolism of adult males." American Journal of Clinical Nutrition **38**(3): 411-9.
Greger, J. L. and M. J. Baier (1983). "Excretion and retention of low or moderate levels of aluminium by human subjects." Food & Chemical Toxicology **21**(4): 473-7.
Greger, J. L. and J. E. Sutherland (1997). "Aluminum exposure and metabolism." Critical Reviews in Clinical Laboratory Sciences **34**(5): 439-474.
Guo-Ross, S. X., E. Y. Yang, T. J. Walsh and S. C. Bondy (1999). "Decrease of glial fibrillary acidic protein in rat frontal cortex following aluminum treatment." Journal of Neurochemistry **73**(4): 1609-1614.
Gutteridge, J. M., G. J. Quinlan, I. Clark and B. Halliwell (1985). "Aluminium salts accelerate peroxidation of membrane lipids stimulated by iron salts." Biochimica et Biophysica Acta **835**(3): 441-7.

Guy, S. P., D. Jones, D. M. A. Mann and R. F. Itzhaki (1991). "Human Neuroblastoma-Cells Treated with Aluminum Express an Epitope Associated with Alzheimers-Disease Neurofibrillary Tangles." Neuroscience Letters **121**(1-2): 166-168.
Harrington, C. R., C. M. Wischik, F. K. McArthur, G. A. Taylor, J. A. Edwardson and J. M. Candy (1994). "Alzheimers-disease-like changes in tan protein processing - association with aluminium accumulation in brains of renal dialysis patients." Lancet **343**(8904): 993-997.
Harris, W. R. (1996). "Binding and transport of aluminum by serum proteins." Coordination Chemistry Reviews **149**: 347-365.
Harris, W. R., G. Berthon, J. P. Day, C. Exley, T. P. Flaten, W. F. Forbes, T. Kiss, C. Orvig and P. F. Zatta (1996). "Speciation of aluminum in biological systems." Journal of Toxicology & Environmental Health **48**(6): 543-568.
Hensley, K., J. M. Carney, M. P. Mattson, M. Aksenova, M. Harris, J. F. Wu, R. A. Floyd and D. A. Butterfield (1994). "A model for beta-amyloid aggregation and neurotoxicity based on free radical generation by the peptide: relevance to Alzheimer disease." Proceedings of the National Academy of Sciences of the United States of America **91**(8): 3270-4.
Herzog, P. and K. H. Holtermuller (1982). "Effect of antacids on mineral metabolism in persons with healthy kidneys. Double-blind study using an antacid containing magnesium aluminum silicate hydrate." MMW Munchener Medizinische Wochenschrift **124**(42): 921-3.
Hongve, D., S. Johansen, E. Andruchow, E. Bjertness, G. Becher and J. Alexander (1996). "Determination of aluminium in samples from bone and liver of elderly norwegians." Journal of Trace Elements in Medicine & Biology **10**(1): 6-11.
Huang, Y., M. M. Herman, J. Liu, C. D. Katsetos, M. R. Wills and J. Savory (1997). "Neurofibrillary lesions in experimental aluminum-induced encephalopathy and alzheimers-disease share immunoreactivity for amyloid precursor protein, a-beta, alpha(1)-antichymotrypsin and ubiquitin-protein conjugates." Brain Research **771**(2): 213-220.
ICMR (1999). "Risk of aluminium toxicity in the Indian context." ICMR Bulletin **29**(8): 85-90.
ICRP (1975). International Commission on Radiological Protection, Publication 23: Report of Task Group on Reference Man. Oxford, Pergamon Press.
Iregren, A., B. Sjogren, K. Gustafsson, M. Hagman, L. Nylen, W. Frech, M. Andersson, K. G. Ljunggren and A. Wennberg (2001). "Effects on the nervous system in different groups of workers exposed to aluminium." Occupational & Environmental Medicine **58**(7): 453-460.
Ittel, T. H., S. Kinzel, A. Ortmanns and H. G. Sieberth (1996). "Effect of iron status on the intestinal absorption of aluminum: a reappraisal." Kidney International **50**(6): 1879-88.
Jacqmin, H., D. Commenges, L. Letenneur, P. Barberger-Gateau and J. F. Dartigues (1994). "Components of drinking water and risk of cognitive impairment in the elderly." American Journal of Epidemiology **139**(1): 48-57.
Jones, K. R., M. J. Black and D. E. Oorschot (1998). "Do aluminium and/or glutamate induce Alzheimer PHF-like formation? An electron microscopic study." Journal of Neurocytology **27**(1): 59-68.
Jones, K. R. and D. E. Oorschot (1998). "Do aluminium and/or glutamate induce Alz-50 reactivity? A light microscopic immunohistochemical study." Journal of Neurocytology **27**(1): 45-57.
Jouhanneau, P., G. M. Raisbeck, F. Yiou, B. Lacour, H. Banide and T. B. Drueke (1997). "Gastrointestinal absorption, tissue retention, and urinary excretion of dietary aluminum in rats determined by using al-26." Clinical Chemistry **43**(6 Part 1): 1023-1028.
Jugdaohsingh, R., D. M. Reffitt, C. Oldham, J. P. Day, L. K. Fifield, R. P. Thompson and J. J. Powell (2000). "Oligomeric but not monomeric silica prevents aluminum absorption in humans." American Journal of Clinical Nutrition **71**(4): 944-9.
Julka, D., R. Sandhir and K. D. Gill (1995). "Altered cholinergic metabolism in rat cns following aluminum exposure - implications on learning performance." Journal of Neurochemistry **65**(5): 2157-2164.
Kaehny, W. D., A. P. Hegg and A. C. Alfrey (1977). "Gastrointestinal absorption of aluminum from aluminum-containing antacids." New England Journal of Medicine **296**(24): 1389-90.
Kasa, P., P. Szerdahelyi and H. M. Wisniewski (1995). "Lack of topographical relationship between sites of aluminum deposition and senile plaques in the alzheimers disease brain." Acta Neuropathologica **90**(5): 526-531.
Kataoka, T., M. Mori, T. M. Nakanishi, S. Matsumoto and A. Uchiumi (1997). "Highly sensitive analytical method for aluminum movement in soybean root through lumogallion staining." Journal of Plant Research **110**(1099): 305-309.
Kawahara, M., M. Kato and Y. Kuroda (2001). "Effects of aluminum on the neurotoxicity of primary cultured neurons and on the aggregation of beta-amyloid protein." Brain Research Bulletin **55**(2): 211-217.

Kawahara, M., K. Muramoto, K. Kobayashi, H. Mori and Y. Kuroda (1994). "Aluminum promotes the aggregation of alzheimers amyloid beta-protein in vitro." Biochemical & Biophysical Research Communications **198**(2): 531-535.
Kilburn, K. H. (1998). "Neurobehavioral impairment and symptoms associated with aluminum remelting." Archives of Environmental Health **53**(5): 329-335.
Kilburn, K. H. (1999). "Does exposure to fine aluminium dust affect the brain?" Lancet **354**(9190): 1575-1577.
Kiss, T. (1995). "Interaction of aluminum with biomolecules - any relevance to alzheimers disease." Archives of Gerontology & Geriatrics **21**(1): 99-112.
Laczko, I., E. Vass, K. Soos, J. L. Varga, S. Szaraz, M. Hollosi and B. Penke (1996). "Ca2+- and al3+-induced conformational transitions of amyloid fragment h-ile-ile-gly-leu-met-nh2." Archives of Biochemistry & Biophysics **335**(2): 381-387.
Lal, B., A. Gupta, R. C. Murthy, M. M. Ali and S. V. Chandra (1993). "Aluminum ingestion alters behaviour and some neurochemicals in rats." Indian Journal of Experimental Biology **31**(1): 30-5.
Lauricella, A. M., G. Garbossa and A. Nesse (2001). "Dissimilar behavior of lymph cells in response to the action of aluminum. In vitro and *in vivo* studies." International Immunopharmacology **1**(9-10): 1725-1732.
Letzel, S., C. J. G. Lang, K. H. Schaller, J. Angerer, S. Fuchs, B. Neundorfer and G. Lehnert (2000). "Longitudinal study of neurotoxicity with occupational exposure to aluminum dust." Neurology **54**(4): 997-1000.
Leveque, C., D. Soulie, J. L. Sarrazin, F. Hor, M. Desgeorges and Y. S. Cordoliani (1996). "[Toxic aluminum encephalopathy. Predominant involvement of the limbic system on MRI]." Journal of Neuroradiology. Journal de Neuroradiologie **23**(3): 168-72.
Li, W., K. K. Y. Ma, W. Sun and H. K. Paudel (1998). "Phosphorylation sensitizes microtubule-associated protein tau to al3+-induced aggregation." Neurochemical Research **23**(12): 1467-1476.
Lin, J. L., Y. J. Yang, S. S. Yang and M. L. Leu (1997). "Aluminum utensils contribute to aluminum accumulation in patients with renal disease." American Journal of Kidney Diseases **30**(5): 653-8.
Lione, A. (1985). "Aluminum toxicology and the aluminum-containing medications." Pharmacology & Therapeutics **29**(2): 255-85.
Liu, J., G. F. Nordberg and W. Frech (1996). "Aluminium accumulation in some tissues of rats with compromised kidney function induced by cadmium-metallothionein." Pharmacology & Toxicology **78**(5): 289-295.
Long, J. F., L. A. Nagode, C. L. Steinmeyer and G. Renkes (1994). "Comparative effects of calcitriol and parathyroid hormone on serum aluminum in vitamin D-depleted rabbits fed an aluminum-supplemented diet." Research Communications in Chemical Pathology & Pharmacology **83**(1): 3-14.
Lovell, M. A., J. D. Robertson, W. J. Teesdale, J. L. Campbell and W. R. Markesbery (1998). "Copper, iron and zinc in alzheimers disease senile plaques." Journal of the Neurological Sciences **158**(1): 47-52.
Lukiw, W. J. and N. G. Bazan (2000). "Neuroinflammatory signaling upregulation in Alzheimer's disease." Neurochemical Research **25**(9-10): 1173-1184.
Makjanic, J., B. McDonald, C. P. Li-Hsian Chen and F. Watt (1998). "Absence of aluminium in neurofibrillary tangles in Alzheimer's disease." Neuroscience Letters **240**(3): 123-6.
Makjanic, J., B. McDonald and F. Watt (1997). "Nuclear microscopy study of neurofibrillary tangles in alzheimers-disease." Nuclear Instruments & Methods in Physics Research Section B Beam Interactions with Materials & Atoms **130**(1-4): 439-443.
Marsden, S. N., I. S. Parkinson, M. K. Ward, H. A. Ellis and D. N. Kerr (1979). "Evidence for aluminium accumulation in renal failure." Proceedings of the European Dialysis & Transplant Association **16**: 588-96.
Martyn, C. N., D. J. Barker, C. Osmond, E. C. Harris, J. A. Edwardson and R. F. Lacey (1989). "Geographical relation between Alzheimer's disease and aluminum in drinking water." Lancet **1**(8629): 59-62.
Martyn, C. N., D. N. Coggon, H. Inskip, R. F. Lacey and W. F. Young (1997). "Aluminum concentrations in drinking water and risk of Alzheimer's disease." Epidemiology **8**(3): 281-6.
Mattson, M. P., M. A. Lovell, W. D. Ehmann and W. R. Markesbery (1993). "Comparison of the Effects of Elevated Intracellular Aluminum and Calcium Levels on Neuronal Survival and Tau Immunoreactivity." Brain Research **602**(1): 21-31.
Matyja, E. (2000). "Aluminum enhances glutamate-mediated neurotoxicity in organotypic cultures of rat hippocampus." Folia Neuropathologica **38**(2): 47-53.

Mauras, Y., J. C. Renier, A. Tricard and P. Allain (1983). "Demonstration of the gastrointestinal absorption of silicon from an alumino-silicate compound." Therapie **38**(2): 175-8.
McLachlan, D. R. C., M. D. Bergeron, J. E. Smith, D. Boomer and S. L. Rifat (1996). "Risk for neuropathologically confirmed alzheimers disease and residual aluminum in municipal drinking water employing weighted residential histories." Neurology **46**(2): 401-405.
McLachlan, D. R. C., A. J. Dalton, T. P. A. Kruck, M. Y. Bell, W. L. Smith, W. Kalow and D. F. Andrews (1991). "Intramuscular Desferrioxamine in Patients with Alzheimers- Disease." Lancet **337**(8753): 1304-1308.
Moore, P. B., J. P. Day, G. A. Taylor, I. N. Ferrier, L. K. Fifield and J. A. Edwardson (2000). "Absorption of aluminium-26 in Alzheimer's disease, measured using accelerator mass spectrometry." Dementia & Geriatric Cognitive Disorders **11**(2): 66-69.
Moore, P. B., J. A. Edwardson, I. N. Ferrier, G. A. Taylor, D. Lett, S. P. Tyrer, J. P. Day, S. J. King and J. S. Lilley (1997). "Gastrointestinal absorption of aluminum is increased in downs syndrome." Biological Psychiatry **41**(4): 488-492.
Moreno, A., P. Dominguez, C. Dominguez and A. Ballabriga (1991). "High serum aluminium levels and acute reversible encephalopathy in a 4-year-old boy with acute renal failure." European Journal of Pediatrics **150**(7): 513-4.
Muller, G., V. Bernuzzi, D. Desor, M. F. Hutin, D. Burnel and P. R. Lehr (1990). "Developmental alterations in offspring of female rats orally intoxicated by aluminum lactate at different gestation periods." Teratology **42**(3): 253-61.
Muller, M., M. Anke and H. Illinggunther (1998). "Aluminium in foodstuffs." Food Chemistry **61**(4): 419-428.
Muma, N. A. and S. M. Singer (1996). "Aluminum-induced neuropathology: transient changes in microtubule-associated proteins." Neurotoxicology & Teratology **18**(6): 679-90.
Mundy, W. R., T. M. Freudenrich and P. R. S. Kodavanti (1997). "Aluminum potentiates glutamate-induced calcium accumulation and iron-induced oxygen free radical formation in primary neuronal cultures." Molecular & Chemical Neuropathology **32**(1-3): 41-57.
Murayama, H., R. W. Shin, J. Higuchi, S. Shibuya, T. Muramoto and T. Kitamoto (1999). "Interaction of aluminum with PHF tau in Alzheimer's disease neurofibrillary degeneration evidenced by desferrioxamine-assisted chelating autoclave method." American Journal of Pathology **155**(3): 877-885.
Nagy, E. and K. Jobst (1994). "The kinetics of aluminium-containing antacid absorption in man." European Journal of Clinical Chemistry & Clinical Biochemistry **32**(3): 119-121.
Navak, P. and A. K. Chatterjee (2001). "Effects of aluminium exposure on brain glutamate and GABA systems: an experimental study in rats." Food & Chemical Toxicology **39**(12): 1285-1289.
Neelam, M. S. Bamji and M. Kaladhar (2000). "Risk of increased aluminium burden in the Indian population: contribution from aluminium cookware." Food Chemistry **70**(1): 57-61.
Neill, D., A. Leake, D. Hughes, A. B. Keith, G. A. Taylor, D. Allsop, B. K. Rima, C. Morris, J. M. Candy and J. A. Edwardson (1996). "Effect of aluminium on expression and processing of amyloid precursor protein." Journal of Neuroscience Research **46**(4): 395-403.
Ohman, L. O. and R. B. Martin (1994). "Citrate as the main small molecule binding al3+ in serum." Clinical Chemistry **40**(4): 598-601.
O'Mahony, D., J. Denton, J. Templar, M. O'Hara, J. P. Day, S. Murphy, J. B. Walsh and D. Coakley (1995). "Bone aluminium content in Alzheimer's disease." Dementia **6**(2): 69-72.
Oteiza, P. I., C. G. Fraga and C. L. Keen (1993). "Aluminum has both oxidant and antioxidant effects in mouse brain membranes." Archives of Biochemistry & Biophysics **300**(1): 517-21.
Pennington, J. A. T. and S. A. Schoen (1995). "Estimates of Dietary Exposure to Aluminum." Food Additives and Contaminants **12**(1): 119-128.
Platt, B., G. Fiddler, G. Riedel and Z. Henderson (2001). "Aluminium toxicity in the rat brain: Histochemical and immunocytochemical evidence." Brain Research Bulletin **55**(2): 257-267.
Poulos, B. K., M. Perazzolo, V. M. Y. Lee, R. Rudelli, H. M. Wisniewski and D. Soifer (1996). "Oral aluminum administration during pregnancy and lactation produces gastric and renal lesions in rat mothers and delay in cns development of their pups." Molecular & Chemical Neuropathology **29**(1): 15-26.
Priest, N. D. (1993). "The Bioavailability and Metabolism of Aluminum Compounds in Man." Proceedings of the Nutrition Society **52**(1): 231-240.
Priest, N. D. (2001). "The biological behaviour and bioavailability of aluminium in man, with special reference to studies employing Al-26 as a tracer." monograph, in prep.
Priest, N. D., D. Newton, J. P. Day, R. J. Talbot and A. J. Warner (1995). "Human metabolism of aluminium-26 and gallium-67 injected as citrates." Human & Experimental Toxicology **14**(3): 287-293.

Priest, N. D., R. J. Talbot, J. G. Austin, J. P. Day, S. J. King, K. Fifield and R. G. Cresswell (1996). "The bioavailability of al-26-labelled aluminium citrate and aluminium hydroxide in volunteers." Biometals **9**(3): 221-228.
Priest, N. D., R. J. Talbot, D. Newton, J. P. Day, S. J. King and L. K. Fifield (1998). "Uptake by man of aluminium in a public water supply." Human & Experimental Toxicology **17**(6): 296-301.
Radunovic, A., F. Ueda, K. B. Raja, R. J. Simpson, J. Templar, S. J. King, J. S. Lilley, J. P. Day and M. W. B. Bradbury (1997). "Uptake of 26-al and 67-ga into brain and other tissues of normal and hypotransferrinaemic mice." Biometals **10**(3): 185-191.
Rajwanshi, P., V. Singh, M. K. Gupta, V. Kumari, R. Shrivastav, M. Ramanamurthy and S. Dass (1997). "Studies on aluminium leaching from cookware in tea and coffee and estimation of aluminium content in toothpaste, baking powder and paan masala." Science of the Total Environment **193**(3): 243-249.
Ranau, R., J. Oehlenschlager and H. Steinhart (2001). "Aluminium levels of fish fillets baked and grilled in aluminium foil." Food Chemistry **73**(1): 1-6.
Recker, R. R., A. J. Blotcky, J. A. Leffler and E. P. Rack (1977). "Evidence of aluminum absorption from the gastrointestinal tract and bone deposition by aluminum carbonate ingestion with normal renal function." Journal of Laboratory & Clinical Medicine **90**(5): 810-5.
Reiber, S., W. Kukull and P. Standishlee (1995). "Drinking water aluminum and bioavailability." Journal American Water Works Association **87**(5): 86-100.
Reusche, E., V. Koch, H. J. Friedrich, D. Nunninghoff, P. Stein and P. M. Rob (1996). "Correlation of drug-related aluminum intake and dialysis treatment with deposition of argyrophilic aluminum-containing inclusions in cns and in organ systems of patients with dialysis-associated encephalopathy." Clinical Neuropathology **15**(6): 342-347.
Reusche, E., V. Koch, B. Lindner, A. P. Harrison and H. J. Friedrich (2001). "Alzheimer morphology is not increased in dialysis-associated encephalopathy and long-term hemodialysis." Acta Neuropathologica **101**(3): 211-216.
Reusche, E., P. Pilz, G. Oberascher, B. Lindner, R. Egensperger, K. L. Gloeckner, E. Trinka and B. Iglseder (2001). "Subacute fatal aluminum encephalopathy after reconstructive otoneurosurgery: A case report." Human Pathology **32**(10): 1136-1140.
Riihimaki, V., H. Hanninen, R. Akila, T. Kovala, E. Kuosma, H. Paakkulainen, S. Valkonen and B. Engstrom (2000). "Body burden of aluminum in relation to central nervous system function among metal inert-gas welders." Scandinavian Journal of Work, Environment & Health **26**(2): 118-130.
Roberts, N. B., A. Clough, J. P. Bellia and J. Y. Kim (1998). "Increased absorption of aluminium from a normal dietary intake in dementia." Journal of Inorganic Biochemistry **69**(3): 171-6.
Rocha, L., C. Garcia, A. de Mendonca, J. P. Gil, D. T. Bishop and M. C. Lechner (1999). "N-acetyltransferase (NAT2) genotype and susceptibility to sporadic Alzheimer's disease." Pharmacogenetics **9**(1): 9-15.
Rollin, H. B., P. Theodorou and T. A. Kilroesmith (1991). "Deposition of Aluminum in Tissues of Rabbits Exposed to Inhalation of Low Concentrations of Al2o3 Dust." British Journal of Industrial Medicine **48**(6): 389-391.
Rondeau, V., D. Commenges, H. Jacqmin-Gadda and J. F. Dartigues (2000). "Relation between aluminum concentrations in drinking water and Alzheimer's disease: An 8-year follow-up study." American Journal of Epidemiology **152**(1): 59-66.
Rondeau, V., H. Jacqmin-Gadda, D. Commenges and J. F. Dartigues (2001). "Re: Aluminum in drinking water and cognitive decline in elderly subjects: The Paquid cohort." American Journal of Epidemiology **154**(3): 288-290.
Ryan, D. H. (1994). "A scottish record linkage study of risk factors in medical history and dementia outcome in hospital patients." Dementia **5**(6): 339-347.
Salahudeen, A. K., B. Deogaygay, E. Fleischmann and J. D. Bower (2000). "Race-dependent survival disparity on hemodialysis: higher serum aluminum as an independent risk factor for higher mortality in whites." American Journal of Kidney Diseases **36**(6): 1147-54.
Sarin, S., V. Gupta and K. D. Gill (1997). "Alterations in lipid composition and neuronal injury in primates following chronic aluminium exposure." Biological Trace Element Research **59**(1-3 Special Issue SI): 133-143.
Sarin, S., D. Julka and K. D. Gill (1997). "Regional alterations in calcium homeostasis in the primate brain following chronic aluminium exposure." Molecular & Cellular Biochemistry **168**(1-2): 95-100.
Savory, J., C. Exley, W. F. Forbes, Y. Huang, J. G. Joshi, T. Kruck, D. R. McLachlan and I. Wakayama (1996). "Can the controversy of the role of aluminum in Alzheimer's disease be resolved? What are the suggested approaches to this controversy and methodological issues to be considered?" Journal of Toxicology & Environmental Health **48**(6): 615-35.

Savory, J. and R. M. Garruto (1998). "Aluminum, tau protein, and alzheimers-disease - an important link." Nutrition **14**(3): 313-314.
Savory, J., M. M. Herman, R. T. Erasmus, J. C. Boyd and M. R. Wills (1994). "Partial reversal of aluminium-induced neurofibrillary degeneration by desferrioxamine in adult male rabbits." Neuropathology & Applied Neurobiology **20**(1): 31-37.
Savory, J., Y. Huang, M. M. Herman, M. R. Reyes and M. R. Wills (1995). "Tau immunoreactivity associated with aluminum maltolate-induced neurofibrillary degeneration in rabbits." Brain Research **669**(2): 325-329.
Savory, J., Y. Huang, M. R. Wills and M. M. Herman (1998). "Reversal by desferrioxamine of tau protein aggregates following two days of treatment in aluminum-induced neurofibrillary degeneration in rabbit - implications for clinical trials in alzheimers-disease." Neurotoxicology **19**(2): 209-214.
Schintu, M., P. Meloni and A. Contu (2000). "Aluminum fractions in drinking water from reservoirs." Ecotoxicology & Environmental Safety **46**(1): 29-33.
Schonholzer, K. W., R. A. L. Sutton, V. R. Walker, V. Sossi, M. Schulzer, C. Orvig, E. Venczel, R. R. Johnson, D. Vetterli, B. Dittrichhannen, P. Kubik and M. Suter (1997). "Intestinal absorption of trace amounts of aluminium in rats studied with (26)aluminium and accelerator mass spectrometry." Clinical Science **92**(4): 379-383.
Schrier, R. W. and C. W. Gottschalk, Eds. (1997). Diseases of the Kidney. Boston, Little, Brown.
Schutze, K., E. Hentschel, P. Happonen and J. Akkila (1995). "Sucralfate effervescent tablet: treatment of peptic ulcer disease and change in serum aluminium concentration." Hepato Gastroenterology **42**(3): 240-5.
Sharpe, F. R. and D. R. Williams (1995). "Content, chemical speciation, and significance of aluminum in beer." Journal of the American Society of Brewing Chemists **53**(2): 85-92.
Shea, T. B. and M. L. Beermann (1994). "Multiple interactions of aluminum with neurofilament subunits - regulation by phosphate-dependent interactions between c-terminal extensions of the high and middle molecular weight subunits." Journal of Neuroscience Research **38**(2): 160-166.
Shea, T. B., M. L. Beermann and R. A. Nixon (1995). "Aluminum treatment of intact neuroblastoma cells alters neurofilament subunit phosphorylation, solubility, and proteolysis." Molecular & Chemical Neuropathology **26**(1): 1-14.
Shea, T. B. and T. Husain (1995). "Inhibition of proteolysis enhances aluminum-induced perikaryal neurofilament accumulation but does not enhance tau accumulation." Molecular & Chemical Neuropathology **26**(3): 195-212.
Shea, T. B., E. Wheeler and C. Jung (1997). "Aluminum inhibits neurofilament assembly, cytoskeletal incorporation, and axonal transport. Dynamic nature of aluminum-induced perikaryal neurofilament accumulations as revealed by subunit turnover." Molecular & Chemical Neuropathology **32**(1-3): 17-39.
Shoskes, D. A., C. A. Radzinski, N. W. Struthers and R. J. Honey (1992). "Aluminum toxicity and death following intravesical alum irrigation in a patient with renal impairment." Journal of Urology **147**(3): 697-9.
Sim, M., R. Dick, J. Russo, B. Bernard, P. Grubb, E. Krieg, C. Mueller and C. McCammon (1997). "Are aluminium potroom workers at increased risk of neurological disorders." Occupational & Environmental Medicine **54**(4): 229-235.
Singer, S. M., C. B. Chambers, G. A. Newfry, M. A. Norlund and N. A. Muma (1997). "Tau in aluminum-induced neurofibrillary tangles." Neurotoxicology **18**(1): 63-76.
Sjogren, B. (1997). Health in the Aluminium Industry: Biological Estimates of Aluminium Exposure and its Effects on the Nervous System of Occupationally Exposed Workers. International Conference on Managing Health Issues in the Aluminium Industry, Montreal, Canada, Middlesex University Press, London, England.
Sjogren, B., A. Iregren, W. Frech, M. Hagman, L. Johansson, M. Tesarz and A. Wennberg (1996). "Effects on the nervous system among welders exposed to aluminium and manganese." Occupational & Environmental Medicine **53**(1): 32-40.
Sjogren, B., K. G. Ljunggren, O. Almkvist, W. Frech and H. Basun (1996). "A follow-up study of five cases of aluminosis." International Archives of Occupational & Environmental Health **68**(3): 161-4.
Smans, K. A., P. C. D'Haese, G. F. Van Landeghem, L. J. Andries, L. V. Lamberts, G. N. Hendy and M. E. De Broe (2000). "Transferrin-mediated uptake of aluminium by human parathyroid cells results in reduced parathyroid hormone secretion." Nephrology Dialysis Transplantation **15**(9): 1328-36.
Soni, M. G., S. M. White, W. G. Flamm and G. A. Burdock (2001). "Safety evaluation of dietary aluminum." Regulatory Toxicology & Pharmacology **33**(1): 66-79.

Stauber, J. L., T. M. Florence, C. M. Davies, M. S. Adams and S. J. Buchanan (1999). "Bioavailability of Al in alum-treated drinking water." Journal American Water Works Association **91**(11): 84-93.
Strong, M. J., R. M. Garruto, J. G. Joshi, W. R. Mundy and T. J. Shafer (1996). "Can the mechanisms of aluminum neurotoxicity be integrated into a unified scheme." Journal of Toxicology & Environmental Health **48**(6): 599-613.
Struys-Ponsar, C., O. Guillard and P. van den Bosch de Aguilar (2000). "Effects of aluminum exposure on glutamate metabolism: a possible explanation for its toxicity." Experimental Neurology **163**(1): 157-64.
Struysponsar, C., A. Kerkhofs, A. Gauthier, M. Soffie and P. V. Deaguilar (1997). "Effects of aluminum exposure on behavioral parameters in the rat." Pharmacology, Biochemistry & Behavior **56**(4): 643-648.
Swain, C. and G. B. N. Chainy (1998). "Effects of aluminum sulphate and citric acid ingestion on lipid peroxidation and on activities of superoxide dismutase and catalase in cerebral hemisphere and liver of developing young chicks." Molecular & Cellular Biochemistry **187**(1-2): 163-172.
Talbot, R. J., D. Newton, N. D. Priest, J. G. Austin and J. P. Day (1995). "Inter-subject variability in the metabolism of aluminium following intravenous injection as citrate." Human & Experimental Toxicology **14**(7): 595-599.
Taylor, G. A., I. N. Ferrier, I. J. McLoughlin, A. F. Fairbairn, I. G. McKeith, D. Lett and J. A. Edwardson (1992). "Gastrointestinal absorption of aluminium in Alzheimer's disease: response to aluminium citrate." Age & Ageing **21**(2): 81-90.
Taylor, G. A., P. B. Moore, I. N. Ferrier, S. P. Tyrer and J. A. Edwardson (1998). "Gastrointestinal absorption of aluminium and citrate in man." Journal of Inorganic Biochemistry **69**(3): 165-170.
Testolin, G., D. Erba, S. Ciappellano and G. Bermano (1996). "Influence of organic acids on aluminium absorption and storage in rat tissues." Food Additives & Contaminants **13**(1): 21-27.
Thorne, B. M., T. Donohoe, K. N. Lin, S. Lyon, D. M. Medeiros and M. L. Weaver (1986). "Aluminum ingestion and behavior in the Long-Evans rat." Physiology & Behavior **36**(1): 63-7.
Tjalve, H. and I. Henriksson (1999). "Uptake of metals in the brain via olfactory pathways." Neurotoxicology **20**(2-3): 181-195.
Tsunoda, M. and R. P. Sharma (1999). "Altered dopamine turnover in murine hypothalamus after low-dose continuous oral administration of aluminum." Journal of Trace Elements in Medicine & Biology **13**(4): 224-31.
Tsunoda, M. and R. P. Sharma (1999). "Modulation of tumor necrosis factor alpha expression in mouse brain after exposure to aluminum in drinking water." Archives of Toxicology **73**(8-9): 419-426.
Vandervoet, G. B. and F. A. Dewolff (1998). "Intestinal absorption of aluminium - effect of sodium and calcium." Archives of Toxicology **72**(2): 110-114.
Varner, J. A., W. J. Horvath, C. W. Huie, H. R. Naslund and R. L. Isaacson (1994). "Chronic aluminum fluoride administration. I. Behavioral observations." Behavioral & Neural Biology **61**(3): 233-41.
Vyas, S. B. and L. K. Duffy (1995). "Stabilization of secondary structure of Alzheimer beta-protein by aluminum(III) ions and D-Asp substitutions." Biochemical & Biophysical Research Communications **206**(2): 718-23.
W.H.O. (1997). International Programme on Chemical Safety, Environmental Health Criteria 194, Aluminium. Geneva, World Health OrganizationWorld Health Organization.
Walton, J., C. Tuniz, D. Fink, G. Jacobsen and D. Wilcox (1995). "Uptake of trace amounts of aluminum into the brain from drinking water." Neurotoxicology **16**(1): 187-190.
Watt, F. (1996). "Nuclear microscope analysis in Alzheimer's and Parkinson's disease: A review." Cellular & Molecular Biology **42**(1): 17-26.
WHO (1997). International Programme on Chemical Safety, Environmental Health Criteria 194, Aluminium. Geneva, World Health Organization.
WHO (1998). Giudelines for drinking water quality, 2nd ed. Addendum to Vol. 1. Recommendations. Geneva, World Health Organization**:** 3-4.
Wilhelm, M., J. Passlick, T. Busch, M. Szydlik and F. K. Ohnesorge (1989). "Scalp hair as an indicator of aluminium exposure: comparison to bone and plasma." Human Toxicology **8**(1): 5-9.
Wisniewski, H. M. (1994). "Aluminium, tau protein, and alzheimers disease." Lancet **344**(8916): 204-205.
Woodson, G. C. (1998). "An interesting case of osteomalacia due to antacid use associated with stainable bone aluminum in a patient with normal renal function." Bone **22**(6): 695-8.

Wu, Y. H., Z. M. Zhou, Y. L. Xiong, Y. L. Wang, J. H. Sun, H. B. Liao and X. D. Luo (1998). "Effects of aluminum potassium sulfate on learning, memory, and cholinergic system in mice." Chung Kuo Yao Li Hsueh Pao Acta Pharmacologica Sinica **19**(6): 509-12.

Xie, C. X., M. P. Mattson, M. A. Lovell and R. A. Yokel (1996). "Intraneuronal aluminum potentiates iron-induced oxidative stress in cultured rat hippocampal neurons." Brain Research **743**(1-2): 271-277.

Xie, C. X., J. St Pyrek, W. H. Porter and R. A. Yokel (1995). "Hydroxyl radical generation in rat brain is initiated by iron but not aluminum, as determined by microdialysis with salicylate trapping and GC-MS analysis." Neurotoxicology **16**(3): 489-96.

Xie, C. X. and R. A. Yokel (1996). "Aluminum facilitation of iron-mediated lipid peroxidation is dependent on substrate, ph, and aluminum and iron concentrations." Archives of Biochemistry & Biophysics **327**(2): 222-226.

Yase, Y., S. Yoshida, T. Kihira, I. Wakayama and J. Komoto (2001). "Kii ALS dementia." Neuropathology **21**(2): 105-9.

Yen-Koo, H. C. (1992). "The effect of aluminum on conditioned avoidance response (CAR) in mice." Toxicology & Industrial Health **8**(1-2): 1-7.

Yokel, R. A. (1989). "Aluminum produces age related behavioral toxicity in the rabbit." Neurotoxicology & Teratology **11**(3): 237-42.

Yokel, R. A. (2000). "The toxicology of aluminum in the brain: A review." Neurotoxicology **21**(5): 813-828.

Yokel, R. A., D. D. Allen and D. C. Ackley (1999). "The distribution of aluminum into and out of the brain." Journal of Inorganic Biochemistry **76**(2): 127-132.

Yokel, R. A. and J. P. Ocallaghan (1998). "An aluminum-induced increase in gfap is attenuated by some chelators." Neurotoxicology & Teratology **20**(1): 55-60.

Yokel, R. A., S. S. Rhineheimer, R. D. Brauer, P. Sharma, D. Elmore and P. J. McNamara (2001). "Aluminum bioavailability from drinking water is very low and is not appreciably influenced by stomach contents or water hardness." Toxicology **161**(1-2): 93-101.

Yokel, R. A., S. S. Rhineheimer, P. Sharma, D. Elmore and P. J. McNamara (2001). "Entry, half-life, and desferrioxamine-accelerated clearance of brain aluminum after a single Al-26 exposure." Toxicological Sciences **64**(1): 77-82.

Yumoto, S., H. Nagai, M. Imamura, H. Matsuzaki, K. Hayashi, A. Masuda, H. Kumazawa, H. Ohashi and K. Kobayashi (1997). "Al-26 uptake and accumulation in the rat brain." Nuclear Instruments & Methods in Physics Research Section B Beam Interactions with Materials & Atoms **123**(1-4): 279-282.

Yumoto, S., H. Nagai, H. Matsuzaki, H. Matsumura, W. Tada, E. Nagatsuma and K. Kobayashi (2001). "Aluminium incorporation into the brain of rat fetuses and sucklings." Brain Research Bulletin **55**(2): 229-234.

Zafar, T. A., C. M. Weaver, B. R. Martin, R. Flarend and D. Elmore (1997). "Aluminum (al-26) metabolism in rats." Proceedings of the Society for Experimental Biology & Medicine **216**(1): 81-85.

Zapatero, M. D., A. Garcia de Jalon, F. Pascual, M. L. Calvo, J. Escanero and A. Marro (1995). "Serum aluminum levels in Alzheimer's disease and other senile dementias." Biological Trace Element Research **47**(1-3): 235-40.

Appendix 22: Review of the scientific literature on aluminium (January 2002 to October 2003) prepared for the Lowermoor Subgroup by the Department of Health Toxicology Unit, Imperial College, London

Note: this was a paper prepared for discussion by the Lowermoor subgroup. It does not necessarily represent the views of the subgroup

AN UPDATE OF PUBLICATIONS RELATING TO THE TOXICITY OF ALUMINIUM, 2002-October 2003

A report prepared for the Department of Health Committee on Toxicity, Lowermoor Subgroup by the Department of Health Toxicology Unit at Imperial College London.

1 Introduction

Aluminium (Al) toxicity was reviewed in detail in an update of the 1997 WHO (IPCS) Environmental Health Criteria 194 report on Aluminium, prepared for the COT-Lowermoor Subgroup in Spring 2002 (LSG/02/7). This report is a further update, describing relevant publications from the period Jan 2002-October 2003 (by publication date).

The data included have been restricted to toxic and/or other biological effects of Al in humans and in animal models. In vitro/mechanistic studies have not been described, but a bibliography of these recent publications is provided in Appendix 1.

2 Aluminium toxicity publications 2002-2003

2.1 General literature

The US Food and Drug Administration (FDA) published a final monograph on antiperspirant drug products for over-the-counter human use (Food and Drug Administration, 2003). Section II. F. of this ruling details comments on the safety of aluminium ingredients, including critical discussion of some publications regarding the potential toxicity of aluminium by various routes of intake, in particular, neurotoxicity and the possible involvement of aluminium in Alzheimer's and Parkinson's diseases and amyotrophic lateral sclerosis (ALS).

The FDA concluded that the literature showed that high doses and long-term industrial exposures to aluminium can be associated with recognisable specific neurological effects, but that the evidence to date was insufficient to link aluminium to Alzheimer's disease, Parkinson's disease or ALS. It was noted that people with renal dysfunction should be alerted to consult a doctor before using or continuing to use Al-containing antiperspirant products. It was also recommended that a general warning be included to keep antiperspirant drug products away from infants, who may be at higher risk from Al exposure due to immature renal function. In support of this, the agency stated that it "… acknowledges that small amounts of aluminum can be absorbed from the GI tract and through the skin. Assuming a person has normal renal function, accumulation of aluminum resulting from usual exposures to antiperspirant drug products (application to the underarms once or twice daily) and subsequent absorption is considered minimal. However, people with renal dysfunction have an impairment in normal renal excretion of aluminum… The agency considers it prudent to alert these people to consult a doctor before using or continuing to use these products on a regular basis and is including a warning in the final monograph: 'Ask a doctor before use if you have kidney disease'."

2.2 Human data

2.2.1 Acute/sub-acute exposure

(Owen *et al*., 2002) carried out a retrospective study to evaluate mortality rates (from July 1988 to December 1997) in the population of a region of Cornwall supplied by water from the Lowermoor treatment works at the time of the 1988 aluminium sulphate contamination incident. The ratio of standardised mortality ratios (SMRs) for subjects living in an area supplied by the Lowermoor works (n = 11 114), as compared with those in an adjacent area with a different water supply (n = 5359) was 1.08 (95% CI, 0.97-1.21). The SMR for the Lowermoor-supplied region was lower than that for the county of Cornwall as a whole (81.6; 95% CI, 77.2-86.2) and lower than that for the England and Wales standard population (77.7; 95% CI, 73.5-82.0).

2.2.2 Chronic exposure

Renal failure patients

Encephalopathy due to aluminium overload in renal failure patients is a well-documented syndrome (see LSG/02/7) and further publications will generally not be described here. One recent case report described autopsy findings in a 59-year-old female encephalopathy patient, who had chronic renal failure and took 3.0 g hydroxy-aluminium gel per day during a 15-year period. Aluminium deposition and neuropathological changes in the brain were noted, but there were no signs of Alzheimer's disease (AD), supporting the hypothesis that aluminium alone is not causal for AD (Shirabe *et al*., 2002).

Occupational exposure

(Polizzi *et al*., 2002) reported that foundry workers who had previously (≥ 10 years before) been exposed to aluminium dust (low-level occupational exposure for several years) had significantly higher serum aluminium concentrations and blood iron concentrations than a control group without occupational exposure. A positive relationship was observed between serum aluminium concentration and some tests of cognitive function.

2.3 Animal data

Studies described have been restricted to those in which aluminium administration was by the oral route.

2.3.1 Biodistribution

(Ogasawara *et al*., 2002) reported that oral administration of 270 mg/l aluminium (as hydroxide or chloride, in tap water) and citric acid (molar ratio aluminium : citric acid = 1:2) for 7 weeks did not increase brain aluminium levels in rats.

2.3.2 Acute exposure

(Micic *et al*., 2003) reported that oral application of a single, high dose of aluminium chloride (3.7 g/kg bw $AlCl_3.6H_2O$, ~ 414 mg/kg bw aluminium) resulted in a biphasic pattern of increased superoxide dismutase (SOD) activity in the brains of Mongolian gerbils during the subsequent 4 days (up to 200% and 171% increase as compared

with control animals at 24 hours and 96 hours, respectively, after treatment; no significant difference between treated and control animals at 48 hours). Twenty of the 52 treated animals died within 24 hours of aluminium treatment, the other 32 animals survived until the end of the experiment, but showed signs of sickness such as slow gait, splaying of extremities and loss of appetite.

2.3.3 Reproductive/developmental effects

A reproductive toxicity study in which high dose (probably 1000 mg/kg diet, ~ 150 mg/kg bw/day, although this is unclear[98]) was fed to female Swiss Webster mice from conception to weaning showed reduced weaning weight associated with aluminium treatment. Pregnancy weight gain was not affected. Maternal food intake was not reported (Golub *et al*., 2003).

2.3.4 Sub-chronic/chronic exposure

Neurobehavioural effects

Treatment for 6 months with 0.1% aluminium, as sulphate in drinking water (~ 200 mg/kg bw/day aluminium) did not affect tests of spatial working memory in rats (von Linstow *et al*., 2002).

Treatment of young and old male rats for 100 days with 100 mg/kg bw/day Al[99] (as nitrate nonahydrate, in drinking water, + citric acid) did not affect performance in behavioural tests. The total number of synapses in the left CA1 fields of hippocampal formation decreased with both age (~ 22% lower in control aged vv. control young rats) and aluminium exposure (~ 32% lower in aluminium -loaded young vv. control young rats; ~ 8% lower in aluminium-loaded aged vv. control aged rats) (Colomina *et al*., 2002).

Gavage treatment of rats with 50 or 200 mg/kg bw/day aluminium chloride (~ 10 or 40 mg/kg bw/day aluminium, described by the authors as one twentieth and one fifth of the oral LD_{50}, respectively) for 8 weeks (5 days/week) had no significant effect on central electrophysiological or behavioural parameters evaluated. Brain aluminium levels were increased by ~ 34% and 153% in the low and high-dose aluminium groups, respectively, as compared with a control group (Baydar *et al*., 2003).

Neuropathology

Chronic (24 month) exposure of mice to a diet containing very high levels of aluminium (15600 mg/kg di*et al*uminium hydroxide, ~ 810 mg/kg bw/day aluminium), with or without low levels of Ca and Mg, resulted in a significant increase in tau-positive neurons in the brains of these animals (Kihira *et al*., 2002).

(El Rahman, 2003) reported that gavage treatment of rats with aluminium (43, 86 or 172 mg/kg bw/day, as sulphate) for 35 days was associated with pathological changes in brain tissue. These changes included congestion of cerebral blood vessels (all

[98] The dose given is unclear - described variously throughout the report as 1000 μg/g, 1000 mg/g and 1000 μg/kg diet.
[99] It is not entirely clear from the report whether the dose was 100 mg/kg bw/day Al or 100 mg/kg bw/day Al nitrate.

doses) and haemorrhage (2 higher doses); meningeal damage (highest dose); neuronal degeneration of the cerebral cortex (all groups, dose-dependent), subcortical region, base of the brain and hippocampus (2 higher doses). Dose-dependent increases in brain glutamate and glutamine, decreases in GABA, and increases in brain aluminium levels were observed.

Neurophysiology

(Chen *et al*., 2002) reported that neonatal exposure of rats to aluminium from birth to weaning (day 21) affected electrophysiological indicators of pre- and post-synaptic mechanisms of (central) synaptic transmission which were evaluated at 90-120 days. (Exposure was *via* breast milk, dams were given water contain 0.3% aluminium chloride [~ 120 mg/kg bw/day Al]).

Neurochemistry

Cholinesterase activity

Brain acetylcholinesterase (AChE) activity was increased (around 1.5-fold) in mice given 10 mg/day aluminium (~ 500 mg/kg bw/day, in water, as chloride or lactate) for 1-3 months (Zatta *et al*., 2002).

(Dave *et al*., 2002) reported that dietary supplementation with aluminium (100 mg/kg bw/day aluminium chloride, ~ 20 mg/kg bw/day aluminium) for 100-115 days was associated with inhibition of rat brain AChE activity (V_{max} of soluble fraction component I of soluble form decreased by 34%; V_{max} of components I and II of membrane-bound form decreased by 20% and 19%, respectively), whilst butyrylcholinesterase (BChE) activities in heart and liver were increased (V_{max} soluble fraction components I and II heart increased 2.3-fold; V_{max} components I and II membrane bound heart increased 74% and 160%, respectively; V_{max} components I and II soluble form liver increased by 58% and 83%, respectively; V_{max} components I and II membrane-bound liver increased by 91% and 168%, respectively).

5-hydroxytryptamine (5-HT)

(Kumar, 2002) reported that oral administration of aluminium to rats as aluminium chloride (320 mg/kg bw, ~ 36 mg/kg bw/day Al, by gavage) for periods of 4 to 60 days had varying effects on brain 5-HT levels depending on the brain region and duration of exposure. The authors suggested that these changes may be related to the cholinergic toxicity of aluminium.

Neuronal nitric oxide synthase (nNOS)

Rats were exposed to 0, 5 and 10 mM aluminium chloride (in drinking water) beginning 3 weeks after birth and continuing through mating and gestation, and suckling (pups exposed for 3 weeks gestation, 3 weeks suckling). Pups were then analysed for nNOS-immunoreactive neurons in regions of the cortex; levels were increased (10%) in the 5mM group and decreased (17%) in the 10 mM group. The authors suggested that impaired expression of nNOS induced by aluminium treatment may be neurotoxic because it disturbs the link between glutamatergic and monoaminergic neurons (Kim, 2003).

Oxidative stress

Chronic treatment (8 months) with drinking water containing 0.2% aluminium nitrate affected indices of oxidative stress in rat brain regions (catalase activity increased 49% cortex, 11% midbrain; GST activity decreased 49% cortex, 46% cerebellum, 26% pons, 23% mid-brain; GPx levels increased 18% cerebellum; TBARs increased ~ 100%; GSSG increased ~ 30%; GSH no significant change). Blood δ-ALAD were decreased by ~ 25% and ZPP increased by ~ 40%. Aluminium levels were significantly increased by the treatment (~ 5-fold increase in blood; ~ 2-fold increase in brain) (Flora *et al*., 2003).

(Pratico *et al*., 2002) reported that feeding an aluminium-enriched diet (2 mg/kg diet, ~ 0.3 mg/kg bw/day aluminium) for 9 months to transgenic mice which over-express human amyloid precursor protein led to an increase in markers of oxidative stress and increased amyloid β peptide formation and deposition in the brain. These effects were ameliorated by co-inclusion of vitamin E in the diet.

2.4 In vitro/mechanistic studies

Several recent papers have described studies of the effects of aluminium in vitro. Many of these studies have used neural cell cultures to investigate the possible effects/mechanisms of aluminium involvement in neurodegenerative syndromes such as Parkinson's and Alzheimer's disease and ALS. These studies are not described here.

3 Summary

Very few new studies have been published regarding potential adverse effects of aluminium in healthy (i.e. non-renal failure) human subjects. One study (Owen *et al*., 2002) compared mortality rates in subjects likely to have been exposed to aluminium sulphate-contaminated water following the 1988 Lowermoor incident with those in a neighbouring area (not Lowermoor-supplied). The rate for the "supplied" population was slightly higher (1.08), but the difference was not significant, and rates in both areas were lower than national rates and those for the county of Cornwall. (This paper has previously been discussed by the LSG).

Several recently-published studies have evaluated effects of oral aluminium dosing in animal models. The majority of these studies have focussed on neurological effects. Studies in rats showed no effects of chronic aluminium supplementation (10-200 mg/kg bw/day[100] for several weeks or months) on behavioural measures. Some adverse effects (neuropathological and neurophysiological) were observed in cases where chronic treatment with very high levels of aluminium was given. Gavage treatment of rats with high levels of aluminium sulphate (43-172 mg/kg bw/day aluminium) for 5 weeks was also associated with neuropathological and

[100] For comparison, the maximum theoretical Al concentration in the water supply following the Lowermoor incident was estimated as 21 mg/kg bw/day for a 60 kg adult (based on daily intake of 2l water containing 620 mg/l Al [the maximum estimated concentration in the cold water supply – see LSG/03/07]. The time period of exposure is unclear, but perhaps in the region of several hours or days.

neurochemical changes (El-Rahman, 2002). One study showed that high-dose aluminium supplementation (0.3% aluminium chloride in drinking water, ~ 120 mg/kg bw/day aluminium) to rat dams from birth to weaning affected indicators of neurotransmission in offspring several months later (Chen *et al*., 2002). Gavage treatment of rats with aluminium chloride (320 mg/kg bw/day $AlCl_3.6H_2O$, ~ 36 mg/kg bw/day aluminium) for periods of 4 to 60 days was associated with increased, decreased or unaltered brain 5-HT levels, depending on the specific region of the brain and the duration of treatment (Kumar, 2002).

October 2003

Reference List to Appendix 22

Baydar,T., Papp,A., Aydin,A., Nagymajtenyi,L., Schulz,H., Isimer,A., and Sahin,G. (2003). Accumulation of aluminum in rat brain: does it lead to behavioral and electrophysiological changes? Biol. Trace Elem. Res. *92*, 231-244.

Chen,J., Wang,M., Ruan,D., and She,J. (2002). Early chronic aluminium exposure impairs long-term potentiation and depression to the rat dentate gyrus *in vivo*. Neuroscience *112*, 879-887.

Colomina,M.T., Roig,J.L., Sanchez,D.J., and Domingo,J.L. (2002). Influence of age on aluminum-induced neurobehavioral effects and morphological changes in rat brain. Neurotoxicology *23*, 775-781.

Dave,K.R., Syal,A.R., and Katyare,S.S. (2002). Effect of long-term aluminum feeding on kinetics attributes of tissue cholinesterases. Brain Res. Bull. *58*, 225-233.

El Rahman,S.S. (2003). Neuropathology of aluminum toxicity in rats (glutamate and GABA impairment). Pharmacol. Res. *47*, 189-194.

Flora,S.J., Mehta,A., Satsangi,K., Kannan,G.M., and Gupta,M. (2003). Aluminum-induced oxidative stress in rat brain: response to combined administration of citric acid and HEDTA. Comp Biochem. Physiol C. Toxicol. Pharmacol. *134*, 319-328.

Food and Drug Administration (2003). Antiperspirant drug products for over-the-counter human use; final monograph. Final rule. Fed. Regist. *68*, 34273-34293.

Golub,M.S., Germann,S.L., and Keen,C.L. (2003). Developmental aluminum toxicity in mice can be modulated by low concentrations of minerals (Fe, Zn, P, Ca, Mg) in the diet. Biol. Trace Elem. Res. *93*, 213-226.

Kihira,T., Yoshida,S., Yase,Y., Ono,S., and Kondo,T. (2002). Chronic low-Ca/Mg high-Al diet induces neuronal loss. Neuropathology. *22*, 171-179.

Kim,K. (2003). Perinatal exposure to aluminum alters neuronal nitric oxide synthase expression in the frontal cortex of rat offspring. Brain Res. Bull. *61*, 437-441.

Kumar,S. (2002). Aluminium-induced changes in the rat brain serotonin system. Food Chem. Toxicol. *40*, 1875-1880.

Micic,D.V., Petronijevic,N.D., and Vucetic,S.S. (2003). Superoxide dismutase activity in the mongolian gerbil brain after acute poisoning with aluminum. J. Alzheimers. Dis. *5*, 49-56.

Ogasawara,Y., Sakamoto,T., Ishii,K., Takahashi,H., and Tanabe,S. (2002). Effects of the administration routes and chemical forms of aluminum on aluminum accumulation in rat brain. Biol. Trace Elem. Res. *86*, 269-278.

Owen,P.J., Miles,D.P., Draper,G.J., and Vincent,T.J. (2002). Retrospective study of mortality after a water pollution incident at Lowermoor in north Cornwall. BMJ *324*, 1189.

Pratico,D., Uryu,K., Sung,S., Tang,S., Trojanowski,J.Q., and Lee,V.M. (2002). Aluminum modulates brain amyloidosis through oxidative stress in APP transgenic mice. FASEB J. *16*, 1138-1140.

Shirabe,T., Irie,K., and Uchida,M. (2002). Autopsy case of aluminum encephalopathy. Neuropathology. *22*, 206-210.

von Linstow,R.E., Platt,B., and Riedel,G. (2002). No spatial working memory deficit in beta-amyloid-exposed rats. A longitudinal study. Prog. Neuropsychopharmacol. Biol. Psychiatry *26*, 955-970.

Zatta,P., Ibn-Lkhayat-Idrissi,M., Zambenedetti,P., Kilyen,M., and Kiss,T. (2002). *In vivo* and in vitro effects of aluminum on the activity of mouse brain acetylcholinesterase. Brain Res. Bull. *59*, 41-45.

Appendix 23: Review of the scientific literature on aluminium (October 2003 to April 2005) prepared for the Lowermoor subgroup by the Department of Health Toxicology Unit, Imperial College, London

Note: this was a paper prepared for discussion by the Lowermoor subgroup. It does not necessarily represent the views of the subgroup

AN UPDATE OF PUBLICATIONS RELATING TO ALUMINIUM TOXICITY October 2003-April 2005.

A report prepared for the Department of Health Committee on Toxicity, Lowermoor Subgroup by the Department of Health Toxicology Unit at Imperial College London.

1. Aluminium toxicity was reviewed in detail in an update of the 1997 WHO (IPCS) Environmental Health Criteria 194 report on aluminium, prepared for the COT Lowermoor Subgroup in Spring 2002 and updated in 2003. This following report is an update of studies from 2003 to date, relating to biological and toxic effects of aluminium in humans and in animal models. The report is divided into two main sections: A] neurotoxicity and effects on the brain, and B] other toxic and biological effects. Reports of experimental studies in animals were only included if aluminium treatment was given by the oral route.

A. Neurotoxicity and effects on the brain

Human data

Epidemiological studies of cognitive impairment, dementia and Alzheimer's disease

2. An association was observed between serum aluminium concentrations and Alzheimer's disease in a group of 35 elderly patients evaluated for potential correlations between serum trace element concentrations and presence of cognitive impairment and/or dementia. Patients were divided into 4 groups: control [n = 11], cognitive impairment non-dementia (CIND) [n = 8], Alzheimer's disease (AD) [n = 8], vascular dementia (VaD) [n = 8]). The paper reports that trace element serum concentrations were in a normality range in all subjects. Serum aluminium concentrations (mean ± SD, in mg/ml) were 0.215 ± 0.106, 0.353 ± 0.145, 0.735 ± 0.158, 0.303 ± 0.183, respectively[101]. A significant negative correlation was also noted between MODA scores ('Milan Overall Dementia Assessment' - a test for the presence of dementia) and serum aluminium concentration in this group of 35 subjects (ie, higher aluminium correlated with lower cognitive function; $r = -0.628$, $p<0.0001$). MODA scores were also negatively correlated with copper serum concentrations, and positively correlated with selenium, cobalt, chromium and iron levels (Smorgon *et al*., 2004).

3. (Gillette-Guyonnet *et al*., 2005) reported an evaluation of potential associations between drinking water composition (aluminium, silica and calcium content) and cognitive impairment in a group of 7598 women aged ≥ 75 in France (the EPIDOS study cohort). Daily intakes of aluminium, silica and calcium supplied by drinking water were 0.0231 ± 0.025, 10.17 ± 10.01 and 134 ± 154.1 mg, respectively (mean ± SD). Cognitive performance was positively correlated with daily silica intake, but not with aluminium or calcium intakes. The authors concluded that the study did not show any evidence for aluminium as a risk factor for Alzheimer's disease.

Inhalation

[101] There is a question regarding the units cited by the authors here, as most reports cite standard serum Al concentrations in a range around ~ 10 μg/l.

4. (Buchta *et al*., 2003) described evaluations made in 1999 and 2001 as part of a longitudinal study of 98 welders with occupational exposure to aluminium welding fumes, as compared to a control group of 50 car-production workers at the same plant in Germany. Median plasma aluminium concentrations were approximately 10 (range ~ 2-40) μg/l in 1999 and 4 (range ~ 1-11) μg/l in 2001, whilst median urinary aluminium concentrations were around 40-70 (range ~ 2-250) μg/l [or 30-40 (range ~ 5-230) μg /g creatinine] (data for control subjects were not reported). There were no significant differences between test and control subjects in psychomotor performance and other neurobehavioural tasks, except that test subjects showed slower reaction times. The difference in reactions times between the groups did not change during the period of evaluation, and the authors suggested that it may be due to pre-exposure differences between the groups. Further evaluations were scheduled to be carried out in 2003.

5. A study in China showed differences in neurobehavioural parameters between a group of 32 men with occupational (14.91 ± 6.31 years, mean ± SD) aluminium exposure, as compared with a control group (workers at a flour plant). The aluminium workers had significantly higher scores for confusion and tension/anxiety, lower scores for standard reaction times, and lower scores for DSY (described as "digital symbol") and PA (pursuit aiming) tests. Other parameters tested were not significantly different between the two groups[102]. Mean urinary aluminium concentrations were 40.08 ± 9.36 and 26.84 ± 8.93 μg/mg creatine, in test and control groups, respectively (He *et al*., 2003).

Renal failure patients

6. Calcium intoxication was suspected in a group of 27 end-stage renal disease patients in Curacao, Netherlands Antilles, who presented with symptoms including nausea, vomiting and hypercalcaemia. Despite subsequently changing to a low-calcium dialysate, a number of the patients developed microcytic anaemia and neurological symptoms. Ten patients died of convulsions, sepsis and coma. Analysis showed mean ante mortem serum aluminium concentrations of 808 (359-1275) μg/l and 255 (113-490) μg/l in deceased patients and survivors, respectively (normal aluminium concentration < 10 μg/l, or < 50 μg/l in non-symptomatic dialysis patients). Investigations revealed high calcium and aluminium levels in the dialysis water supply due to leaching from a replacement supply pipe (de Wolff *et al*., 2002).

7. A patient with chronic renal failure, but not on dialysis, developed fatal aluminium-related encephalopathy due to self-dosing with large doses of antacids (total cited as at least 3 kg) for approximately 3 years (Zatta *et al*., 2004).

Reviews

8. (Gupta *et al*., 2005) published a review of the literature regarding potential associations of aluminium and Alzheimer's disease (AD). They concluded that aluminium is undoubtedly neurotoxic, that the involvement of aluminium as a factor

[102] The scoring systems are not explained in the report and it is not clear to the non-specialist what increases or decreases in scores indicate, except that, in the discussion, the authors state that Al workers performed better in neurobehavioural tests than controls, with quicker reaction times.

in AD cannot be discarded. However, whether aluminium is a sole factor in AD and whether it is a factor in all AD cases still needs to be understood.

Animal studies

Rats

9. (Jing *et al*., 2004) reported that treatment of adult male rats for 3 months with 500 mg/kg bw/day aluminium (in water solution, by perfusion through the stomach) led to increased brain aluminium content, changes in synaptic ultrastructure in the hippocampus and frontal cortex, and adverse effects on measures of memory function.

10. Wistar rats treated intragastrically with 500 mg/kg bw/day aluminium chloride (~ 100 mg/kg bw/day aluminium) for one month, followed by continuous exposure *via* drinking water containing 1600 ppm aluminium chloride for up to 5 months, showed impaired ability in tests of learning and memory function (Morris water maze). Subsequent treatment for 2 months with *Ginkgo biloba* extract was reported to ameliorate these effects (Gong *et al*., 2005).

11. Zhang *et al*. (2003) reported that they carried out a study to assess the potential of a herbal medicine (*Dipsacus asper*) to protect against cognitive impairment and overexpression of hippocampal β-amyloid protein induced by chronic aluminium exposure in rats (salt not specified). In this study groups of male, Sprague-Dawley rats (total aluminium -treated n = 84) were treated for 90 days with drinking water containing 0.3% aluminium chloride. Treated animals showed decreased performance in the one measure of cognitive function evaluated (passive avoidance task/step through latency), as compared with a group of 15 control animals treated with distilled water (mean latency of aluminium-exposed rats reported as only 19% that for control group). Treated animals also showed increased staining for β-amyloid protein in the brain (123 % more positive Aβ cells in aluminium-treated compared with control rats). Subsequent treatment with *Dipsacus asper* was reported to ameliorate some of these effects (Zhang *et al*., 2003).

12. Brain myelin phospholipid profiles were altered in male, albino rats treated with 100 mg/kg bw/day aluminium chloride (estimated to be ~ 20.3 mg/kg bw/day aluminium) in the diet, for 90 to 100 days. The authors noted that many of the changes observed were similar to those seen in the brains of subjects with Alzheimer's disease (Pandya *et al*., 2004).

13. Dietary supplementation for 4 months with 0.03 g/day aluminium chloride (estimated to be ~ 75 mg/kg bw/day aluminium chloride or ~ 15 mg/kg bw/day aluminium) was reported to alter the kinetic behaviour of brain Na^+/K^+ ATPase in adult, male rats (Silva and Goncalves, 2003).

14. (Fattoretti *et al*., 2003) measured copper, zinc and manganese concentrations in three brain regions (prosencephalon + mesencephalon, PME; cerebellum; pons-medulla, PMD) of aged, male Wistar rats treated with drinking water containing 2 g/l aluminium chloride ($AlCl_3.6H_2O$) (estimated to be ~ 11 mg/kg bw/day aluminium) for 6 months. Aluminium content increased in all three regions. The only other significant changes observed were increased PMD copper content and cerebellum zinc content. Histological examination showed an increase in the hippocampal area

occupied by mossy fibres. Treated animals were reported to show aggressive behaviour. A subsequent report by the same authors, apparently describing the same experiments and data, determined that all the changes (increases) measured in copper, zinc and manganese levels in PME and PMD regions were significant, whilst no significant changes occurred in the cerebellum (Fattoretti *et al*., 2004).

15. Treatment of male albino rats for 90 days with 2% aluminium chloride in drinking water (described by the authors as equivalent to 50 mg/kg bw/day aluminium chloride, or ~ 10 mg/kg bw/day aluminium) was reported to enhance lead deposition when co-treatment with 2.5% lead acetate was given. Some effects of leas and/or aluminium treatment were also noted on brain AChE and lipid peroxidation levels and on motor neurological functions (Shakoor *et al*., 2003).

16. (Kaur and Gill, 2005) reported that intragastric application of 10 mg/kg bw/day aluminium (as lactate) to male, albino rats for 12 weeks altered brain intrasynaptosomal calcium homeostasis.

17. Treatment of male and female HSd:W1 rats with 91.8 mg/kg bw/day aluminium lactate (8.42 mg/kg bw/day aluminium[103]) +/- 3.0 g/kg bw/day ethanol for 90 days by gavage was associated with decreased brain synaptosomal ATPase and AChE activities. The difference was detected two weeks, but not immediately, after discontinuation of treatment (Kohila *et al*., 2004).

18. Indicators of lipid peroxidation and lactate dehydrogenase (LDH) activity were increased, whilst AChE activity was decreased, in the brains of male Sprague-Dawley rats treated orally with 34 mg/kg bw aluminium chloride, on alternate days, for a period of 30 days (El Demerdash, 2004).

Mice

19. Aluminium accumulated in the brains and other organs of male ddy mice given drinking water supplemented with 0.1 mg/ml (~ 16.7 mg/kg bw/day) aluminium, as chloride (ionic) or maltolate (complex), for up to 120 days. In aluminium maltolate-treated rats, brain aluminium accumulation peaked at 60 days, then fell, which the authors interpreted as suggesting that aluminium accumulation in the brain is a reversible process. Brain tissue from aluminium maltolate-treated, but not aluminium chloride-treated animals showed indicators of oxidative stress (TBARS and NOx levels), and clusters of neurofilament cells upon immunostaining (Kaneko *et al*., 2004).

20. Increased levels of some indicators of inflammation were observed in the brains of male B/6C3F1 mice treated with drinking water containing 0.01, 0.01 or 1 mM aluminium, as lactate (0.26, 2.6, 26 mg/l aluminium; ~ 0.043, 0.43, 4.3 mg/kg bw/day aluminium) for 10 wks, but there was no clear pattern of dose-response and no increase in brain aluminium levels (Campbell *et al*., 2004).

Rabbits

[103] It is not entirely clear whether the dose was 91.8 mg/kg bw/day Al lactate or Al.

21. Groups of 6 male New Zealand white rabbits were treated every other day, by gavage, with 40 mg/kg bw L-ascorbic acid (AA) and/or 34 mg/kg bw aluminium[104] (cited by the authors as 1/25 LD_{50}), for 16 weeks. Aluminium treatment was associated with indicators of increased oxidative damage in plasma, liver, brain, testes and kidney, decreases in liver and testes AST, ALT, ALP and AcP enzyme activities, whilst plasma, liver, testes and brain LDH activities were increased. The activities of acetylcholinesterase (AChE) were decreased in brain and plasma. Some haematological parameters were also affected. Co-administration of ascorbic acid provided some protection against these effects (Yousef, 2004).

B. Other biological and toxic effects

Human data

Inhalation and effects on the respiratory system

22. (Fishwick *et al*., 2004) reported that workplace exposure to aluminium fume was associated with reduced respiratory function (FEV_1) (at least 5% reduction after 15 min exposure) in welders in New Zealand.

23. Studies have described evaluations of asthmatic manifestations in workers at aluminium smelting plants ("potroom asthma"). It is not currently clear what is the specific cause of these effects (workers are exposed to a mixture of particulates and gases including aluminium oxide), although the major candidate is suggested to be fluoride compounds (Barnard *et al*., 2004; Sjaheim *et al*., 2004).

Dermal absorption and effects

24. A 43 year old woman who presented with bone pain and fatigue showed normal values for biochemical/haematological analyses, but an elevated plasma aluminium concentration of ~ 3.9 μM (~ 10.4 μg/dl, or ~ 100 μg/l) (normal values ~ 10 μg/l or less). Neuropsychologic and electroencephalographic tests were normal. The patient had no history of aluminium antacid use or occupational exposure to aluminium, and raised levels were attributed to use for the preceding 4 years of ~ 1 g/day aluminium-containing antiperspirant cream. Bone pain symptoms disappeared within a few months of discontinuation of antiperspirant use (Guillard *et al*., 2004).

25. (Akyol *et al*., 2004) described the case of a 9 year old boy who exhibited contact sensitivity to aluminium. This was apparent as an accidental finding when positive reactions at all test sites were observed in allergen patch-test evaluations (presumably due to the use of aluminium test chambers). The authors attributed this aluminium sensitivity to prior exposure to aluminium-absorbed vaccines (although they noted that the patient had received his childhood vaccinations without any adverse effects).

26. Some reports have described the development of persistent itching nodules at the site of injection of aluminium-containing vaccines in children (Bergfors *et al*.,

[104] It is not entirely clear from the report whether the dose was 34 mg/kg bw Al or $AlCl_3$.

2003; Netterlid *et al*., 2004; Thierry-Carstensen and Stellfeld, 2004; Frederiksen and Tofte, 2004).

Others

27. (Cimma *et al*., 2004) reported that consuming foods cooked in Al pots was not associated with adverse effects on parameters of calcium metabolism or increased serum aluminium concentrations in young Bangladeshi children with calcium-deficient rickets (*note: data taken from the abstract: the full text of this paper was not available during the preparation of this report).*

Animal studies

Developmental/reproductive effects

28. (Wiles *et al*., 2003) evaluated the bioavailability and toxicological effects of montmorillonite clays (which are frequently added to animal feeds, and of which aluminium is a major component) by supplementing clay minerals to pregnant Sprague-Dawley rats throughout pregnancy at a level of 2% (w/w). Aluminium was not detected above background levels in any tissues evaluated and no effects were seen on fetal or maternal toxicity *(note: these data taken from the abstract: the full text of this paper was not available during the preparation of this report).*

Haematological effects

29. Groups of adult female Wistar rats were exposed for 18 months to tap water, 35 mM sodium citrate solution, or a solution of 35 mM sodium citrate + 30 mM aluminium sulphate (~ 810 mg/l aluminium, or ~ 46 mg/kg bw/day aluminium). Aluminium treatment was associated with significant decreases in red blood cell count, haematocrit, serum iron concentration, and an increase in bone marrow δ-ALA-D activity (Farina *et al*., 2005)

Absorption/bioavailability

30. (Arnich *et al*., 2004) reported a comparative study of the intestinal absorption of aluminium, manganese, nickel and lead in rats using the *in situ* intestinal perfusion technique. Perfused metal solutions at concentrations likely to occur during oral intoxication were used. The authors reported that aluminium (48 and 64 mM), even as citrate complex, crossed the brush border with difficulty (0.4% of the perfused amount). Of this, ~ 60 % was retained in the intestine and the remainder was found in target tissues (*note: data taken from the abstract, the full text of this paper was not available during the preparation of this report).*

31. (Yumoto *et al*., 2003) used aluminium^{26} chloride as a tracer to measure aluminium^{26} incorporation into the brain of suckling rats by accelerator mass spectrometry. Lactating rats were subcutaneously injected with aluminium^{26} chloride from day 1 to day 20 postpartum. Suckling rats were weaned from day 21 postpartum. From day 5 to day 20 postpartum, the amounts of aluminium^{26} measured in the cerebrum, cerebellum, spinal cord, liver, and kidneys of suckling rats increased significantly. After weaning, the amounts of aluminium^{26} in the liver and kidneys decreased remarkably. Alternatively, in the cerebrum, cerebellum, and spinal cord, as

much as 12 to 20% of the aluminium[26] amounts present on day 20 postpartum remained in the tissues on day 730 postpartum. The authors concluded that considerable amounts of the aluminium[26] taken up into the brain of suckling rats through maternal milk remain in their brain throughout their lifetime (*note: these data taken from the abstract: the full text of this paper was not available during the preparation of this report).*

May 2005

Reference List to Appendix 23

Akyol,A., Boyvat,A., and Kundakci,N. (2004). Contact sensitivity to aluminum. Int. J. Dermatol. *43*, 942-943.

Arnich,N., Cunat,L., Lanhers,M.C., and Burnel,D. (2004). Comparative in situ study of the intestinal absorption of aluminum, manganese, nickel, and lead in rats. Biol. Trace Elem. Res. *99*, 157-171.

Barnard,C.G., McBride,D.I., Firth,H.M., and Herbison,G.P. (2004). Assessing individual employee risk factors for occupational asthma in primary aluminium smelting. Occup. Environ. Med. *61*, 604-608.

Bergfors,E., Trollfors,B., and Inerot,A. (2003). Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer. Vaccine *22*, 64-69.

Buchta,M., Kiesswetter,E., Otto,A., Schaller,K.H., Seeber,A., Hilla,W., Windorfer,K., Stork,J., Kuhlmann,A., Gefeller,O., and Letzel,S. (2003). Longitudinal study examining the neurotoxicity of occupational exposure to aluminium-containing welding fumes. Int. Arch. Occup. Environ. Health *76*, 539-548.

Campbell,A., Becaria,A., Lahiri,D.K., Sharman,K., and Bondy,S.C. (2004). Chronic exposure to aluminum in drinking water increases inflammatory parameters selectively in the brain. J. Neurosci. Res. *75*, 565-572.

Cimma,J.P., Arnaud,J., Labarere,J., Guillard,O., Nugues,F., Marrauld,A., Durand,C., Farvacque,J.M., Bottari,S.P., and Haque,S. (2004). Effect of consumption of food cooked in aluminium or stainless-steel pots on Bangladeshi children with calcium-deficient rickets: an eight month trial. J. Trace Elem. Med. Biol. *17*, 249-253.

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Subgroup Report on the Lowermoor Water Pollution Incident . 2005. Ref Type: Report

de Wolff,F.A., Berend,K., and van der Voet,G.B. (2002). Subacute fatal aluminum poisoning in dialyzed patients: post-mortem toxicological findings. Forensic Sci. Int. *128*, 41-43.

El Demerdash,F.M. (2004). Antioxidant effect of vitamin E and selenium on lipid peroxidation, enzyme activities and biochemical parameters in rats exposed to aluminium. J. Trace Elem. Med. Biol. *18*, 113-121.

Farina,M., Rotta,L.N., Soares,F.A., Jardim,F., Jacques,R., Souza,D.O., and Rocha,J.B. (2005). Hematological changes in rats chronically exposed to oral aluminum. Toxicology *209*, 29-37.

Fattoretti,P., Bertoni-Freddari,C., Balietti,M., Giorgetti,B., Solazzi,M., and Zatta,P. (2004). Chronic aluminum administration to old rats results in increased levels of brain metal ions and enlarged hippocampal mossy fibers. Ann. N. Y. Acad. Sci. *1019*, 44-47.

Fattoretti,P., Bertoni-Freddari,C., Balietti,M., Mocchegiani,E., Scancar,J., Zambenedetti,P., and Zatta,P. (2003). The effect of chronic aluminum(III) administration on the nervous system of aged rats: clues to understand its suggested role in Alzheimer's disease. J. Alzheimers. Dis. *5*, 437-444.

Fishwick,D., Bradshaw,L., Slater,T., Curran,A., and Pearce,N. (2004). Respiratory symptoms and lung function change in welders: are they associated with workplace exposures? N. Z. Med. J. *117*, U872.

Frederiksen,M.S. and Tofte,H. (2004). Immunisation with aluminium-containing vaccine of a child with itching nodule following previous vaccination. Vaccine *23*, 1-2.

Gillette-Guyonnet,S., Andrieu,S., Nourhashemi,F., de,L.G., V, Grandjean,H., and Vellas,B. (2005). Cognitive impairment and composition of drinking water in women: findings of the EPIDOS Study. Am. J. Clin. Nutr. *81*, 897-902.

Gong,Q.H., Wu,Q., Huang,X.N., Sun,A.S., and Shi,J.S. (2005). Protective effects of Ginkgo biloba leaf extract on aluminum-induced brain dysfunction in rats. Life Sci. *77*, 140-148.

Guillard,O., Fauconneau,B., Olichon,D., Dedieu,G., and Deloncle,R. (2004). Hyperaluminemia in a woman using an aluminum-containing antiperspirant for 4 years. Am. J. Med. *117*, 956-959.

Gupta,V.B., Anitha,S., Hegde,M.L., Zecca,L., Garruto,R.M., Ravid,R., Shankar,S.K., Stein,R., Shanmugavelu,P., and Jagannatha Rao,K.S. (2005). Aluminium in Alzheimer's disease: are we still at a crossroad? Cell Mol. Life Sci. *62*, 143-158.

He,S.C., Qiao,N., and Sheng,W. (2003). Neurobehavioral, autonomic nervous function and lymphocyte subsets among aluminum electrolytic workers. Int. J. Immunopathol. Pharmacol. *16*, 139-144.

Jing,Y., Wang,Z., and Song,Y. (2004). Quantitative study of aluminum-induced changes in synaptic ultrastructure in rats. Synapse *52*, 292-298.

Kaneko,N., Yasui,H., Takada,J., Suzuki,K., and Sakurai,H. (2004). Orally administrated aluminum-maltolate complex enhances oxidative stress in the organs of mice. J. Inorg. Biochem. *98*, 2022-2031.

Kaur,A. and Gill,K.D. (2005). Disruption of neuronal calcium homeostasis after chronic aluminium toxicity in rats. Basic Clin. Pharmacol. Toxicol. *96*, 118-122.

Kohila,T., Parkkonen,E., and Tahti,H. (2004). Evaluation of the effects of aluminium, ethanol and their combination on rat brain synaptosomal integral proteins in vitro and after 90-day oral exposure. Arch. Toxicol. *78*, 276-282.

Netterlid,E., Bruze,M., Hindsen,M., Isaksson,M., and Olin,P. (2004). Persistent itching nodules after the fourth dose of diphtheria-tetanus toxoid vaccines without evidence of delayed hypersensitivity to aluminium. Vaccine *22*, 3698-3706.

Pandya,J.D., Dave,K.R., and Katyare,S.S. (2004). Effect of long-term aluminum feeding on lipid/phospholipid profiles of rat brain myelin. Lipids Health Dis. *3*, 13.

Priest,N.D. (2004). The biological behaviour and bioavailability of aluminium in man, with special reference to studies employing aluminium-26 as a tracer: review and study update. J. Environ. Monit. *6*, 375-403.

Shakoor,A., Gupta,P.K., and Kataria,M. (2003). Influence of aluminium on neurotoxicity of lead in adult male albino rats. Indian J. Exp. Biol. *41*, 587-591.

Silva,V.S. and Goncalves,P.P. (2003). The inhibitory effect of aluminium on the (Na+/K+)ATPase activity of rat brain cortex synaptosomes. J. Inorg. Biochem. *97*, 143-150.

Sjaheim,T., Halstensen,T.S., Lund,M.B., Bjortuft,O., Drablos,P.A., Malterud,D., and Kongerud,J. (2004). Airway inflammation in aluminium potroom asthma. Occup. Environ. Med. *61*, 779-785.

Smorgon,C., Mari,E., Atti,A.R., Dalla,N.E., Zamboni,P.F., Calzoni,F., Passaro,A., and Fellin,R. (2004). Trace elements and cognitive impairment: an elderly cohort study. Arch. Gerontol. Geriatr. Suppl 393-402.

Thierry-Carstensen,B. and Stellfeld,M. (2004). Itching nodules and hypersensitivity to aluminium after the use of adsorbed vaccines from SSI. Vaccine *22*, 1845.

Wiles,M.C., Huebner,H.J., Afriyie-Gyawu,E., Taylor,R.J., Bratton,G.R., and Phillips,T.D. (2003). Maternal and developmental assessment of montmorillonite clays commonly added to animal feeds: toxicity evaluation and metal bioavailability in the pregnant rat. Toxicologist *72(S-1)*, 251.

Yousef,M.I. (2004). Aluminium-induced changes in hemato-biochemical parameters, lipid peroxidation and enzyme activities of male rabbits: protective role of ascorbic acid. Toxicology *199*, 47-57.

Yumoto,S., Nagai,H., Kobayashi,K., Tamate,A., Kakimi,S., and Matsuzaki,H. (2003). 26Al incorporation into the brain of suckling rats through maternal milk. J. Inorg. Biochem. *97*, 155-160.

Zatta,P., Zambenedetti,P., Reusche,E., Stellmacher,F., Cester,A., Albanese,P., Meneghel,G., and Nordio,M. (2004). A fatal case of aluminium encephalopathy in a patient with severe chronic renal failure not on dialysis. Nephrol. Dial. Transplant. *19*, 2929-2931.

Zhang,Z.J., Qian,Y.H., Hu,H.T., Yang,J., and Yang,G.D. (2003). The herbal medicine Dipsacus asper wall extract reduces the cognitive deficits and overexpression of beta-amyloid protein induced by aluminum exposure. Life Sci. *73*, 2443-2454.

Appendix 24: Review of the scientific literature on aluminium (May 2005 to July 2006) prepared for the Lowermoor subgroup by the secretariat

Note: this was a paper prepared for discussion by the Lowermoor subgroup. It does not necessarily represent the views of the subgroup

AN UPDATE OF PUBLICATIONS RELATING TO ALUMINIUM TOXICITY May 2005-July 2006

Introduction

1. The last update of literature data on the toxicity and epidemiology of aluminium covered the period up to April 2005. This one covers the period up to end July 2006. Pub Med and Toxline were searched using the terms toxic*, brain, neuro, renal, liver, bioavailability, epidem*, Alzheimer. As before, studies using oral or dermal exposure were identified and obtained. Those which were considered to provide data relevant to the derivation of a No or Low Observed Adverse Effect Level, or to provide useful mechanistic data or other relevant information, were identified and are reviewed below.

Animal studies

Behavioural effects in adults

2. Impaired motor performance and learning ability was seen in male rats treated for 12 weeks with 10 mg aluminium/kg bw/day as aluminium lactate when compared to controls. The dose route was described as "intragastric".The rats were described as 'lacking neuromuscular coordination and seeming totally disorientated and confused when training compared to control animals'. In view of this observation, which is unusual at such a low dose level, and other results of this study reported below, it is not clear whether the administration was by the oral route (Kaur *et al*, 2006).

Developmental effects

3. In a study designed to assess the potential combined influence of maternal restraint stress and aluminium exposure on postnatal development and behaviour, F_0 female rats were exposed to aluminium in drinking water before mating and throughout gestation and lactation (Colomina *et al*, 2005) and the F_1 generation continued to be exposed post-weaning. The doses used were 50 and 100 mg Al/kg bw/day administered as the nitrate nonahydrate and given with citric acid to enhance absorption. The high dose caused decreases in maternal food and water consumption, and in maternal and F_1 body weight. Delayed sexual maturation was seen in F_1 rats at both doses. High dose F_1 rats also exhibited reduced forelimb grip strength and facilitated performance in learning tests when tested postweaning.

4. In a further paper from the same laboratory, male F_1 rats from dose groups as above were tested at one and two years of age in an open-field test of motor activity and/or a water maze to test spatial learning (Roig *et al*, 2006). The rats had continued to receive the same aluminium treatments in drinking water until testing, so exposure was prenatal and chronic. No significant differences between the groups were seen in the open-field test. In the water maze, there were no significant differences compared to controls but the high Al dose rats had a decreased performance compared to low Al dose rats. The authors concluded that this may indicate a biphasic response on memory.

Effects on brain biochemistry

5. Becaria *et al* (2006) found that aluminium given as the lactate in drinking water to male mice at doses of 1.35 or 13.5 mg/kg bw/day increased levels of the cytokines IL-1 and IL-4, and of apolipoprotein in brain. TNF-α and malondialdehyde levels, and N-NOS immunoreactivity were also increased at the high dose, but not at the low dose. No effects were seen on beta-amyloid levels. Aluminium administration also caused changes in TNF-α and IL levels in spleen and serum samples. Concurrent administration of copper (2.5 mg/kg bw/day as the sulphate) had no effect except on apolipoprotein levels, where a synergistic effect was seen at the high aluminium dose.

6. In the study by Kaur *et al* (2006) described above brains were taken for assessment of several parameters. The hippocampus, cerebral cortex and corpus striatum were examined separately. Treatment of rats with Al (10 mg/kg bw/day for 12 weeks; route of administration unclear) caused increased cAMP dependent protein kinase activity in the striatum and increased Ca^{2+}/CaM dependent protein kinase activity (by 38-51%) in all 3 brain regions. Phosphoprotein phosphatase activity was significantly depleted in the cerebral cortex. Phosphorylation of high molecular weight neurofilament by protein kinase A (cAMP mediated) was increased in the cerebral cortex of treated animals but phosphorylation by Ca^{2+}/CaM dependent protein kinase was increased in all 3 regions. Immunocytochemical studies of smears from the brains of treated rats showed abnormal accumulation of coagulated and disrupted neurofilaments in all 3 regions. A 205kDa MW neurofilament was identified. The authors suggest that disruption of neuronal architecture through the fragmentation and aggregation of neurofilament proteins might be one of the molecular mechanisms by which aluminium exerts its neurotoxic effects.

7. Kaizer *et al* (2005) administered 2.7 mg Al/kg bw/day (salt unpecified) by gavage to male mice, with or without citrate, on 5 days/week for 12 weeks. Controls received water only and a further group received citrate only. Treatment with aluminium+citrate increased acetylcholinesterase activity in the cerebral cortex and hippocampus compared to the other groups. In the hypothalamus, activity was higher in the aluminium+citrate group but lower in the aluminium-only group than in the other two groups. The authors state that this may be a reflection of the known biphasic effects of aluminium on acetylcholinesterase. TBARS production in the hippocampus and cortex was increased compared to controls all treated groups. This paper has some inconsistencies.

8. In a study to study the effects of aluminium administration on the cortical expression of NADPH-diaphorase, nitric oxide synthase (nNOS) and neuropeptide Y (NPY), rats were administered 165 mg aluminium/kg bw/day (salt unspecified) in drinking water for periods of 0.5 to 12 months (Rodella *et al*, 2006). Drinking water consumption was reduced by 8 ml/day in the treated group compared to controls, who received tap water only. In control rats, about 1% of neurons were clearly NADPH-diaphorase positive; nNOS overlapped NADPH-diaphorase histochemistry quantitatively and qualitatively. Rats given aluminium for 0.5 months were similar to controls but those treated for 1-6 months showed a progressive decrease in the number of NADPH-d and nNOS positive neurons, which then plateaued. Aluminium-treated animals also showed a decrease in NADPH-d/NPY double stained neurons with an apparent increase in NPY single stained neurons, which peaked at 3 months.

9. Silva *et al* (2006) studied whether the known inhibition of (Na^+/K^+)ATPase by aluminium is associated with a change in (Na^+/K^+)ATPase isoforms. Young male rats received aluminium (24 mg/kg bw/day) as the chloride fed in curdled cheese for 4 months. Controls received cheese only. At termination, brain cortical synaptosomes were prepared from all rats. Leakage of cytosolic LDH activity, an indicator of cell damage, was similar in the treated and control groups, indicating that chronic exposure to aluminium failed to produce significant damage of synaptosomal membranes. No differences were seen in ATP, ADP or AMP levels but the (Na^+/K^+)ATPase[ATP phosphohydrolase (Na^+/K^+-exchanging)] activity of freeze-thawed synaptosomes was significantly reduced (30%) in treated compared to control rats. No significant changes in protein exposure of the 3 of the α-subunit isoforms were observed between synaptosomes from Al-treated and control rats.

10. A number of papers have used aluminium to induce adverse effects in order to investigate the ability of other chemicals to inhibit the action of aluminium. In a poorly-written paper, Abd-Elghaffar *et al* (2005) report that administration of 20 mg/l aluminium chloride (equivalent to 0.9-1.3 mg Al/kg bw/day) in drinking water to male rabbits for 3 months increased brain levels of malondialdehyde and 4-hydroxyalkenals and lowered superoxide dismutase levels. There was atrophy and apoptosis of neurons in the cortex and hippocampus, associated with neurofibrillary degeneration and argyrophilic inclusion. These effects were abolished or ameliorated by melatonin administered concurrently or subsequently.

11. 10 mg Al/kg bw/day, given to male rats as the chloride in drinking water for 5 weeks, was reported to increase hippocampal lipid peroxidation (measured by TBARS) and protein oxidation (protein carbonyl concentrations), and to lower superoxide dismutase levels (Jyoti and Sharma, 2006). Necrotic changes and accumulation of lipofuscin were also seen. These effects were ameliorated or absent in groups administered aluminium chloride with either i.p. L-Deprenyl or extract of *Bacopa monniera*, a 'nerve tonic' used in Ayurvedic medicine.

12. Aluminium (324 mg/kg bw/day) given as the chloride in drinking water to male rats for six weeks caused a significant increase in lipid peroxidation and a marked elevation in levels of the glial markers glial fibrillary acidic protein (GFAP), S100B, TNF-α and IL-1β in hippocampus and frontal cortex (Nedzvetsky *et al*, 2006). No effect was seen on glutathione levels. The increase in all parameters was significantly reduced by concurrent administration of 100 mg/kg bw/day vitamin E (route of administration unclear).

Accumulation of aluminium in brain and other organs

13. Several of the above studies, and others, measured aluminium concentrations in brain and, in some cases, other organs. These data are presented in Table 1.

Table 1: Aluminium concentrations in brain and other organs

Dose of aluminium and duration of dosing	Mean conc Al in brain (units)	Mean conc Al in other organs and tissues (units)	Reference

40.4 mg/kg bw/day 5 d/week for 8 weeks	c.1.8 mg/kg No control group	Serum: c. 60 ng/ml Femur: c. 9 mg/kg Kidney: c. 3.8 mg/kg	Baydar *et al*, 2005
F_0 rats given 50 or 100 mg/kg bw/day premating and during pregnancy and lactation, F_1 rats received same doses in drinking water postnatally. Killed on postnatal day 68.	F1 brains showed no evidence of Al accumulation	N/A	Colomina *et al*, 2005
10 mg/kg bw/day for 12 weeks. Not clear if administration by the oral route.	Cortex Controls : 0.51 ± 0.07 Al : 3.42 ± 0.87		Kaur *et al*, 2006
Exposure prenatally and thereafter to 2 years of age to 50 or 100 mg/kg bw/day.	Cortex Controls : 3.4 ± 9.7 50 Al : 1.0 ± 2.4 100 Al : 31.7 ± 18.2		Roig *et al*, 2006

Reference list to Appendix 24

Abd-Elghaffar SK, El-Sokkary GH and Sharkawy AA (2005). Aluminum-induced neurotoxicity and oxidative damage in rabbits: Protective effect of melatonin. Neuroendocrinology Letters 26(5): 609-616

Andrasi E, Pali N, Molnar Z and Kosel S (2005). Brain aluminum, magnesium and phosphorus contents of control and Alzheimer-diseased patients. J Alzheimer's Disease 7: 273-284.

Baydar T, Nagymajtenyi L, Isimer A and Sahin G (2005). Effect of folic acid supplementation on aluminum accumulation in rats. Nutrition 21: 406-410

Becaria A, Lahiri DK, Bondy SC, Chen D, Hamadeh A, Li H, Taylor R and Campbell A (2006). Aluminum and copper in drinking water enhance inflammatory or oxidative events specifically in the brain. J Neuroimmunology 176: 16-23.

Colomina MT, Roig JL, Torrente M, Vicens P and Domingo JL (2005). Concurrent exposure to aluminum and stress during pregnancy in rats: Effects on postnatal development and behavior of the offspring. Neurotoxicology and Teratology 27: 565-574

Darbre PD (2006). Metallooestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. J Applied Toxicology 26(3):191-7.

Exley C, Begum A, Woolley MP and Bloor RN (2006). Aluminum in tobacco and cannabis and smoking-related disease. The American Journal of Medicine 119: 119(3):276.e9-11

Gruis KL, Teener JW and Blaivas M (2006). Pediatric macrophagic myofasciitis associated with motor delay. Clinical Neuropathology(4): 172-179.

Jyoti A and Sharma D (2006). Neuroprotective role of *Bacopa monniera* extract against aluminium-induced oxidative stress in the hippocampus of rat brain. Neurotoxicology 27(4): 451-457.

Kaizer RR, Correa MC, Spanevello RM, Morsch VM, Mazzanti CM, Goncalves JF and Schetinger MRC (2005). Acetylcholinesterase activation and enhanced lipid peroxidation after long-term exposure to low levels of aluminum on different mouse brain regions. J Inorganic Biochemistry 99: 1865-1870.

Kaur A, Joshi K, Walker Minz R and Dip Gill K (2006). Neurofilament phosphorylation and disruption: A possible mechanism of chronic aluminium toxicity in Wistar rats. Toxicology 219: 1-10.

Nagasawa K, Akagi J, Koma M, Kakuda T, Nagia K, Shimohama S and Fujimoto S (2006). Transport and toxic mechanism for aluminum citrate in human neuroblastoma SH-SY5Y cells. Life Sci. 79(1):89-97.

Nakagawa Y, Kawashima T, Yamada T, Harano M, Monji A, Yuzuriha T and Iwaki T (2005). Aluminum chloride does not facilitate deposition of human synthetic amyloid β1-42 peptide in the rat ventricular system of a short-term infusion model. Neuropathology 25: 195-200.

Nedzvetsky VS, Tuzcu M, Yasar A, Tikhomirov AA and Baydas G (2006). Effects of Vitamin E against aluminum neurotoxicity in rats. Biochemistry (Moscow) 71 (3): 239-244.

Religa D, Strozyk D, Cherny RA, Valitakis I, Haroutunian V, Winblad B, Naslund J and Bush AI (2006). Elevated cortical zinc in Alzheimer disease. Neurology 67: 69-75.

Rodella LF, Ricci F, Borsani E, Rezzani R, Stacchiotti A, Mariani C and Bianchi R (2006). Exposure to aluminum changes the NADPH-diaphorase/NPY pattern in the rat cerebral cortex. Arch Histol Cytol 69(1): 13-21.

Roig JL, Fuentes S, Colomina MT, Vicens P and Domingo JL (2006). Aluminum, restraint stress and aging: Behavioral effects in rats after 1 and 2 years of aluminum exposure. Toxicology 218: 112-124.

Shirley DG and Lote CJ (2005). Renal handling of aluminium. Nephron Physiol 101: 99-103.

Silva VS, Duarte AI, Rego AC, Oliveira CR and Goncalves PP (2005). Effect of chronic exposure to aluminium on isoform expression and activity of rat (Na^+/K^+)ATPase. Toxicological Sciences 88(2): 485-494.

Walton JR (2006). Aluminum in hippocampal neurons from humans with Alzheimer's disease. NeuroToxicology 27(3):385-94.

Appendix 25: Review of the scientific literature on aluminium (August 2006 to December 2006) prepared for the Lowermoor subgroup by the secretariat

Note: this was a paper prepared for discussion by the Lowermoor subgroup. It does not necessarily represent the views of the subgroup

AN UPDATE OF PUBLICATIONS RELATING TO ALUMINIUM TOXICITY, August – December 2006

Introduction

1. The last update of literature data on the toxicity and epidemiology of aluminium covered the period up to July 2006 (LSG/06/02). This one covers the period up to end December 2006. Pub Med and Toxline were searched using the terms toxic*, brain, neuro, renal, liver, bioavailability, epidem*, Alzheimer. As before, studies using oral or dermal exposure were identified and obtained. Those which were considered to provide data relevant to the derivation of a No or Low Observed Adverse Effect Level, or to provide useful mechanistic data or other relevant information, were identified and are reviewed below. Appendix 1 contains a short summary of each individual paper reviewed. Members are asked to consider the papers and to advise on whether any of the new data should be discussed in the text of the report.

Animal studies

Neurological effects

2. In a study designed to investigate the effect of aluminium on the vestibulo-ocular reflex (VOR), Mameli *et al* (2006) administered aluminium chloride in drinking water to male rats for 90 days at mean doses of 11.1, 21.5 and 43.1 mg/kg bw/day. Ninety rats were tested at each dose level with one third per level beginning at 3, 10 or 24 months of age. Controls received sodium chloride solution. The concentration of aluminium in the diet was given as 5.5 microgram/ml but dietary intake was not assessed.

3. General health of the animals remained good throughout the study. The VOR was analysed in basal condition and during aluminium exposure to detect changes of the post-rotatory nystagmus (PRN). Significant impairment of the VOR was seen in the group receiving 43.1 mg Al/mg kw/day but not in the other two dose groups. In 7% of animals, impairment was detectable as early as 30 days after exposure began.

4. Aluminium concentrations in blood were not significantly different from controls in any dose group. There was a dose-related increase in aluminium concentrations compared to controls in the brainstem-cerebellum in the top 2 dose groups, and in the telencephalon in all three dose groups (no statistical analysis was done on these comparisons). Immunohistochemical analysis of animals in the high dose group found no difference in number or shape of activated or resting astrocytes, and no evidence of any amyloid deposits.

Behavioural and biochemical effects

5. Nehru *et al* (2006) administered aluminium by gavage as aluminium chloride to groups of female rats for 6 weeks in order to assess the effects of subsequent administration of the drug centrophenoxine, a drug used to treat the symptoms of senile dementia and Alzheimer's disease (AD). The dose level of aluminium is not entirely clear, it is described as "aluminium as aluminium chloride (100 mg/kg bw/day)". At the end of the treatment period, the rats underwent active avoidance

testing which, according to the authors, assessed cognitive behaviour, and passive avoidance testing, stated to assess short-term memory. Aluminium treatment alone caused impaired performance in both avoidance tests and significantly decreased the activities of the following enymes in the brain: AChE, hexokinase, LDH, succinate dehydrogenase, and Mg^{2+}-dependent ATPase. Rats treated with centrophenoxine alone or aluminium followed by centrophenoxine gave similar results in the avoidance tests as controls, and post-treatment with centrophenoxine either fully or partially restored the activities of the brain enzymes.

6. In a further study from the same laboratory (Nehru and Bhalla, 2006), gavage administration of aluminium as aluminium chloride (40 mg/kg bw/day) to female rats reduced mean body and brain weights and reduced the brain content of reduced GSH, total GSH and oxidized GSH, and the activity of GSH reductase in various regions of the brain. In most cases, subsequent treatment with centrophenoxine restored the content of the analytes and, in all cases, it restored GSH reductase activity.

7. Walton (2006) gave six rats 20 mg aluminium/l in drinking water as aluminium chloride from 16 months of age until they began to show marked physical deterioration and were sacrificed (on average 29.8 months of age). The concentration of aluminium in the basal diet was measured and overall aluminium intake was calculated to average 0.36 mg/kg bw/day from 5 to 16 months of age and 1.52 mg/kg bw/day thereafter. At 5 months of age, the rats were trained to perform a continuous reward alternation T-maze task which is stated to have both working memory and reference memory components. They were tested weekly for the conclusion of their lifespan and the mean memory performance was compared for each rat over 15 consecutive weeks during middle age (12-23 months) and old age ($\geq$ 24 months). Two rats obtained significantly lower mean memory scores in old age than in middle age and exhibited soft signs said to be associated with dementia. One rat obtained a significantly higher mean score in old age.

8. Hippocampal neurons in brain sections all aged rat brain sections showed varying extents of aluminium accumulation. Brains from the two rats showing a fall-off in maze performance had abundant neurons at an advanced state of aluminium accumulation, as did brains from some of the other aged rats. In comparison, brains from 6-month old rats not given supplemented drinking water were entirely aluminium-negative.

Human study

9. It has been suggested that a deficiency of aluminium binding to the C2 variant of the transferrin (Tf) protein may increase the amount of unbound aluminium which could cross the blood-brain barrier, thereby increasing the risk of neurotoxic effects. Rondeau *et al* (2006) investigated whether carrying the common C1 and C2 alleles of the Tf gene and exposure to aluminium in tap water predisposes individuals to a greater risk of dveloping AD. They also studied the combined genetic effects of Tf and ε4 allele of the apolipoprotein E (ApoE) gene.

10. A sub-sample of 292 individuals was analysed, including 55 cases of AD, taken from 2 established cohorts, of whom 181 lived in areas with drinking water containing high levels of aluminium (> 0.1 mg/l) and 111 in areas with low aluminium levels (<0.1 mg/l). There was found to be no difference in the frequency of

the different Tf genotypes between the control and the AD populations. Logistic regression analysis did not demonstrate an increased risk of AD in Tf C2 carriers and there was no significant interaction between Tf C2 allelic polymorphism and aluminium exposure. The presence of ApoE ε4 was associated with a higher risk of AD but neither the overall interaction between ApoE ε4 and Al exposure, nor the overall interaction between ApoE ε4 and Tf C2, were significant.

In vitro study

11. Aluminium failed to inhibit the degradation of beta-amyloid (Aβ) by cathepsin D, which is stated to be a candidate enzyme in Aβ degradation (Sakamoto *et al*, 2006). However, preincubation of cathepsin D with aluminium inhibited the apparent degradation of acid-denatured haemoglobin in a dose-related manner, and significantly inhibited cathepsin degradation of $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides. Desferrioxime prevented the inhibitory effect of aluminium.

Reference list to Appendix 25

Banks WA, Niehoff ML, Drago D and Zatta P (2006). Aluminum complexing enhances amyloid β protein penetration of blood-brain barrier. Brain Research 1116: 215-221.

Mameli O, Caria MA, Melis P, Zambenedetti P, Ramila M and Zatta P (2006). Effect of aluminum consumption on the vestibulo-ocular reflex. Metab Brain Dis 21: 89-107.

Nehru B, Bhalla P and Garg A (2006). Evidence for centrophenoxine as a protective drug in aluminium induced behavioural and biochemical alteration in rat brain. Molecular and Cellular Biochem 290: 33-42.

Nehru B and Bhalla P (2006). Reversal of an aluminium induced alteration in redox status in different regions of rat brain by administration of centrophenoxine. Molecular and Cellular Biochem 290: 185-191.

Rondeau V, Iron A, Letenneur L, Commenges D, Duchene F, Arveiler B and J-F Dartigues (2006). Analysis of the effect of aluminum in drinking water and transferrin C2 allele on Alzheimer's disease. European J of Neurology 13: 1022-1025.

Sakamoto T, Saito H, Ishii K, Takahashi H, Tanabe S and Ogasawara Y (2006). Aluminum inhibits proteolytic degradation of amyloid β peptide by cathepsin D: A potential link between aluminum accumulation and neuritic plaque deposition. FEBS Letters 580: 6543-6549.

Walton JR (2006). A longitudinal study of rats chronically exposed to aluminum at human dietary levels. Neurosci. Lett. 412(1):29-33

Appendix 26: Review of the scientific literature on aluminium (January 2007 to September 2011) prepared for the Lowermoor subgroup by the Department of Health Toxicology Unit, Imperial College, London

Note: This was a paper prepared for discussion by the Lowermoor subgroup. It does not necessarily represent the views of the subgroup

1. Aluminium toxicity was reviewed in detail in an update of the 1997 WHO (IPCS) Environmental Health Criteria 194 report on aluminium, prepared for the COT Lowermoor Subgroup in Spring 2002 and updated in 2003. The last update of literature data on the toxicity and epidemiology of aluminium covered the period up to Dec 2006. This review covers the period up to September 2011. Pub Med and Toxline were searched using the terms toxic*, brain, neuro, renal, liver, bioavailability, epidem*, Alzheimer. As before, studies using oral or dermal exposure were identified and obtained. Those which were considered to provide data relevant to the derivation of a No or Low Observed Adverse Effect Level, or to provide useful mechanistic data or other relevant information, were identified and are reviewed below. Members are asked to consider the papers and to advise on whether any of the new data should be discussed in the text of the report.

Human Studies - Neurotoxicity and effects on the brain

Epidemiological studies of cognitive impairment, dementia and Alzheimer's disease

2. Gao et al (2008) examined the relationship between trace elements (including aluminium) measured in individual biological samples and cognitive function in a rural, elderly Chinese Population. Cognitive assessment was conducted in face-to-face interviews using the Community Screening Instrument for Dementia (CSID), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning Test, the CERAD Word List Recall Test, the IU Story Recall, Animal Fluency test, and the IU Token test. The authors using the average of the standardized scores of the six cognitive tests to create a composite cognitive score. Plasma was extracted from fasted blood samples collected from 188 participants and the levels of seven trace elements, Aluminium (Al), calcium (Ca), cadmium (Cd), copper (Cu), iron (Fe), lead (Pb), and zinc (Zn), in the plasma samples were determined by inductively coupled plasma-mass spectrometry. Three trace elements (calcium, cadmium, and copper) were found to be significantly related to the composite cognitive score. However, Al did not show significant association with the composite *z* score.

3. Two regions in Turkey (Kirazli and Cipla-Halieli regions) with different Al levels in their water supplies were used to assess the effects of high Al in water resources on human health (Bakar et al., 2010). In the Kirazli region, the Al concentrations varied between 13.7-15.70 ppm. This region is characterised by fairly acidic content ($p < 4$) due to the existence of volcanic rocks. In contrast, the people living in the Ciplak-Halilei region obtain their water from alluvium aquifers, where the Al concentration is less than 0.2 ppm. Despite the differences in the Al levels in their water supplies, Bakar et al. (2010) found no statistical significant difference between the Al levels, vitamin B_{12} and TSH levels of the participants living in the two regions. However, a significant difference was detected for folic acid levels between the two groups ($p < 0.05$).

4. Another study, the PAQUID study is an ongoing prospective population based cohort study of the epidemiology of dementia and Alzheimer's disease in an elderly population in France. The first publication in 2000 described the PAQUID cohort and its initial findings (Jacqmin-Gadda et al., 1994). The second publication involved an 8-year follow up study (Rondeau et al., 2000). Please see Appendix 1 for full paper of

Rondeau et al. (2009) paper. In 2009, Rondeau et al. reports on the relationship between Aluminium in drinking water and cognitive decline in elderly people in a 15 year follow up study. In this study, individuals were also recruited from the ALMA (Aluminium-Maadie of Alzheimer) study. Al exposure was assessed using geographic exposure techniques and individual exposures, taking into account daily consumption of tap and bottled water. In examining the relationship between cognitive function and water consumption, the authors found that cognitive decline was greater in subjects with a high daily Al intake (> 0.1 mg/day or an increase of 0.1 mg/day) or higher geographic exposure to Al. When they examined the relationship between dementia or Alzheimer's disease and water composition, using the COX model, the risk of dementia was higher for subjects with a higher Al intake (>/ 0.1 mg/d) with an RR = 2.26, p= 0.049). Conversely, they found an increase of 10 mg/day of silica intake was associated with a reduced risk of dementia (RR = 0.89, p = 0.036). Using the geographical measure of tap water exposure, concentrations of Al were not associated with the risk of dementia or Alzheimer's disease (RR values were not included in paper).

Acute/sub-acute exposure

5. In a double-blind randomised controlled prospective study, Molloy et al. (2007) examined the relationship between gastro-intestinal absorption of Al from Aluminium-containing antacids and its dependence on age. The study also examined the acute effects of oral ingestion of a common Al compound (Antacid w) on neuropsychological function and its acute and/or sub-acute effects on cognition in individuals with dementia and normal cognitive function was also explored. Subjects received a single dose of Aluminium orally (Antacid w) for 3 days, followed by a 3-week washout, and then a 3-day matched placebo administration, or vice-versa. The study found large inter-individual variation in Al serum levels after the initial dose of antacid. An isoform of apolipoprotein E, ApoE4, has been shown to confer dramatically increased risk for late-onset AD (LOAD) (Roses et al., 1996); however, the basis for this remains one of the major unanswered questions of disease pathogenesis. ApoE plays critical roles in regulating brain Ab peptide levels, as well as their deposition and clearance (Holtzman, 2001; Zlokovic et al., 2005).The authors did not find any evidence that Al absorption was modified by ApoE status. No significant differences were observed in the neuropsychological test after the Al ingestion in normal volunteers or in patients with cognitive impairment. To conclude, the study demonstrated an absence of short-term cognitive effects following Al ingestion, contained in a single dose of antacid in normal volunteers or those suffering from dementia.

Occupational exposure

6. Kiesswetter et al. (2007) and Kiesswetter et al. (2009) carried out two parallel longitudinal studies investigating Al exposure and neurobehavioural health of Al welders over 4 years in the train/truck construction industry and the automobile industry, respectively. Intermediate results of these studies were published by Buchta et al (2003 and 2005). The study of workers in the train and truck industry examines the neurobehavioural health effects in high and long-term exposed workers. The study in the automobile industry involved neurobehavioural examinations in the early phase of working life of Al-welders with moderate Al exposure. Exposures of welders were examined during day shifts corresponding to the three neurobehavioural

examinations. External exposure was assessed by measurement of total dust in the air and internal exposure was assessed by measurement of Al in the urine and plasma. The neurobehavioural tests comprised of verbal intelligence, logic thinking, psychomotor behaviour, memory and attention testing. Computer aided testing involved the use of tests from the motor performance series (MLS) and the European Neurobehavioural Evaluation System (Euro-NES). For the tram/train industry, the Al workers who had been working as an Al welder for an average of 15 years, showed no significantly increased symptom levels compared to the control group. The study did not find a correlation between bio-monitoring and performance variables nor did it find a significant difference between the Al exposed workers and the control groups in the neurobehavioural performance tests over the 4 years. The study of the automobile industry replicated the findings of the first train/truck industry study. They too did not find any significant difference in neurobehavioural effects in the performance tests between the Al exposed compared to the control groups.

7. Gibbs et al. (2007a) describes the mortality of Quebec Al smelter workers employed before 1951. The mortality of three cohorts from three Quebec smelter plants from all causes was slightly but significantly above that of the province of Quebec. The study found most of the specific causes of death showing excesses were cancers, with significant excesses in all cohorts combined ($p< 0.01$) and specifically cancer of the trachea, bronchus and lung, bladder, digestive system and stomach ($p< 0.01$). For non-cancer causes of death, there were excesses of death for Alzheimer's disease ($p < 0.01$), in one of the three plants. Gibbs and Sevigny (2007) monitored the changes over time of mortality in workers first employed in Quebec Al smelters after 1st January 1950. They compared their results with those of the previous study of workers employed before 1951 (Gibbs et al. 2007). They found that the all cause mortality of men first employed after 1950 was significantly lower than the previously reported mortality of men employed before 1950. They also reported that mortality from the main cancer causes contributing to the large cancer excesses previously reported appeared to be diminishing. With respect to Alzheimer's disease, in the post-1950 workers mortality from this cause was lower than expected in all cohorts. The authors suggest that this finding from the post 1950 worker does not support a role for employment in the Al smelter plants in Alzheimer's disease development.

8. Santibanez et al. (2007) evaluated the quality of published studies with the aim of assessing the strength of association between AD and occupational exposure to pesticides, solvents, electromagnetic field (EMF), lead and Al. The authors followed recommendations from previous published papers on the best methods for data collection in order to minimize bias. Based on protocols and questionnaires used in other publications with similar aims, a specially designed questionnaire was applied to each of the selected studies in order to assess the quality of each of the studies. Each article was independently assessed by two epidemiologists. Twenty-four studies (21 case-control and 3 cohort studies) were assessed and the global quality index (GQI) and bias index of each study was calculated. For the 24 studies, the median for the GQI was 36.6 % with a range of 19.4 – 62.9 %. All case-control studies but one showed a GQI below 50%. Quality in the cohort studies was greater and more homogenous than in case-control studies. The most common potential bias is that of misclassification in the exposure, present in 18/24 studies, followed by the use of surrogate informants (12/17), then misclassifications of disease (11/24) and then selection bias (10/24). For specific occupational exposures, 11 studied the

relationship between AD and solvents, 7 with EMF, 6 with pesticides and 3 with Al. For Al, all the studies were all case-control studies. One of the studies, Salib and Hillier (1996) was the second in the quality ranking of the case-control studies. Results from the study showed no association between occupational exposure to Al and AD (RR = 0.95, 95% CI 0.5-1.9). In the other two studies, the associations were also non-significant (Graves et al., 1998; Gun et al., 1997).

9. Meyer-Baron et al. (2007) performed a meta-analysis to assess the impact of occupational exposure to Al on cognitive and motor performance. Special emphasis was placed on the analysis of confounding factors. The sample consisted of nine studies with 449 exposed and 315 reference subjects. Criteria for the inclusion of studies included the following: 1) published epidemiological study of an occupationally exposed group, 2) mean value of Al in urine for the exposed group, 3) investigation of neurobehavioral performance by means of standardized neuropsychological tests on cognitive and motor performance and 4) mean and standard deviation of test results reported for the exposed and the control group. Exposure originated from occupations in the welding, smelting or electrolysis industries. Mean urine Al concentrations ranged from 13 – 133 µg/L, with mean exposure durations from 4.7 – 19.2 years. A total of six neuropsychological tests met the inclusion criteria, with a total of 10 performance variables analysed (7 pertained to aspects of attention, two to motor and one to constructional performance). Nine overall effect sizes indicated an inferior performance of the exposed group – except Santa Ana test (non-preferred hand) for which a marginal positive effect size was calculated. A significant overall result (d_{re} = -0.43) was found for the digit symbol test only, which measures speed related components of cognitive and motor performance. The effect sizes of the individual studies suggest a decrease in the digit symbol performance with increasing urinary Al.

Human studies and other effects

10. Buranatrevedh et al. (2010) conducted a quantitative health risk assessment for workers who were exposed to metals in an Al production plant. It should be noted that a number of assumptions were used by the authors for each step of the risk assessment and these are outlined in the paper. For the hazard identification step, the authors identified 6 metals in the Al production plant and these included managanese, Al, copper, zinc, magnesium and iron. The workers were exposed to these metals via inhalation of fumes from heat during the foundry process. For the dose-response assessment, the authors estimated the RfCs of Al by inhalation as 0.00061 mg/m^3 for acute and subacute exposure and 0.000065 mg/m^3 for chronic exposure (it was noted in the text that as the purpose of the study was the protection of health of the workers, the lowest RfC was used to adopt a conservative point of view). They estimated the RfD for Al as 0.000141 mg/kg/d for acute and sub-acute exposure and 0.000015 mg/kg/d for chronic exposure. For exposure assessment for the workers exposed to these metals in the plant, the authors used air sampling data at the remelt furnace in the cast house of the plant. The maximum daily dose (MDD) for the exposure assessment of non carcinogenic effects was determined as 0.000463 mg/kg/d for Al. For the risk characterization step for non-carcinogenic effects of Al used in the plant, the risk was estimated to be 30.87. This indicated a 31 times increased risk of developing non-carcinogenic effects from Al compared with normal workers. This study did not consider confounding issues of non-occupational exposure and other individual risk factors.

11. In a relatively small study, Ferreira et al. (2009) analysed the concentration of a number of metals including Al in water samples collected in elderly people's houses and retirement homes in Riberiao, Brazil. The mean Al concentration was determined as 0.186 mg/L in retirement homes and 0.295 mg/L in elderly people's houses. According to the authors and their interpretation of the WHO guidelines, the analysed Al concentration exceeded the practicable guideline value of 0.2 mg/L in 28% of samples collected. The study observed that 11% of the elderly living at monitored homes and 19 % living in retirement homes presented with Alzheimer disease diagnosis.

12. Sofuogla and Kavcar (2008) determined the Al concentrations and other metals in black tea consumed by the Izmirian people in Turkey, the daily tea consumption rate of the Izmir population and the associated exposure and health risk levels. Al was one of the most abundant measured metals in the black tea at 2.76 mg/L median concentration (mean value 2.91 mg/L, 95 % CI 2.70-3.12). Median and 90th % daily tea intake was estimated as 0.35 and 1.1 L/day, respectively. The authors estimated the daily exposure of an individual to Al solely from the ingestion of black tea and reported that the chronic daily intake (CDI) for Al ranged from 4 to 73 µg/kg/d, with a mean value of 21.4 µg/kg/d (95% CI; 16.3 - 26.5). They reported that the Al levels in black tea were not associated with Alzheimer's disease in their population study.

13. In a clinical pathology study by Itoh et al (2008) (abstract only), brain imaging of a 20 year old female patient with progressive leukoencephalopathy showed large abnormal signals in the white matter of her brain. The results for the electron spectroscopic imaging of the biopsied brain tissue showed the electron-dense deposits to be associated with Al accumulation in the myelin sheath.

14. Yumoto et al. (2009) evaluated the presence of Al in autopsied brains (hippocampus and temporal lobe) from five patients with AD using transmission electron microscopy (TEM-LDx). They found Al in the amyloid fibres in the cores of senile plaques located in the hippocampus and in the temporal lobe. The concentration of Al ranged from ~ 35-50 ppm. They did not detect Al in the extracellular space in senile plaques or in the cytoplasm of nerve cells. They also demonstrated the co-localisation of Al and beta-amyloid peptides in amyloid fibres at the core of senile plaques. Using TED-EDX analysis, Collingwood et al. (2008) demonstrated the presence of Al in isolated plaque core fragments (~ 1-2 um in diameter) from frozen cortical brain tissues, sourced from two pathologically confirmed cases of AD. While Collingwood et al. (2008) reported that Al was detected in 50% of isolated plaque core fragments, Yumoto et al. (2009) found Al in 100 % of the senile plaque cores examined.

15. It has been suggested that the interaction of β-amyloid (Aβ) with endogenous brain copper, zinc and iron and other biometals may contribute to the peptide's accumulation and toxicity in the brain in Alzheimer's disease (AD). Strozyk et al. (2009) tested whether there is a biochemical relationship between Aβ and biometal levels in humans, investigating the association of CSF copper, zinc and other metals including Al to CSF Aβ42 in a large cohort of ventricular fluid autopsy samples. They found a strong inverse correlation between CSF-Aβ42 and CSF metals copper, zinc, iron, manganese and chromium but found no association with Al. The authors comment that the inverse association that they have identified between CSF Aβ levels

and biological metals underscores the importance of brain metal homeostasis as a potential factor in the evolution of AD pathology.

16. Walton et al. (2010) examined hippocampal CA1 cells from brains of aged humans, with or without disease (10 brain samples, 5 AD cases and 5 controls), for hyperphosphorylated tau and aluminium during early neurofibrillary tangle (NFT) formation and growth. The study found photographic evidence of pre-tangle and early NFT stages characterised by one or more cytoplasmic pools of an Al/hyperphosphorylated tau complex with the soma, supporting a role for Al in NFT formation.

17. Milacic et al (2009) provides an overview of analytical approaches for speciation of Al in human serum and the progressive developments in analytical techniques such as anion – exchange CIM-monolithic columns in combination with ICP-MS detection.

18. Aslam et al. (2009) developed a non-invasive measurement of Al in human bone, using a technique known as "in vivo neutron activation" analysis. The authors determined the levels of Al in the hands of 18 referent subjects and six Al welders. The minimal limit of detection was 28 μg Al/g Ca. The estimated Al concentration in control subjects ranged from (-9.6 ± 11.6) μg Al/g Ca to (60.3 ± 10.4) μg Al/g Ca, with a mean of (27.1 ± 16.1) μg Al/g Ca. The measurement for welders ranged from (34.2 ± 19.8) μg Al/g Ca to (44.6 ± 18.5) μg Al/g Ca and the mean was 41.2 ± 4.5 μg Al/g Ca. These results should be interpreted with caution as 1) the study was not specifically designed to examine the Al accumulation and 2) the in vivo detection limit of 28 μg Al/g Ca was close to the average level for the control samples. In follow-up research, the authors have aimed to improve the in vivo minimal detection limit and now report an in vivo minimal detection limit of 12 μg Al/g Ca.

Human studies on macrophagic myofasciitis (MMF)

19. Further work has been reported on the syndrome of macrophagic myofasciitis (MMF), which is a rare condition, characterised by localised inflammatory foci of macrophages with associated necrosis, identified at deltoid muscle biopsy. These foci contain aluminium salts and it was proposed by Gheradi et al (2001) that they were caused by long term persistence of vaccine-derived aluminium hydroxide and were responsible for a generalised condition whose symptoms include fatigue and muscle and joint pain. Couette et al. (2007) demonstrated that almost all MMF patients (25 in total in the study) exhibited characteristic deficits in neuropsychological testing, consistent with cognitive complaint. However, the cognitive deficits did not correlate with pain, fatigue, depression or disease duration. Exley et al. (2008) described the coincidence of MMF, chronic fatigue syndrome and aluminium overload in a 43 year old man with no history of previous illness. An estimate of the patient's body burden of Al was obtained from the analysis of five consecutive 24h urine samples. The authors suggest a possible mechanism whereby vaccination involving Al-containing adjuvants could trigger the cascade of immunological events that are associated with autoimmune conditions, including CFS and MMF. They also demonstrated that regular drinking of a silicon-rich mineral water over a 3 month period dramatically reduced the body burden of aluminium from one of overload to a level of burden which may be considered to be within the normal range (Exley et al., 2008). Lach and Cupler (2008) described the clinical and pathological findings in eight children (7 months to 6 years old) with biopsy proven MMF, overlapping with a variety of

neuromuscular disorders. All the children had routine vaccinations between 2 months and 1 year before the muscle biopsy. All biopsies showed identical granulomas composed of periodic acid Schiff-positive and CD68-positive macrophages. Characteristic aluminium hydroxide crystals were identified by electron microscopy in 2 cases. The biopsy established diagnoses other than macrophagic myofasciitis in 5 patients (spinal muscular atrophy in two patients, Duchenne muscular dystrophy in one patient, phospho-glycerate kinase deficiency in one patient, and cytochrome c oxidase deficiency in one patient). Three children with manifestations and/or a family history of mitochondrial disease had morphologically normal muscle. The study concluded that there was no correlation between histological findings of macrophagic myofasciitis in biopsies and the clinical symptoms.

20. Kalil et al. (2008) investigated neuromuscular symptoms in three MMF diagnosed children (aged between 13 months and 3(1/2) years), all of whom had received regular vaccinations which all contained Al-adjuncts. They underwent clinical, familial, and laboratory investigations, electroneuromyography, muscle biopsy with transmission electron microscopy, scanning electron microscopy/energy dispersive spectroscopy (SEM/EDS), and, in one case, brain magnetic resonance imaging. Two patients were hypotonic and one presented with myotonia. Muscle biopsy of all patients presented macrophagic infiltrates with intracytoplasmic Al content. The authors reported that the diverse clinical picture does not support a direct relationship between local morphologic findings and systemic symptoms. Muller et al. (2009) described the occurrence of two separate types of muscular dystrophy (a merosinopathy and a dystrophinopathy) in two unrelated individuals with MMF. The author's believe that the detection of these two separate conditions was made possible by the use of invasive muscle biopsy techniques. Newer non-invasive detection methods such as genetic analysis would not have detected these dystrophies.

21. In 2008, the WHO Global Advisory Committee on Vaccine Safety (GACVS) published a statement following a review of the evidence on MMF, aluminium adjuncts and vaccine safety. It concluded that the evidence supports the idea that MMF represents a simple marker of vaccination with long-term persistence of aluminium at the injection site and a local inflammatory response to it, without other symptoms or consequences. It concluded that there was no evidence of a health risk from Al-containing vaccines or any justification for changing current vaccination practices. The GACVS continues to keep a watching brief on this topic from on-going studies.

Human Exposure

22. Burrell and Exley (2010) determined whether commercially available infant milk formulations were contaminated with Al. They measured the concentration of Al in milk formulae and found the content varied from ca 200 - 700 μg/L. Aluminium is not knowingly added to infant formulae but this result would suggest that an infant could ingest up to 600 μg of Al per day.

23. Al-Ashmawy (2011) analysed the Al concentration of 60 random samples of bulk farm milk, market milk, locally manufactured milk and milk powder in Egypt. The Al content of the examined bulk farm milk ranged from 0.003-0.009 mg/L but this level of Al was classed as negligible as it was below the provisional accepted permissible levels (PALPs) of 0.05 mg/L reported by IPCS (2009) and WHO (2007). In contrast,

the Al content of market milk was higher and in the range of 0.021-0.184 mg/L with 65% of sampled market milk having Al levels above PALPs. The Al content in processed cheese wrapped in Al foil was higher than those found in cheese samples packed in glass containers from the same dairy plant (0.034-5.718 compared to 0.077 to 2.939 mg/kg). The Al content in milk powder ranged from 0.130 – 02.484 mg/kg, with 20 % of all sampled milk powder exceeding the PALP (0.01-0.4 mg/kg) recommended by the FAO/WHO Joint Expert Committee on Food Additives (JECFA). The authors also calculated the Maximum Estimated Daily Intake (MEDI mg/kg/d) for Al in bulk farm milk, control market milk, market milk boiled in Al cookware, market milk boiled in stainless-steel cookware, processed cheese wrapped in Al foil, processed cheese packed in glass containers, and milk powder as 0.03, 0.61, 0.63, 0.61, 4.28, 2.20 and 1.67 mg/kg/d, and these represented 3.0%, 61.0%, 63.0%, 61.0%, 428.0%, 220.0%, and 166.0% of the provisional Tolerable Daily Intake (PTDI).

24. Paranthanan and Harrison (2010) reviewed and described drinking water incidents with chemical contamination reported to the Chemical Hazards and Poison Division (CHaPD) of the Health Protection Agency (HPA) in the UK between 1st Jan 2006 and 31st Dec 2008. Using the National database, they identified 82 incidences (77 in England, 5 in Wales) with confirmed chemical contamination of drinking water. The paper provided 6 examples of particular incidences, two which pertained to Al. The first incident involved elevated Al levels in a drinking water treatment reservoir, caused by disruption of the power supply by a weather storm affecting the lime batching plant. This incident occurred at night when the water treatment works (WTW) was unmanned, triggering an alarm offsite. This WTW supplied water to a few domestic properties and a number of service reservoirs. Sampling of the water at properties fed directly from the WTW showed elevated levels of Al, with the highest being 489 µg/L. The national average was reported as 20 µg/L. The levels were reported to be back to normal background levels within hours. In a second incident advice was sought from a pregnant woman on possible health effects following identification of elevated Al levels in her private drinking water supply. Sampling of water from the kitchen tap confirmed a level of Al at 5450 µg/L (legal standard 200 µg/L). The duration of the potential exposure to elevated Al was thought to be 3 years. Despite exceeding water quality standards, toxicology advice was that the estimate intake was many times below the levels at which effects were seen in animal studies and adverse effects were not expected.

Reviews on Aluminium

25. A number of review papers are available in the literature. Zatta et al. (2009) reviewed the most recent evidence linking metal ion imbalance and Ab aggregation. They also examined the participation of Al-Ab complex as a cofactor in the pathogenesis of AD. Verstraeten et al. (2008) reviewed the role of molecular mechanism such as oxidative stress, membrane biophysics alterations, deregulation of cell signalling, and the impairment of neurotransmission as key aspects involved Al and lead neurotoxicity. Similarly, Kumar and Gill (2009) reviewed the neuropathologies associated with Al exposure, examining the neurobehavioural effects and oxidative functions of the cell. Gonclaves and Silva (2007) reviewed the evidence linking Al-induced effects to neurotransmission and how the impairment of neurotransmission can produce neurobehavioural disorder outcomes. Bondy (2010) provided a review of research advances into the potential role of Al in the acceleration

and promotion of some indices, such as inflammation, characteristic with brain aging. The role played by silica in drinking water in relation to AD and other neurological disorders and its potential beneficial effects in decreasing Al bioavailability was reviewed by Gillette-Guyonett et al. (2007). Frisardi et al. (2010) reviewed the role played by Al in neurotoxicity and discussed the role of other elements in drinking water on cognitive impairment and/or their role in the modification of Al neurotoxicity.

26. Krewski et al. (2007) preformed a human health risk assessment for aluminium, aluminium oxide and Al hydroxide using the 4 step process: 1) Hazard Identification, 2) Exposure Assessment, 3) Dose-Response Assessment and 4) Risk Characterisation. For hazard identification, they reported that there is strong evidence that aluminium can cause irritation following exposure via either inhalation or injection. They also found modest evidence of an effect for reproductive toxicity following oral exposure, for neurological toxicity following either oral or injection exposure, and for bone toxicity following injection exposure. For exposure assessment, they quantified aluminium intake and uptake for a variety of pathways, food, water, air and drugs. They identified relevant exposure levels of concern for the general population as part of the Dose-Response assessment and these included irritation following inhalation of 50 mg/m^3, neurological effects due exposure to 100 µg aluminium/L drinking water, reproductive toxicity due to oral intake of 400 mg/kg bw/d and irritation following a single injection. They characterised the risk by calculating the MOE (exposure level of concern divided by actual exposure). They report that the MOE values were large for local irritation following inhalation (7000) and reproductive toxicity associated with oral intake (2900). For irritation following injection, the MOE was less than unity, although the severity of this endpoint is limited. For neurological effects associated with drinking water exposure, they found that the MOE may be as small as unity. They report a margin of exposure for occupationally exposed populations of 8, compared to 7000 for general population exposure to airborne Al. For subgroups at special risk, such as dialysis patients who may be exposed to substantial quantities of injected fluids and their increased susceptibility, the authors reported that the MOE for this pathway may be less than unity. They highlight a number of research areas that would help future risk assessments on Al.

Evaluations of Aluminium

27. In 2008, the UK Committee on Toxicity published a statement on the 2006 UK total diet study (TDS) of metals and other elements (http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2008/cotstatement200808) and the Committee commented on the survey results and assessed if the levels of any of the elements in the diet posed a risk to human health. The results of the 2006 TDS show an apparent increase in dietary exposure to aluminium (5.4 mg/day) compared to that reported in the 2000 and 1997 total diet studies (4.7 mg/day and 3.4 mg/day, respectively). It was noted that this value is within the estimated mean dietary exposure of European adults (1.6-13 mg/day) (EFSA, 2008). The Committee commented on the acknowledgement throughout Europe that, for certain groups of the population, including infants and young children, exposure to aluminium will exceed the PTWI of 1 mg/kg/bw, recommended by JECFA in 2007 and the European Food Safety Authority (EFSA) in 2008. It further stated that consumption of tap water has the potential to increase high-level exposure to aluminium by 3-7%, such that the worst case high level intake of preschool children

could exceed the PTWI by 2.7-fold. The Committee concluded that "whilst the estimates of dietary exposure to aluminium were not markedly higher than previous estimates, they present uncertainty with regard to the safety of aluminium in food in the light of the recent reduction in the PTWI, which is exceeded by some population subgroups".

28. In 2010, the WHO published new guidelines for Drinking Water Quality, which included a review of the guideline values for aluminium. WHO commented that "a health-based value derived from the 2006 JECFA PTWI of 1 mg/kg bw would be 0.9 mg/L, based on the allocation of 20 % of the PTWI to drinking water and assuming a 60 kg man drinking 2 litres of water a day. However, there remain uncertainties as to the extent of aluminium absorption from drinking-water, which depends on a number of parameters, such as the aluminium salt administered, pH (for aluminium speciation and solubility), bioavailability and dietary factors." The guidelines recognise the beneficial effects of the use of aluminium as a coagulant in water treatment to reduce microbial contamination. Taking this into account and considering the potential health concerns (i.e. neurotoxicity) of aluminium, a practicable level was derived based on optimisation of the coagulation process in drinking-water plants using aluminium-based coagulants, to minimize aluminium levels in finished water. These practical levels were 0.1 mg/L or less in large water treatment facilities and 0.2 mg/L or less in small facilities.

Animal Studies

Animal neurotoxicity studies – *Rats*

29. (*Please note that studies described in paragraphs 29-31 all originate from the same research laboratory).* A pilot longitudinal study by Walton (2007a) and a main longitudinal study by Walton (2009a) were conducted in rats to assess whether chronic Al exposure at human-relevant dietary levels can alter performance on a hippocampal-dependent continuous alteration spatial memory discrimination T-maze task. Three groups of rats were chronically exposed to ~ 0.4, 0.5 and 1.7 mg/kg/d (1.5 mg/kg/d in the pilot study) designated as low, intermediate and higher Al doses. In the pilot study, 33% (2/6) of rats developed cognitive deterioration in a group that consumed an equivalent amount of Al to the higher end of the human dietary Al range. In the main longitudinal study, 100% (10/10) of the rats that consumed the lowest Al dose level were able to perform the T-maze task with equal ability in old age as middle age. However, 20 % (2/10) of the rats that consumed the intermediate dose and 70 % (7/10) of those that consumed Al in the highest dose group range achieved significantly lower mean performance scores in old age compared to middle age. They also exhibited behavioural signs observed in dementia while in the T-maze. The main study also found that rats with impaired performance had significantly higher serum Al levels ($p< 0.01$) and cell counts indicating a larger percentage of Al-loaded pyramidal cells in the entrohinal cortex ($p <0.05$). Also, the percentage of Al-loaded entrohinal cortex cells correlated inversely with the decrease in the T-maze performance scores between middle age and old age ($R = 0.76$, $p< 0.0005$). There were two outcomes from the longitudinal project, some rats remained cognitively intact and others developed cognitive deterioration.

30. Using the brain tissue from rats obtained from the previous longitudinal studies of an animal model for AD, Walton and Wang (2009) studied amyloid precursor protein

(APP) attributes in aged rats. APP is an integral glycoprotein that is important in neurite sprouting, branching and elongation. Its product β-amyloid presents a major feature of AD. The authors aimed to determine whether brain tissue from rats that exhibited cognitive deterioration, as a result of chronic exposure to human relevant levels of dietary Al show early evidence of the amyloid cascade. The authors found that the hippocampal and cortical tissue from the cognitively-deteriorated rats showed elevated APP-gene expression, significantly more dense APP deposits in the cytoplasm of neural cells and APP-immunoreactive neurites that were swollen and varicose, compared to the results from cognitively intact rats. In another study by Walton (2009b), again using the brain tissue from rats obtained from the previous longitudinal studies of an animal model for AD, the author attempted to identify neuropathological features that distinguish the brains of aged rats with cognitive deterioration from the cognitively intact control rats. They found that Al accumulates in the hippocampal pyramidal neurons of most aged rat (i.e. both cognitively intact and cognitively damaged rats). However, cognitively damaged rats have 3-fold more such cells than controls. The authors reported the presence of distinctive lesions in all cognitively deteriorated rats but were absent from all cognitively intact controls. These lesions were shown to expand in size as pyramidal cells became Al-loaded and microtubule-depleted.

31. Using an rat model for AD, Walton (2007b) compared the effect of chronic ingestion of high dose Al (1.6 mg/kg/d from 12 months of age onwards) with that of a control dose of Al (0.4 mg/kg/d) on 1) oxidative damage leading to the formation of amyloid plaques and 2) effect of oxidative damage on PP2A activity, resulting in hyperphosphorylation of tau and the formation of neurofibrillary tangles (NFTs). The author found that PP2A activity was significantly reduced (49%) compared to control values. The staining results showed that chronic ingestion of high levels of Al caused Al loading in some aged rat neurons, accompanied by oxidative damage, hyperphosphorylated tau, neurophil threads and granulovacuolar degeneration. The results of this study suggest that neuronal Al can account for early stages of plaque and tangle formation in an animal model of AD.

32. Newairy et al. (2009) investigated the alterations in biochemical parameters, free radicals and antioxidant enzymes in the liver, kidney and brain of male rats, following oral ingestion of Aluminium chloride ($AlCl_3$) (34 mg/kg/d). They found that treatment with $AlCl_3$ caused an elevation in thiobarbituric acid reactive substances (TBARS), indicative of lipid peroxidation. Treatment also caused a decrease in the antioxidant enzymes GST, SOD, CAT, GSH-Px in the liver, kidney and brain. Liver enzyme activities (AST, ALT and LDH) were significantly increased in the plasma of $AlCl_3$ treated rats. They also found that plasma total protein, albumin and HDL-c were decreased, while glucose, urea, creatinine, bilirubin, total lipid LDL-c, cholesterol and triglyceride were increased compared to controls.

33. (*Please note that studies described in paragraphs 33-35 all originate from the same research laboratory).* In an oral drinking water study, Jyoti et al. (2007) administered 50 mg/kg/d of $AlCl_3$ to male Wistar rats for 5 weeks. They found that Al-treated rats had elevated levels of lipid peroxidation (measured by TBARS and 4-HNE production, $p< 0.05$) and enhanced protein carbonyl contents ($p< 0.05$) as an indicator of protein oxidation in the cerebral cortex. They also reported a decrease in SOD, GST, GPx and non-enzymatic antioxidant GSH activity in the cerebral cortex of Al-treated rats compared to control rats.

34. Sethi et al. (2008) studied the effect of long-term oral Al administration ($AlCl_3$; 50 mg/kg/d for 6 months in drinking water) at the electrophysiological, biochemical and behavioural levels to investigate the possible pathophysiological effects associated with Al-toxicity in both young (4 months) and old (18 months) male Wistar rats. In the electrophysiological studies, they found that Al treatment resulted in hyperexcitability in the EEG, confirmed by significantly increased multiple unit action potential recordings in both young and old Al-treated rats. Al-treatment also adversely affected the spatial learning and memory abilities of both young and old rats. The authors reported that the antioxidant system was compromised. Al-treatment induced oxidative damage to lipids and affected antioxidant associated proteins and enzymes (Na-K ATPase, PKC, SOD, GST and GPx).

35. In a follow on study from Sethi et al. (2008), Sharma et al. (2009) designed a study to evaluate the protective effect of curcumin on aluminium induced neurtoxicity changes in ageing-related parameters in brain regions. They studied the effect of long term (6 months) treatment of 4 month and 18-month old male rats with $AlCl_3$ (50 mg/kg/d for 6 months in drinking water) on parameters such as lipid peroxidation, Na+ and K+ ATPase, protein kinase C (PKC) and cellular antioxidant enzymes in the cerebral cortex and hippocampus parts of the brain. Results are presented for $AlCl_3$ treatment only. Treatment with $AlCl_3$ resulted in an increase in protein kinase C (PKC), acetylcholine esterase (AChE) and the levels of lipid peroxidation, while the activities of SOD, GPx, GST, Na+ ATPase and K+ ATPase were significantly decreased in both brain regions of both age groups.

36. A 90-day oral treatment of rats with $AlCl_3$ (100 mg/kg/d) by Tripathi et al. (2008) found significant changes in the metabolic profile of serum of $AlCl_3$-treated rats, with elevated levels of alanine, glutamine, B-hydroxy butyrate and decreased levels of acetone found in their serum compared to controls. Serum ALP, AST and ALT levels were significantly increased in Al-treated rats. Metabolic profiling of 90-day $AlCl_3$-treated rats urine showed significant decreased levels of citrate, creatinine, allantonin, trans-aconitate and succinate and significantly increased levels of acetate when compared to control rats. The livers of control rats showed normal histological structure, whereas Al-treated rat's livers showed degenerative changes in numerous hepatocytes such as enlargement of cells, light and foamy cytoplasm filled with vacuoles, increased density of nuclear chromatin. Similarly, the kidney of control rats showed normal histopathological structures, while Al treated kidneys showed hypertrophy of epithelial cells and degeneration of epithelia of glomerali with mononuclear cell infiltrates. In the behavioural tests, significant changes were found in spontaneous motor activity (SMA) ($p \sim 0.1$), catalepsy ($p \sim 0.001$), muscle coordination ($p \sim 0.01$) and passive avoidance ($p \sim 0.001$) in Al-treated rats compared to control rats.

37. (*Please note that studies described in paragraphs 37-38 all originate from the same research laboratory).* Khanna and Nehru (2007) investigated the response of neurons and glial cells from the cerebral cortex to oxidative stress induced by Al following treatment of female SD rats with 100mg/kg/d of $AlCl_3$ in drinking water for 8 weeks. The authors found that neurons and glial cells showed a varied pattern of antioxidant enzymes. In control samples, TBARS levels were significantly higher in glial cell fractions than neuronal cells, with corresponding glial cells having higher levels of GSH, GSSG, GPx, and GST while neuronal cells had higher levels of catalase (CAT), superoxide

dismutase (SOD) and glutathione reductase (GR). Aluminium treatment caused significant increases in TBARS levels in neurons compared to glial cells. They also report that the SOD and CAT activity were significantly decreased in neurons and glial cells following exposure to Al for 8 weeks. GSH content decreased significantly ($p< 0.001$) in neurons and GSH content increased significantly in glial cells, when treated with Al. Significant decreases in GSSH content and GPx was observed in neurons and glial cells after treatment with Al. A similar trend was found for total glutathione content of both cell types. GR activity was significantly decreased in neurons ($p<0.05$) but a significant increase in GR activity was observed in glial cells ($p<0.001$) after Al treatment. They also found significant increases ($p<0.05$) increases in GST activity in both cell types after Al treatment.

38. In follow-up studies, Nehru et al. (2007), Bhalla and Dhawan (2009), Bhalla et al. (2010a) and Bhalla et al. (2010b) examined the effect of lithium centrophenoxine in ameliorating oxidative stress, histological alterations, behavioural and neurochemical effects induced by the Al exposure, respectively. The female SD rats were fed $AlCl_3$ (100 mg/kg/d) for 6 weeks (2 months). The results from the Al-only treatment versus controls are presented here. Nehru et al. (2007) observed a significant ($p<0.001$) increase in lipid peroxidation following oral Al treatment compared to controls. They also observed a significant ($p<0.001$) decrease in glutathione level in both the cerebellum and cerebrum as compared to controls. Bhalla et al. (2010a) demonstrated that short term memory was significantly altered after Al exposure and the rats did not learn the task as effectively as that of normal rats, as observed by the decrease in retention trial time. A significant decrease in the levels of serotonin and dopamine was observed and an increase in ROS after Al-treatment in both the cerebellum and cerebrum, which may account for the impaired learning and memory performance in Al-treated animals. Bhalla and Dhawan (2009) reported a significant enhancement in lipid peroxidation ($p \leq 0.001$) and ROS ($p \leq 0.001$) in both the cerebrum and cerebellum compared to normal controls. They also reported a significant increase in Al concentrations in both these areas of the brain following treatment with $AlCl_3$. Bhalla and Dhawan (2009) found that GST activity was significantly decreased in both the cerebrum ($p \leq 0.01$) and cerebellum ($p \leq 0.001$) after Al treatment, while the activities of the antioxidant enzymes CAT, SOD and GR were significantly increased ($p \leq 0.001$) in both the cerebrum and cerebellum. Al treatment also cau sed disorganisation in the layers of the cerebrum, cerebellum and vacuolar spaces, indicating structural damage (Nehru et al., 2007, Bhalla and Dhawan, 2009). Bhalla et al. (2010b) reported that Al treatment resulted in a significant increase in the activity of enzyme nitric oxide synthase an increase in the levels of L-citrulline and an increase in DNA fragmentation as evidenced by an increase in number of comets. Ultrastructural studies revealed an increase in chromatin condensation with discontinuity in nuclear membrane in both the cerebrum and cerebellum of Al treated rats with alterations in the structure of synapse and mitochondrial swelling were also seen.

39. Luo et al. (2007) demonstrated that learning and memory deficits as determined by the Morris Water maze test can be induced by low-dose Al (1600 ppm) in drinking water for 5-8 months (c.0.2 mg/kg bw/day). They also showed that Al reduced SOD activity and increased MDA and ABi-40 levels in the hippocampus.

40. Erazi et al. (2010) demonstrated that treatment of rats with 0.3% $AlCl_3$ (342 mg/kg/d) in drinking water either in adulthood for a 4 month period or from intra-

uterine age followed by a postnatal Al-exposure period of 4 months, induced a significant increase in glial fibrillary acidic protein (GFAP)-immunoreactive astrocytes particularly in the cerebral cortex. Using the same animals, Erazi et al. (2011) examined the effects of Al exposure on tyrosine hydroxylase (TH), the enzyme involved in the production of L-dopamine. They demonstrated that a significant decrease in the numbers of TH-immunoreactive labelled neurons in Al-treated rats compared to controls, with the intra-uterine aged rats more affected that Al-treated adult rats. Both studies also report that Al-treatment induced a significant reduction in locomotor activity in both adult and intrauterine treated rats.

41. Kumar et al. (2009) studied the protective effect of curcumin against Al-induced cognitive dysfunction and oxidative damage in rats. $AlCl_3$ (100 mg/kg/d) was given orally to rats for 6 weeks and the authors found that $AlCl_3$ treatment impaired acquisition of spatial navigation tasks and significant cognitive and memory impairment. No effect of treatment was observed for locomotor activity. Chronic Al treatment caused marked increase in free radical generation, significant increase in brain MDA, nitrate levels, decreased GSH levels, decreased antioxidant enzymes namely GST, SOD and CAT and a significant decline in brain AChE activity compared to controls.

43. Azzaoui et al. (2008) conducted a 90-day sub chronic study to assess the effect of aluminium nitrate (80 mg/L) in drinking water on female rats. The study assessed motor activity (open field test) and recognition memory ability (Novel object recognition memory (NOR) test) and they also measured brain Al concentration. The authors found that exposure to Al in drinking water did not have any significant effect on motor activity in each of the fortnightly testes or during the whole study. They did find that Al caused a significant effect ($P<0.05$) on rat recognition memory, during the whole study period. The index mean of recognition memory was 0.63 ± 0.04 in control rats compared to 0.43 ± 0.06 in Al-treated rats. The authors did not report any significant differences in brain Al concentrations between control and Al-treated rats.

44. Poirier et al. (2011) conducted a double-blind vehicle controlled randomized 12-month neurodevelopmental rat toxicity study by exposing offspring to aluminium citrate (0, 10, 30, 100 and 300 mg/kg/d) *in-utero*, through lactation and in drinking water post weaning. The endpoints assessed in both male and female pups included behavioural endpoints (motor activity, T-maze, auditory startle response, FOB with domain targeting autonomic function activity, neuromuscular function, sensimotor function and physiological function), cognitive function (Morris Swim Maze), brain weight, clinical chemistry, haematology, tissue/blood levels of Al and neuropathy. They found evidence of general toxicity at the highest dose of Al citrate (300 mg/kg/d) in both the dam and pups. In dams, it consisted of diarrhoea. In the pups, the most notable treatment related effect was renal pathology, especially in the anatomically vulnerable males, due to urinary calculi, but also in a subset of high dose females. In addition, the high dose group was characterized by the presence of diarrhoea and bloat, thinness, poor hair coat and haematuria. In the FOB tests, there was evidence of heightened excitability in the mid to high female subgroups receiving Al citrate but not males. In the high dose group, Al exposure led to a significant autonomic or sensimotor dysfunction. They also found a weak association between high Al dose animals and reduced house-cage activity, a very weak association with excitability, some association with neuromuscular performance (may have been due to

BW differences in the groups) and an association with physiological function. Neuromuscular functions on the other hand, were significantly impaired in the mid- and high dose Al citrate cohorts at the level of the hind-limb grip strength and, to a lesser extent, on foot splay, in both male and female rats. The effect was more pronounced in young animals; presumably because animals got larger and stronger over time, they better compensate for the original impairment. A reduced auditory startle response was observed in the day 64 group males and day 120 group females in the high dose group, but not in day 364 group. The evidence is therefore inconsistent and not supportive of an Al dose-related effect. It is either transient or, subject to a specific age and size threshold. The authors did not find any evidence of significant effects on leaving using the T maze in day 23 groups or MWM in day 64, 120 and 364 groups, even at the highest doses of Al citrate. On the basis of the clinical observations and the FOB parameters linked to neuromuscular function, a LOAEL was determined at 100 mg/kg/d and a NOEAL was determined at 30 mg/kg/d.

Animal neurotoxicity studies – *Mice*

45. There have been several publications in the past three years using genetically engineered AD mouse models. One particular model is the Tg2576 AD mouse model, which carries a transgene coding for the 695- amino acid isoform of the human Alzheimer B-amyloid precursor protein (ABPP), derived from a Swedish family with early-onset Alzheimer's disease. The Tg2576 mouse expresses high levels of the mutant ABPP in the cell body of neurons, they exhibit neuronal loss, synaptic alterations, inflammation and gliosis and dendritic alterations, and have a phenotype characterised by memory deficits after 9-10 months of life.

46. (*Please note that studies described in paragraphs 46-48 all originate from the same research laboratory).* Using this AD model, Gomez et al. (2008) evaluated the concentration of metals such as Al, Fe, Cu and Zn hypothetically implicated in neurogenerative diseases in the cerebral regions of the brain, the liver, kidney and bone following chronic exposure to Aluminium lactate. The authors had intended on giving female mice 1 mg/g of diet for 6 months, but due to manufacturer error the dose given to the animals was 370 µg of Al/g of diet, which they calculated to be equivalent to approximately 54 mg/kg bw/day. The authors did not find any significant differences in Al levels in the different brain regions, liver or kidneys of control wild-type (WT) or in transgenic (TG) animals. Al was not detected in bone tissue of either control WT and TG animals. Following exposure to Al, the highest levels of Al were found in the hippocampus, followed by those in cerebellum and cortex. However, there were no significant differences in Al concentrations in any of the brain regions between genotypes. Copper, zinc, manganese and iron in liver, kidney and bone were not affected by Al exposure.

47. Ribes et al. (2008) assessed the behavioural effects of oral Al lactate in the Tg2576 model. WT and Tg2576 male mice received a diet supplemented with 1 mg Al lactate/g of diet (17 mg/kg/d) for 3 months. They investigated the differences in neurogenesis and beta-amyloid production induced by both Al exposure and genotype. The authors found that aluminium exposure did not induce changes in exploratory behaviour to a novel environment measured in an open-field test, either in WT or in transgenic mice. In the Morris Water Maze test (MWM), they found that Al exposure affected WT mice but did not affect the Tg2576 mice during the acquisition period of the MWM test. For neurogenesis, their results showed an overall effect of

animal, where Tg2576 mice had a greater number of new born cells, indicating neurogenesis at early stages of neurodegeneration followed by a decrease at late neurodegenerative states. They also found greater cell proliferation in Tg2576 mice exposed to Al, which may indicate a reactive response of the brain to Al insult. In a follow on study using the same conditions as described in the 2008 study, Ribes et al. (2011) evaluated the general neurotoxicity of Al lactate using a functional observational battery (FOB) and a novel object recognition task. The authors found a decrease in house-cage activity, a decrease in piloerection in all Al-exposed animals and an increased sensorimotor reactivity in Tg2576 mice given Al. No effects were seen on corticosterone levels or Al concentrations in the frontal cortex and cerebellum in either treated or untreated, or in WT or in transgenic mice. Recognition memory was impaired in the Tg2576 mice but Al did not alter the impairement in the transgenic mice (*note: data taken from the Ribes et al. (2011) abstract: the full text of this paper was not available at the time of preparation of this report).* In a another study by the same group, Ribes et al. (2010) gave Tg2576 mice and control mice aluminium lactate (11 g/g of food) for 6 months. The author's found that Al treated Tg2576 mice had impaired acquisition in the MWM test and the memory of Al treated mice was impaired compared to controls. They did not find any effects of Al treatment on cell proliferation, survival and differentiation indicating neurogenesis remained unmodified. These results differ from those obtained in their 2008 study, which was of shorter duration and in which Al was given at a lower dose.

48. Garcia et al. (2010a, 2010b and 2009) investigated the effects of a 6-month dietary Al lactate exposure on the oxidative imbalance and behavioural effects in the hippocampus, cerebellum and cortex of female Tg2576 mice as well as the protective effect of melatonin. The authors refer to the paper by Gomez et al. (2008) for information on the dosing. They had intended on giving the mice 1 mg/g of diet for 6 months, but due to manufacturer error, the dose given to the animals was 370 µg of Al/g of diet, which they calculated to be equivalent to approximately 54 mg/kg bw/day. They also investigated the effects on the antioxidant enzymes in different brain regions. The results of Al-only treatment versus controls and not those related to melatonin treatment are presented here. Garcia et al. (2009) examined general motor activity, habituation and anxiety levels in both wild-type and TG mice and they did not find any significant effects of Al on the general activity of transgenic or wild type mice. The open field test showed an increased number of rearings in Tg256 mice. A significant difference was observed between Al treated and non-treated transgenic mice on day 3 of the acquisition in the water maze, latency and distance test, indicating that Al impaired learning in the TG mice. These results differ from a previous study by this group (Ribes et al., 2008). Ribes et al. (2008) noted differences between genotypes, with an impaired acquisition in Al-exposed wild type mice but not in exposed TG mice. However, differences in study design between the two studies such as dose (was meant to be 10 times lower in Ribes et al, but actually due to errors in dosing according to Gomez et al. (2008), the dose was 3 times lower), period of treatment (3 months verses 6 months), the water maze protocol (more challenging for the animals in Ribes et al. (2008)) as well as sex differences, should be taken into account when assessing the results. In another study by this group, Esparza et al. (2010) analyzed the ability of a chelator deferroxamine (DFO) to remove Al from various cerebral sections of AβPP transgenic mice (Tg2576) that were chronically fed a diet supplemented with Al lactate (1 mg of Al/g food, again this should be 370 µg/g food) for 6 months. They found that the treatment of the Tg2576 mice with DFO by subcutaneous injections at a dose of 0.20 mmol/kg/d,

twice a week for 6 months did not prevent the oxidative effects of Al seen in the Al-treated Tg2576 mice.

49. Pan et al. (2008) investigated the protective effects of curcumin in mice treated with $AlCl_3$ (10 mg/kg/d) orally and D-galactose (20 mg/kg/d, i.p to establish an AD model) for 90 days. The results of interest (Al only) are presented here. In the passive avoidance test, they found that treatment with $AlCl_3$ and D-galactose induced memory impairment, indicating that their mouse model mimics AD pathogenesis. They also observed neuropathological changes in the hippocampus of Al treated mice, condensed dark stained neurons, neurofibrillary degeneration and neuron loss. They found that $AlCl_3$ and D-galactose resulted in BCl-2 down regulation ($p< 0.05$) but they had no effect on BAX protein levels.

50. Rui and Yongjian (2010) exposed ICR mice to $AlCl_3$ (10, 50, 300 mg/kg/d) for 100 days and determined the oxidative damage induced by long-term exposure to high dose Al. They found that a concentration dependent increase in MDA level in both the hippocampus and cortex following $AlCl_3$ treatment. Significance was reached following $AlCl_3$ treatment of 50 mg/kg/d in the hippocampus region, $p< 0.05$) or 10 mg/kg/d in the cortex region ($p< 0.05$). SOD activity was decreased in both the hippocampus and cortex and reached significance at 10 mg/kg/d ($p< 0.05$). $AlCl_3$ treatment resulted in increased levels of nDNA oxidative damage, as determined by the COMET assay and an increase in levels of 8-OHdG. The exposed groups showed a dose dependent increase in 8-OhdG levels in both the hippocampal and cortex derived cells.

51. Dysfunction of the endoplasmic reticulum may be involved in the pathogenesis of Alzheimer's disease. The immunoglobulin heavy-chain binding protein (BiP also known as the glucose-regulated protein, GRP78) is induced in the ER under conditions of stress and activate the unfolded protein response (UFR) signalling pathway, involving ER transmembrane kinases. Kaufman et al. (1999) found that GRP78 is expressed by the UFR and may alleviate the ER stress and/or prevent apoptosis. Katayama et al. (1999) considered GRP78 to play a molecular chaperone in the ER for folded and mutated proteins. Rodella et al. (2008) examined the correlation between the expression of Aβ and GRP78 in the cortex of mice chronically treated with 2.5 % (2,850 mg/kg/d) aluminium sulphate in tap water for 2, 4, 6 and 12 months. In the Al-treated mice, they observed Aβ immunoreactivity around the vessels, mainly at the vessels bifurcations levels, which was not detected in the control mice. They observed Aβ deposits from 2 month onwards following treatment. The highest pattern of immunostaining was observed after 12 months in all cortical areas of the brain but the staining was more evident in the hippocampal cortex. The authors comment that this finding of vascular associated Aβ neuropathology are in agreement with those of Exley and Esiri (2006) who found high levels of brain Al coincident with a severe form of congophilic amyloid angiopathy (CAA) in an individual who were exposed to Al sulphate in their drinking water. A large number of moderately to intensely GRP78 stained neurons were observed in the cerebral cortex of control mice. In Al-treated mice, the immunostaining of GRP78 was lower than in control mice, with 50% moderately stained and the other neurons only faintly Aβ stained. The author commented that this finding of decreased GRP78 immunostaining in the cortex of treated mice are in agreement with the observations of Katayama et al (1999) that GRP78 is reduced in the brains of AD patients.

Animal studies - Other biological and toxic effects

Developmental/reproductive effects

52. In a two generation reproductive study by Hirata-Koizumi et al. (2011), 5 week old F0 Crl:CD(SD) rats were exposed to aluminium sulfate (AS) in drinking water at 0, 120, 600 and 3000 ppm (equivalent to c. 0, 13.7, 68.4 and 342 mg/kg bw/day, using a default drinking water consumption of 114 ml/kg bw/day). After 10 weeks of AS administration, each female rat was mated with a male rat of the same dosage group and pregnant females were allowed to deliver spontaneously and nurse their pups. AS dosing was continued throughout the mating, gestation and lactation period. For the second (F1) generation study, male and female weanlings in each group were selected as parents on PNDs 21-25. F1-selected rats were given drinking water with the respective formulation of AS and were mated, allowed to deliver and nurse their F2 pups and necropsied in the same manner as F0 rats. Treatment via drinking water resulted in decreased water consumption for both sexes in all treatment groups. This change was associated with decreased food consumption in the 600 and 3000ppm groups and decreased body weight in the 3000ppm group.

53. For reproductive indices, continuous drinking of AS-contained water for two generations did not result in changes in copulation, fertility or gestation indices, pre-coital or gestation length, the number of implantations or pups delivered, or the incidence of pups with malformations or variations. In addition, adverse effects were not found in the oestrogen cycles of the mice. The study did observe some developmental effects. Male and female F1 pups and female F2 pups in the 3000ppm group had a lower body weight on PND 21 while no difference was found in the birth weight. They also reported that vaginal opening was slightly delayed in F1 females in the 3000ppm group while no compound-related changes were found in the other developmental landmarks, including male preputial separation. There were no compound-related changes for any developmental neurobehavioral endpoint tested. No changes were observed in the reflex ontogeny of F1 and F2 pups and in spontaneous locomotor activity tested at 4 weeks of age for F1 animals. As for the performance in a water-filled multiple T-maze, a transient decrease in the elapsed time and the number of errors were found in F1 females in the 600ppm group, but this change was not considered to be treatment-related because of the lack of dose-dependency. Overall, they concluded that the no observed adverse effect level of AS in this two-generation study was 600ppm (41.0 mg/kg bw/day) for parental systemic toxicity and reproductive/developmental toxicity. The total ingested dose of aluminium from food and drinking water combined in this 600ppm group was calculated to be 8.06mg Al/kg bw/day.

54. Yousef and Salama (2009) studied the reproductive toxicity of $AlCl_3$ in adult male rats. Treatment of rats with $AlCl_3$ orally (34 mg/kg bw, 1/25 LD_{50}) for 70 days resulted in significant ($P \leq 0.01$) decrease in the relative weights of testes, semin al vesicle and epididymis in treated animals compared to control animals. They found that $AlCl_3$ treated rats had significantly ($P < 0.01$) decreased sperm concentration and motility (%), while increased dead and abnormal sperm as compared to control. In the $AlCl_3$-treated group, histopathologic examinations revealed apparent alterations in the testes, where it induced marked lesions in seminiferous tubules. They also showed significant decrease in plasma testosterone concentration ($P 0.05$) and testicular pr otein ($P \leq 0.01$), significant ($P \leq 0.01$) decrease in the activities of testes catalase (CAT) and glutathione S-transferase (GST), and reduced glutathione (GSH) and 17-ketosteroid reductase

(converts androstenedione to testosterone), and increased the levels of thiobarbituric acid-reactive substances (TBARS) in rats treated with $AlCl_3$ compared to control. The authors also determined the effectiveness of propolis in modulating the $AlCl_3$ induced reproductive toxicity.

55. Turkez et al. (2010) studied the hepatotoxicity and genotoxicity of Aluminium chloride in adult male rats. Treatment of rats with $AlCl_3$ orally (34 mg/kg bw, 1/25 LD_{50}) for 30 days found that the activities of serum marker enzymes (AST, ALT, ALP and LDH) were elevated markedly in rats treated with $AlCl_3$ compared to control rats. Microscopic examination showed that the livers in Aluminium-treated groups had severe pathological damages such as: sinusoidal dilatation, congestion of central vein, lipid accumulation and lymphocyte infiltration. The authors used a liver micronucleated (MN) assay to detect in vivo genotoxic effects of $AlCl_3$ and found that $AlCl_3$ induced a statistically significant ($p< 0.05$) increase in formations of MN hepatocytes. The authors also determined the effectiveness of propolis in modulating the $AlCl_3$ induced genotoxicity and hepatotoxicity in liver of rats.

56. Li et al. (2011) investigated the effects of Al exposure on bone mineral elements, trace elements and bone mineral density (BMD) in rats. The rats were exposed to $AlCl_3$ in drinking water, whereas control rats were given distilled water for up to 150 days. Al-treated rats showed lower deposition of Ca, P, and Mg compared with control rats. They found that the levels of trace elements (Zn, Fe, Cu, Mn, Se, B, and Sr) were significantly lower in the Al-treated group than in the control group from day 60, and the BMD of the femur metaphysis in the Al-treated group was significantly lower than in the control group on days 120 and 150.

57. Zhang et al. (2011) investigate the effect of subchronic (150 days) $AlCl_3$ (430 mg/L) in drinking water on iron (Fe) homeostasis in rats. The study found that chronic exposure to Al disturbed Fe homeostasis. Specifically, they reported that Al-treated rats showed significantly decreased bodyweight and increased Al and Al/Fe levels during the experimental period. Fe levels and mean corpuscular hemoglobin (MCH) were higher on day 150 in the experimental group than in the control group. Transferrin (TF) content and total iron binding capacity (TIBC) were higher, whereas erythrocyte counts and soluble transferring receptor (sTfR) content were lower in the experimental group than in the control group from days 90 and 60, respectively.

Conclusions

58. In conclusion, EFSA has evaluated the toxicity of Al in the context of its use as a food additive and WHO has evaluated the toxicity of Al as a drinking water contaminant since the last review of aluminium by the LSG. Based on the combined evidence from the scientific literature, the EFSA Panel established a tolerable weekly intake (TWI) of 1 mg Al/kg bw. The WHO published new guidelines for Drinking Water Quality. They stated that a health-based value for Al would be 0.9 mg/l based on an allocation of 20% of the PTWI to drinking-water and assuming a 60 kg adult drinking 2 litres of water per day but that this value exceeded practicable levels based on optimisation of the coagulation process in drinking-water plants using aluminium-based coagulants: 0.1 mg/L or less in large water treatment facilities and 0.2 mg/L or less in small facilities. Therefore, no health-based guideline value was recommended. In the UK, the COT also examined intakes of Al from a Total Diet Survey and

commented that the consumption of tap water has the potential to increase high-level exposure to aluminium by 3-7%, resulting in an increased risk of exceeding the JECFA and EFSA PTWI in some at risk groups.

There have been a number of studies published which evaluate the effects of oral aluminium dosing in animal models. The majority of these studies have focussed on neurological effects. However, a small number of laboratories have published a number of papers examining different endpoints from the same animal set. It is difficult to compare the studies from different laboratories, due to differences in the study design and protocols adopted by the different groups or even the same groups for that matter. For example, two groups from the same laboratory adopted a different protocol for the same endpoint (Ribes et al. 2008 and Garcia et al. 2009) making comparison difficult.

Reference list to Appendix 26

Aslam, Davis K, Pejović-Milić A, Chettle DR. Noninvasive measurement of aluminium in human bone: preliminary human study and improved system performance. J Inorg Biochem. 2009; 103(11):1585-90.

Azzaoui, F.Z., Ahami, A.O.T. and Khadmaoui, A. Impact of Aluminum Sub-Chronic Toxicity on Body Weight and Recognition Memory of Wistar Rat. Pakistan Journal of Biological Sciences,2008, 11: 1830-1834.

Bakar C, Karaman HI, Baba A, Sengünalp F. Effect of high aluminum concentration in water resources on human health, case study: Biga Peninsula, northwest part of Turkey. Arch Environ Contam Toxicol. 2010;58(4):935-44.

Bhalla P, Dhawan DK. Protective role of lithium in ameliorating the aluminium-induced oxidative stress and histological changes in rat brain. Cell Mol Neurobiol. 2009, 29(4):513-21.

Bhalla P, Singla N, Dhawan DK. Potential of lithium to reduce aluminium-induced cytotoxic effects in rat brain. Biometals. 2010a;23(2):197-206

Bhalla P, Garg ML, Dhawan DK. Protective role of lithium during aluminium-induced neurotoxicity. Neurochem Int. 2010;56(2):256-62

Bondy SC. The neurotoxicity of environmental aluminum is still an issue. Neurotoxicology. 2010;31(5):575-81.

Buchta, M. et al. Longitudinal study examining the neurotoxicity of occupational exposure to aluminium-containing welding fumes. Int Arch Occup Environ Health 2003; 76:539-48.

Buchta,M, Kiesswetter, E, Schäper, M, Zschiesche, W., Schaller, K.H., Kuhlmann A and Letzel, A. Neurotoxicity of exposures to aluminium welding fumes in the truck trailer construction industry. Environ Tox Pharm, 2005; 19(3), 677-685.

Buranatrevedh, S (2010). Health risk assessment of workers exposed to metals from Aluminium Production Plant. J. Med. Assoc. Thai, 93 (7), 136-141.

Burrell SA, Exley C. There is (still) too much aluminium in infant formulas. BMC Pediatr. 2010,10:63.

Collingwood, J.F. , Chong, R.K.K., Kasama, T. , Cervera-Gontard, L. , Dunin-Borkowski, R.E. , Perry, G , Pósfai, M., Siedlak, S.L., Simpson, E.T. , Smith, M.A., Dobson, J. Three-dimensional tomographic imaging and characterization of iron compounds within Alzheimer's plaque core material. Journal of Alzheimer's Disease 2008, 14(2),235-245**.**

Couette M, Boisse MF, Maison P, Brugieres P, Cesaro P, Chevalier X, Gherardi RK, Bachoud-Levi AC, Authier FJ. Long-term persistence of vaccine-derived aluminum hydroxide is associated with chronic cognitive dysfunction. J Inorg Biochem. 2009;103(11):1571-8.

Donoghue AM, Frisch N, Ison M, Walpole G, Capil R, Curl C, Di Corleto R, Hanna B, Robson R, Viljoen D. Occupational asthma in the aluminum smelters of Australia and New Zealand: 1991-2006. Am J Ind Med. 2011;54(3):224-31

EFSA (2008). Safety of aluminium from dietary intake. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC). *The EFSA Journal*, **754**, 1-34.

Erazi H, Sansar W, Ahboucha S, Gamrani H. Aluminum affects glial system and behavior of rats. C R Biol. 2010;333(1):23-7.

Erazi H, Ahboucha S, Gamrani H. Chronic exposure to aluminum reduces tyrosine hydroxylase expression in the substantia nigra and locomotor performance in rats. Neurosci Lett. 2011; 487(1), 8-11.

Exley, C & Esiri, M. Severe cerebral congophilic angiopathy coincident with increased brain aluminium in a resident of Camelford, Cornwall, UK. Journal of Neurology Neurosurgery and Psychiatry 2006, 77, 877-879.

Exley C, Swarbrick L, Gherardi RK, Authier FJ. A role of the body burden of aluminum in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome. Med Hypotheses. 2009 72(2):135-139.

Ferreira PC, Tonani KA, Julião FC, Cupo P, Domingo JL, Segura-Muñoz SI. Aluminum concentrations in water of elderly people's houses and retirement homes and its relation with elderly health. Bull Environ Contam Toxicol. 2009;83(4):565-9

Ferreira PC, Piai Kde A, Takayanagui AM, Segura-Muñoz SI.Aluminum as a risk factor for Alzheimer's disease. Rev lat Am Enfermagem. 2008;16(1):151-7

Frisardi V, Solfrizzi V, Capurso C, Kehoe PG, Imbimbo BP, Santamato A, Dellegrazie F, Seripa D, Pilotto A, Capurso A, Panza F. Aluminum in the diet and Alzheimer's disease: from current epidemiology to possible disease-modifying treatment. J Alzheimers Dis. 2010;20(1):17-30.

Gao S, Jin Y, Unverzagt FW, Ma F, Hall KS, Murrell JR, Cheng Y, Shen J, Ying B, Ji R, Matesan J, Liang C, Hendrie HC.Trace element levels and cognitive function in rural elderly Chinese. J Gerontol A Biol Sci Med Sci. 2008;63(6):635-641.

García T, Ribes D, Colomina MT, Cabré M, Domingo JL, Gómez M. Evaluation of the protective role of melatonin on the behavioral effects of aluminum in a mouse model of Alzheimer's disease. Toxicology. 2009;265(1-2):49-55.

García T, Esparza JL, Giralt M, Romeu M, Domingo JL, Gómez M. Protective role of melatonin on oxidative stress status and RNA expression in cerebral cortex and cerebellum of AbetaPP transgenic mice after chronic exposure to aluminum. Biol Trace Elem Res. 2010;135(1-3):220-32.

Garcia T, Esparza JL, Nogués MR, Romeu M, Domingo JL, Gómez M. Oxidative stress status and RNA expression in hippocampus of an animal model of Alzheimer's disease after chronic exposure to aluminum. Hippocampus. 2010; 20(1):218-25.

Gherardi RK, Coquet M, Cherin P, Belec L, Moretto P, Dreyfus PA, Pellissier JF, Chariot P and Authier FJ. Macrophagic myofasciitis lesions assess long- term persistence of vaccine-derived aluminium hydroxide in muscle. Brain, (2001): 124 (9): 1821-31.

Gibbs GW, Armstrong B, Sevigny M. Mortality and cancer experience of Quebec aluminum reduction plant workers. Part 2: mortality of three cohorts hired on or before January 1, 1951. J Occup Environ Med. 2007; 49(10):11-5-23.

Gibbs, GW and Sevigny, M. Mortality and Cancer Experience of Quebec Aluminum Reduction Plant Workers. Part 3: Monitoring the Mortality of Workers First Employed After January 1, 1950 Journal of Occupational & Environmental Medicine. 2007, 49(11):1269-1287.

Gillette-Guyonnet S, Andrieu S, Vellas B. The potential influence of silica present in drinking water on Alzheimer's disease and associated disorders. J Nutr Health Aging. 2007;11(2):119-124.

Gómez M, Esparza JL, Cabré M, García T, Domingo JL. Aluminum exposure through the diet: metal levels in AbetaPP transgenic mice, a model for Alzheimer's disease. Toxicology. 2008;249(2-3):214-9.

Gonçalves PP, Silva VS. Does neurotransmission impairment accompany aluminium neurotoxicity? J Inorg Biochem. 2007; 101(9):1291-338.

Graves, A.B., Rosner, D., Echeverria, D., Mortimer, J.A., Larson, E.B. (1998). Occupational exposures to solvents and aluminium and estimated risk of Alzheimer's disease. Occup Environ Med 1998; 55:627-633

Gun RT, Korten AE, Jorm AF, Henderson AS, Broe GA, Creasey H, McCusker E, Mylvaganam A. Occupational risk factors for Alzheimer disease: a case-control study. Alzheimer Dis Assoc Disord. 1997; 11(1):21-7.

Holtzman, D.M. Role of apoe/Abeta interactions in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy. J. Mol. Neurosci. 2001, 17, 147–155.

Itoh M, Suzuki Y, Sugai K, Ozuka N, Ohsawa M, Otsuki T, Goto Y. Progressive leukoencephalopathy associated with aluminum deposits in myelin sheath. J Child Neurol. 2008; 23(8):938-43.

Jacqmin-Gadda H, Commenges D, Letenneur L, Barberger-Gateau, P and Dartigues, J-F. Components of Drinking Water and Risk of Cognitive Impairment in the Elderly. Am. J. Epidemiol. 1994; 139(1): 48-57.

Jyoti, A, Sethi, P and Sharma, D. Bacopa monniera prevents from aluminium neurotoxicity in the cerebral cortex of rat brain. J Ethnopharmacol 2007; 111: 56–62.

Kalil RK, Monteiro A Jr, Lima MI, Silveira EB, Foltran FS, Martins CE, Rizzo IM. Macrophagic myofasciitis in childhood: the role of scanning electron microscopy/energy-dispersive spectroscopy for diagnosis. Ultrastruct Pathol. 2007; 31(1):45-50.

Katayama T., Imaizumi K., Sato N., Miyoshi K., Kudo T., Hitomi J.,Morihara T., Yoneda T., Gomi F., Mori Y. (1999) Presenilin-1 mutations downregulate the signalling pathway of the unfolded-protein response. Nat. Cell Biol. 1:479–485.

Kaufman, R. J. (1999). Stress signaling from the lumen of the endoplasmic reticulum: coordination of gene transcriptional and translational controls. Genes Dev. 13, 1211-1233

Khanna P, Nehru B. Antioxidant enzymatic system in neuronal and glial cells enriched fractions of rat brain after aluminum exposure. Cell Mol Neurobiol. 2007; 27(7):959-69.

Kiesswetter, E et al. Longitudinal study on potential neurotoxic effects of aluminium: I. Assessment of exposure and neurobehavioural performance of Al welders in the train and truck construction industry over 4 years. Int Arch Occup Environ Health 2007, 81:41-67.

Kiesswetter, E et al. Longitudinal study on potential neurotoxic effects of aluminium: II. Assessment of exposure and neurobehavioral performance of Al welders in the automobile industry over 4 years. Int Arch Occup Environ Health 2009, 82:1191-210.

Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J, Kacew S, Lindsay J, Mahfouz AM, Rondeau V. Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. J Toxicol Environ Health B Crit Rev. 2007; 10 Suppl 1:1-269.

Kumar A, Dogra S, Prakash A. Protective effect of curcumin (Curcuma longa), against aluminium toxicity: Possible behavioral and biochemical alterations in rats. Behav Brain Res. 2009; 205(2):384-90.

Kumar V, Gill KD. Aluminium neurotoxicity: neurobehavioural and oxidative aspects. Arch Toxicol. 2009; 83(11):965-78.

Kumar V, Bal A, Gill KD. Aluminium-induced oxidative DNA damage recognition and cell-cycle disruption in different regions of rat brain. Toxicology. 2009; 264(3):137-44.

Lach B, Cupler EJ. Macrophagic myofasciitis in children is a localized reaction to vaccination. J Child Neurol. 2008; 23(6):614-9.

Li X, Hu C, Zhu Y, Sun H, Li Y, Zhang Z. Effects of Aluminum Exposure on Bone Mineral Density, Mineral, and Trace Elements in Rats. Biol Trace Elem Res. 2010 epub, ahead of print

Luo Y, Nie J, Gong QH, Lu YF, Wu Q, Shi JS. Protective effects of icariin against learning and memory deficits induced by aluminium in rats. Clin Exp Pharmacol Physiol. 2007; 34(8):792-5.

Meyer-Baron M, Schäper M, Knapp G, van Thriel C.Occupational aluminum exposure: evidence in support of its neurobehavioral impact. Neurotoxicology. 2007; 28(6):1068-78.

Milacic R, Murko S, Scancar J.Problems and progresses in speciation of Al in human serum: an overview. J Inorg Biochem. 2009; 103(11):1504-13.

Molloy DW, Standish TI, Nieboer E, Turnbull JD, Smith SD, Dubois S. Effects of acute exposure to aluminum on cognition in humans. J Toxicol Environ Health A. 2007; 70(23):2011-9.

Müller HD, Landeghem FK, Schmidt PF, Sommer C, Goebel HH. Macrophagic myofasciitis plus (distinct types of muscular dystrophy). Neuropediatrics 2009; 40(4):174-8.

Nehru B, Bhalla P, Garg A. Further evidence of centrophenoxine mediated protection in aluminium exposed rats by biochemical and light microscopy analysis. Food Chem Toxicol. 2007;45(12):2499-505.

Newairy AS, Salama AF, Hussien HM, Yousef MI. Propolis alleviates aluminium-induced lipid peroxidation and biochemical parameters in male rats. Food Chem Toxicol. 2009; 47(6):1093-8.

Pan R, Qiu S, Lu DX, Dong J. Curcumin improves learning and memory ability and its neuroprotective mechanism in mice. Chin Med J (Engl). 2008; 121(9):832-9.

Paranthaman K, Harrison H. Drinking water incidents due to chemical contamination in England and Wales, 2006-2008. J Water Health. 2010 8(4):735-40

Poirier, J., Semple, H., Davies, J., Lapointe,R., Dziwenka,M., Hiltz, M., Mujibi, D. Double-blind, vehicle-controlled randomized twelve-month neurodevelopmental toxicity study of common aluminum salts in the rat. Neuroscience, 2011, 193, 338-362

Ribes D, Colomina MT, Vicens P, Domingo JL. Effects of oral aluminum exposure on behavior and neurogenesis in a transgenic mouse model of Alzheimer's disease. Exp Neurol. 2008; 214(2):293-300.

Ribes D, Colomina MT, Vicens P, Domingo JL. Impaired spatial learning and unaltered neurogenesis in a transgenic model of Alzheimer's disease after oral aluminum exposure. Curr Alzheimer Res. 2010; 7(5):401-8.

Ribes D, Torrente M, Vicens P, Colomina MT, Gómez M, Domingo JL. Recognition Memory and β-amyloid Plaques in Adult Tg2576 Mice are not Modified After Oral Exposure to Aluminum. Alzheimer Dis Assoc Disord. 2011 [Epub ahead of print]

Rodella LF, Ricci F, Borsani E, Stacchiotti A, Foglio E, Favero G, Rezzani R, Mariani C, Bianchi R. Aluminium exposure induces Alzheimer's disease-like histopathological alterations in mouse brain. Histol Histopathol. 2008; 23(4):433-9.

Rondeau, V, Jacqmin-Gadda H, Commenges D, Helmer C, Dartigues J-F. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol. 2009; 169(4):489-496.

Rondeau, V, Commenges, D, Jacqmin-Gadda H and Dartigues, J-P. Relation between Aluminum Concentrations in Drinking Water and Alzheimer's Disease: An 8-year Follow-up Study. Am. J. Epidemiol. 2000; 152 (1): 59-66.

Roses, A.D. (1996). Apolipoprotein E alleles as risk factors in Alzheimer's disease. Annu. Rev. Med. 47, 387–400.

Rui D, Yongjian Y. Aluminum chloride induced oxidative damage on cells derived from hippocampus and cortex of ICR mice. Brain Res. 2010; 1324:96-102.

Salib E and Hillier, V (1996) A case-control study of Alzheimer's disease and aluminium occupation. The British Journal of Psychiatry 168: 244-249.

Santibáñez M, Bolumar F, García AM. Occupational risk factors in Alzheimer's disease, a review assessing the quality of published epidemiological studies. Occup Environ Med. 2007; 64(11):723-32.

Sethi P, Jyoti A, Singh R, Hussain E, Sharma D. Aluminium-induced electrophysiological, biochemical and cognitive modifications in the hippocampus of aging rats. Neurotoxicology. 2008; 29(6):1069-79.

Sharma D, Sethi P, Hussain E, Singh R. Curcumin counteracts the aluminium-induced ageing-related alterations in oxidative stress, Na(+), K (+) ATPase and protein kinase C in adult and old rat brain regions. Biogerontology. 2008 Nov 20.

Sofuoglu SC, Kavcar P. An exposure and risk assessment for fluoride and trace metals in black tea. J Hazard Mater. 2008; 158(2-3):392-400.

Strozyk D, Launer LJ, Adlard PA, Cherny RA, Tsatsanis A, Volitakis I, Blennow K, Petrovitch H, White LR, Bush AI. Zinc and copper modulate Alzheimer Abeta levels in human cerebrospinal fluid. Neurobiol Aging. 2009; 30(7):1069-77

Tripathi S, Somashekar BS, Mahdi AA, Gupta A, Mahdi F, Hasan M, Roy R, Khetrapal CL. Aluminum-mediated metabolic changes in rat serum and urine: a proton nuclear magnetic resonance study. J Biochem Mol Toxicol. 2008; 22(2):119-27.

Türkez H, Yousef MI, Geyikoglu F. Propolis prevents aluminium-induced genetic and hepatic damages in rat liver. Food Chem Toxicol. 2010; 48(10):2741-6.

Verstraeten SV, Aimo L, Oteiza PI. Aluminium and lead: molecular mechanisms of brain toxicity. Arch Toxicol. 2008; 82(11):789-802.

Walton JR.. Evidence for participation of aluminum in neurofibrillary tangle formation and growth in Alzheimer's disease. J Alzheimers Dis. 2010; 22(1):65-72

Walton JR. An aluminum-based rat model for Alzheimer's disease exhibits oxidative damage inhibition of PP2A activity, hyperphosphorylated tau, and granulovacuolar degeneration. J Inorg Biochem. 2007; 101(9):1275-84.

Walton JR. A longitudinal study of rats chronically exposed to aluminum at human dietary levels. Neurosci Lett. 2007; 412(1):29-33.

Walton JR, Wang MX. APP expression, distribution and accumulation are altered by aluminum in a rodent model for Alzheimer's disease. J Inorg Biochem. 2009; 103(11):1548-54.

Walton JR.. Brain lesions comprised of aluminum-rich cells that lack microtubules may be associated with the cognitive deficit of Alzheimer's disease. Neurotoxicology. 2009; 30(6):1059-69

Walton JR. Functional impairment in aged rats chronically exposed to human range dietary aluminum equivalents. Neurotoxicology. 2009; 30(2):182-93.

World Health Organisation. Evaluation of certain food additives and contaminants. Joint FAO/WHO Expert Committee on Food Additives. Tech Rep Ser. 2007; (940):1-92, 1 p94.

Yumoto S, Kakimi S, Ohsaki A, Ishikawa A. Demonstration of aluminum in amyloid fibers in the cores of senile plaques in the brains of patients with Alzheimer's disease.J Inorg Biochem. 2009;103(11):1579-84.

Yousef MI, Salama AF. Propolis protection from reproductive toxicity caused by aluminium chloride in male rats. Food Chem Toxicol. 2009;47(6):1168-75

Zatta P, Drago D, Bolognin S, Sensi SL. Alzheimer's disease, metal ions and metal homeostatic therapy. Trends Pharmacol Sci. 2009;30(7):346-55.

Zhang L, Li X, Gu Q, Zhu Y, Zhao H, Li Y, Zhang Z. Effects of Subchronic Aluminum Exposure on Serum Concentrations of Iron and Iron-Associated Proteins in Rats. Biol Trace Elem Res. 2011;141(1-3):246-53.

Zlokovic, B.V., Deane, R., Sallstrom, J., Chow, N., and Miano, J.M. (2005). Neurovascular pathways and Alzheimer amyloid beta-peptide. Brain Pathol. 15, 78–83.

Appendix 27: Review of the scientific literature on aluminium (October 2011 to May 2012) prepared for the Lowermoor subgroup by the Department of Health Toxicology Unit, Imperial College, London

Note: This was a paper prepared for discussion by the Lowermoor subgroup. It does not necessarily represent the views of the subgroup

1. Aluminium toxicity was reviewed in detail in an update of the 1997 WHO (IPCS) Environmental Health Criteria 194 report on aluminium, prepared for the COT Lowermoor Subgroup in spring 2002 and updated in 2003. The last update of literature data on the toxicity and epidemiology of aluminium covered the period up to September 2011 (LSG/11/1). This annex covers the period up to May 2012. Pub Med and Toxline were searched using the terms toxic*, brain, neuro, renal, liver, bioavailability, epidem*, Alzheimer. As before, studies using oral or dermal exposure were identified and obtained. Those which were considered to provide data relevant to the derivation of a No or Low Observed Adverse Effect Level, or to provide useful mechanistic data or other relevant information, were identified and are reviewed below. Members are asked to consider the papers and to advise on whether any of the new data should be discussed in the text of the report.

Aluminium Reviews

2. Tomljenovic (2011) provides a review of Alzheimer's disease (AD), aluminium (Al) bioavailability and mechanisms of Al toxicity. The authors discuss the issue of brain compartmentalisation and the experimental data that supports the selectivity of Al for certain brain compartments. The paper contains a very useful table of experimental endpoints related to Al neurotoxicity research.

Evaluations of Aluminium intake

3. Arnich et al (2012) present the results of the dietary exposure assessment of the general French population to trace elements from the 2nd Total Diet Study (TDS) undertaken in France between 2007 and 2009. They also assess the risk with regards to the international health-based guidance values. The TDS consisted of three major steps: (I) food sampling and preparation of samples as consumed, (ii) analysis of the samples, and (iii) dietary exposure assessment by combining the occurrence data with the national consumption data. Results for Al only are presented in this report. Analysis of all food samples found that the Al levels were lower than the Limit of Quantification (LOQ; 0.472 mg/kg fresh weight) and Limit of Detection (LOD; 0.236 mg/kg fresh weight) in 35% of the samples. The highest mean levels were found in crustaceans and molluscs (21.1 mg/kg) and in chocolate (15.6 mg/kg). Concentration of Al was lower than 6 mg/kg in all other foods. The French population's mean exposure to aluminium was estimated at 40.3 µg/kg bw/day in adults and 62.2 µg/kg bw/day in children. At the 95th percentile, exposure is estimated at 69.7 µg/kg bw/day in adults and 118.8 µg/kg bw/day in children. These exposure levels are respectively +50% and +40% higher than those recorded in the 1st French TDS. The main contributors to aluminium adult exposure were hot beverages other than coffee (13%) and vegetables excluding potatoes (11%). In children, the main contributors were vegetables excluding potatoes (8%), pasta (7%), pastries and cakes (6%) and dairy-based desserts (6%). They found that the health-based guidance value of 1 mg/kg bw/week (EFSA, 2008, 2011) was exceeded by only 0.2% of adults and 1.6% of children.

Animal Studies

Animal neurotoxicity studies – *Rats*

4. Wang et al. (2010) and Cui et al. (2012) examined the effects of exposure to 0, 0.2, 0.4, 0.6 % aluminium chloride ($AlCl_3$) (approximately 228, 456, 684 mg/kg bw/day) in drinking water for 3 months on the learning and memory function of Wistar rats (sex not specified). In the first study, Wang et al. (2010) conducted behavioural tests on the rats. They also performed electrophysiological recordings of the long-term potentiation (LTP) induction in CA1 region of Schaffer collateral (SC) of hippocampus and sought to determine whether the activities of protein kinase C (PKC), RAS/RAF/mitogen-activated protein kinase/extracellular signal-regulated kinase (Ras/Raf/MAPK/ERK) signaling cascade and Ca2+–calmodulin kinase II (CaMKII) were influenced by Al accumulation. In the behavioural test, chronic administration of Al for three months dramatically increased the numbers of mistakes and reduced the length of latency in a dose-dependent fashion in a step down test to assess memory. They also observed that treatment with Al attenuated the population spike (PS) amplitude of LTP from the hippocampal CA1 region, with the PS potentiation decreasing with increasing dosages of Al. They found that the activity of membrane PKC was significantly lower in all Al-administered rats than that in control rats ($p < 0.01$). However, no significant difference was observed in cytosolic PKC activity. In contrast, the cytosolic MAPK activity was dramatically decreased in Al-treated rats in comparison to the control group ($p < 0.05$). Treatment of rats with $AlCl_3$ also resulted in dramatically reduced levels of both phosphosylated ERK1/2 and CaMKII without changing the non-phosphorylated in hippocampus of treated rats.

5. In their follow on study, Cui et al. (2012) examined the effects of Al treatment on memory and learning by observing the changes of Ras/Raf/ERK (Ras/ERK) signaling pathway. They observed an increased in Al in the blood and brains of rats treated with Al compared to controls. Following treatment with Al, Raf1, ERK2 and CREB expressions decreased compared to the control in a dose-dependent manner ($p < 0.05$) at the protein level. For Ras, they found an increase in expression at the protein level compared to controls but the expression decreased along the Al exposure groups. Similar trends of expression were observed at the mRNA level. Overall, the studies indicate that Al exposure can affect the normal functioning of multiple signalling pathways, which in turn may lead to learning and memory impairment.

6. Khanna-Sood et al. (2011) investigated the possible effects of chronic aluminium exposure on mitochondrial energy metabolism in different regions of rat brain following Al treatment of female SD rats with 100mg/kg/d of $AlCl_3$ in drinking water for 8 weeks. The possible protective role played by curcumin was also evaluated but only results pertaining to Al will be presented here. Al treatment caused a marked decline in the activity of NADH dehydrogenase (complex I) in cerebral cortex (67%) followed by mid brain (54%) and cerebellum (71%). Succinate dehydrogenase (complex II) also exhibited significant decrease in activity ($P \leq 0.001$) in all the three regions in Al-treated rat brains as compared to controls. Cytochrome oxidase (terminal enzyme of the ETC) presented with 58% decrease in the activity in cerebral cortex of Al-treated animals as compared to controls. They also report that the mitochondria isolated from mid brain and cerebellum of rat brain showed 63 and 74% decrease in the activity of complex IV following 8 weeks of Al exposure, with the decrease found to be highly significant ($P \leq 0.001$) in all the three regions of brain. Assessing mitochondrial function, there was a significant decrease in MTT reduction rate in all the three regions of brain [cerebral cortex ($P \leq 0.01$), mid brain ($P \leq 0.05$), and cerebellum ($P \leq 0.01$)] in Al-treated rat brains as compared to controls. They also

examined oxidative phosphorylation in terms of ATP synthesis, ATP hydrolysis, and ATP levels and found a significant decrease ($P < 0.01$) in ATP synthesis in all the three regions of the brain following Al treatment, ATP deficits (74%) and a significantly increased ATP hydrolysis rate ($P < 0.001$) in the mid brain region of Al-treated rats compared to controls. The study also found a significant decrease in reduced glutathione in cerebral cortex and mid brain only but not in cerebellum region. The stress protein HSP70 was only faintly detectable in the mid brain of Al-treated rats. Histologically, they found that the cerebral region of Al-treated group depicted evidences of hypoxia in the cortical neurons and corpus callosum with significant evidence of perineuronal oedema.

7. In a follow on study, Khanna Sood et al. (2012) examined the inflammatory responses of the glial cells and the effect on stress proteins such as HSP70, using the same conditions as discussed above in Khanna Sood et al. (2011). Again, the role played by curcumin was also evaluated but only results pertaining to Al will be presented here. They report an increased gene expression ($P \leq 0.01$) and protein expression ($P \leq 0.01$) of HSP70 in the glial fractions of the aluminium-exposed animals as compared to the neuronal fraction of the aluminium-exposed rat brains. As a marker of an inflammatory response, treatment with Al caused a significant increase ($P \leq 0.001$) in tumour necrosis factor-α (TNF-α) protein levels as well as a significant increase in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) expression. Following Al treatment, nitrite levels were found to be significantly increased in all the three regions of brain cerebral cortex ($P <= 0.001$), mid brain ($P \leq 0.001$) and cerebellum ($P \leq 0.01$). Histopathological H&E staining of sections of cerebral cortex found significant increase in the focal inflammatory response after Al treatment as compared to normal control where no evidence of inflammation was observed.

8. (Abstract available only). Thirunavukkarasu et al. (2012) investigated the potential protective effect of Manaamitra vatakam, a herbal medicine, against aluminium induced toxicity in rats. Wistar albino rats were given $AlCl_3$ (100 mg/kg bw/d) orally for 90 days. Only the results for Al will be presented here. They found that Al treatment induced neurotoxicity and oxidative stress in the rats by affecting active avoidance and memory impairment, as well as altering antioxidants, such as HSP70, superoxide dismutase, catalase, reduced glutathione, glutathione peroxidase, and acetylcholinesterase in the cortex and hippocampus of rat brain.

Animal neurotoxicity studies – *Mice*

9. Abu-Taweel et al. (2012) assessed the effect of perinatal exposure of female Swiss-Webster dams to $AlCl_3$ in their offspring. They assessed the possible long term physiological mechanism associated with Al toxicity in the offspring by performing neurobehavioral testing, cognitive testing and determining biochemical levels of brain neurotransmitters such as dopamine (DA) and serotonin (5-HT) in the offspring. It should be noted that maternal effects were not discussed in this paper and will form the discussion of another as of yet unpublished paper. Pregnant dams were exposed orally to 0, 300 or 600 mg/kg/day $AlCl_3$ in drinking water from pregnancy day 1 to postnatal day (PD) 15. They observed a dose-dependent reduction in postnatal body weight gain in Al treated offspring and found developments such as the opening of the eyes and appearance of body hair fuzz were also significantly ($p < 0.001$) delayed in

the Al exposed offspring in a dose-dependent manner. In the behavioural tests, the sensory motor reflexes (righting, rotating, and cliff avoidance reflexes) in the Al-exposed offspring were found to be significantly and dose-dependently suppressed throughout the weaning period (from the day of birth to postnatal day 21). During adolescent ages of the male offspring, a significant and dose-dependent deficit was also observed in their locomotor activity at postnatal day 22 (PD 22), In the shuttle-box active avoidance test, which assesses learning capabilities, the Al-exposed offspring (PD 25), showed a statistically significant and dose-dependent decrease in the number of avoidances during the trial period as compared to the control group. In the Morris water-maze task to test cognitive behaviour (at PD 30–36), the offspring of mice treated with Al exhibited longer escape latencies to reach the platform as compared with the control group ($p < 0.01$). However, it was noted that all groups displayed a gradual improvement in performance over the 4 days of testing (training) period. They also found a significant ($p < 0.001$) and dose-dependent inhibition of DA levels in the forebrain region of mice offspring treated with Al as compared to the control group at ages PD 7, PD 14, PD 21, PD 30 and PD 36. On the contrary, the levels of 5-HT were significantly ($p < 0.001$) depleted in the offspring at all developing ages, exposed only to higher dose of Al, whereas, the lower dose had no effect at any developing ages.

10. Kakkar and Kaur (2011) investigated the protective effect of curcumin loaded solid lipid nanoparticles (C-SLNs) in comparison to free curcumin in alleviating $AlCl_3$ induced oxidative stress and biochemical alterations in mice brain. Whole brain histopathology and blood lipid profile were also examined. For the purposes of our paper, we will only present data relevant to Al. Young male Lacca mice were orally given $AlCl_3$ (100 mg/kg) for 18 weeks. In the Morris Water Maze test for spatial memory, $AlCl_3$ treated mice showed an initial increase in escape latency, which continued during the training for spatial navigation task. At 12 weeks there was a significant difference in the mean escape latency of the Al treated group when compared to the control group ($P \leq 0.05$). In their assessment of oxidative parameters, they found that $AlCl_3$ treatment resulted in increased AChE activity, a significant ($p \leq 0.05$) increase in TBARS levels as well significantly lowered activities of glutathione, superoxide dismutase, and catalase in the brain homogenates of mice treated with $AlCl_3$. In the blood, they found decreased triglycerides (TG) and VLDL following Al treatment. Histologically, they observed oedema accompanied by disrupted and degenerated neurons in the area, vacuolization around the neuron/perineuronal space/spongiosis, disruption of the nucleus and congestion in the blood vessels in the brains of $AlCl_3$ treated mice.

11. (The information provided in this paragraph was previously presented in LSG/11/1). There have been several publications in the past three years using genetically engineered AD mouse models. One particular model is the Tg2576 AD mouse model, which carries a transgene coding for the 695- amino acid isoform of the human Alzheimer B-amyloid precursor protein (ABPP), derived from a Swedish family with early-onset Alzheimer's disease. The Tg2576 mouse expresses high levels of the mutant ABPP in the cell body of neurons, they exhibit neuronal loss, synaptic alterations, inflammation and gliosis and dendritic alterations, and have a phenotype characterised by memory deficits after 9-10 months of life.

12. The following study was briefly mentioned in LSG/11/1 (abstract only available at the time). The paper has now been published in full. Ribes et al. (2012) investigated

the behavioural effects of a low dose of Al lactate given orally (1 mg/g, equivalent to 17 mg/kg/d) for 3 months to either wild type or transgenic mice (Tg2576). They investigated the influence of Al on the general state and memory of the animals using a functional observational battery (FOB) and a novel object recognition (NOR) task. Oral exposure to Al lactate induced some general signs of toxicity, piloerection and diminished home-cage activity in both, wild-type and Tg2576 mice. An increased sensorimotor reactivity was also observed in Al-exposed transgenic mice. Decreased climbing activity was seen in all Al exposed animals. In the NOR task, results showed that wild-type groups spent more time exploring the novel object than animals in the transgenic groups, indicating an impairment in event memory in TG mice. In general, Tg2576 animals were more sensitive to Al-induced sensorimotor effects. It was also reported that [beta]-amyloid plaque deposition was found only in Tg2576 (Al-treated and non-treated) mice, with no significant differences in the number of [beta]-amyloid plaques between treated and non-treated Tg2576 mice. It should be noted that in a previous study by Ribes et al. in 2008, Al-treated Tg2576 mice showed a decrease of [beta]-amyloid levels (1 to 40 and 1 to 42). No effects were seen on corticosterone levels or Al concentrations in the frontal cortex and cerebellum in either treated or untreated mice, or in WT or transgenic mice.

Animal studies - Other biological and toxic effects

Hepatotoxicity

13. Bhasin et al. (2012) examined the role of zinc (Zn) in ameliorating the adverse effects of Al toxicity on liver enzyme markers, antioxidant defence system and histoarchitecture. Female Sprague-Dawley rats were either given a daily dose of $AlCl_3$ at a dose of 100 mg/kg bw through oral gavage, a dose of 227 mg/L zinc sulphate solution (equivalent of 1-2 mg Zn/kg bw) in drinking water or a combined treatment of Al and Zn for a total of two months. A significant decrease was observed in liver asparate AST ≤(p 0.05), liver alanine ALT ≤(p 0.01), hepatic lipid peroxidation levels (p≤ 0.05), catalase (CAT, p≤ 0.01) and glutathuione -s-transferase (GST, p≤ 0.01) following two months of treatm ent with $AlCl_3$ compared to levels observed in control rats. In combined zinc and Al treated group, the levels of these parameters were increased back to within normal range. Liver ALP (p≤ 0.05), reduced glutathione (GSH, p≤ 0.001), glutathione reductase (GR, p ≤ 0.05) and superoxide dismutase (SOD, p≤ 0.001) were significantly increased following Al treatment. The authors observed that combined treatment of the rats to both Zn and Al brought the raised levels of reduced GSH, SOD and liver ALP to within normal limits, but had no effect on GR activity. They also observed changes in the liver histoarchitecture after two months of treatment with Al, such as disruption of the hepatic cords, increased vacuolization of the hepatocytes. Co treatment with Zn caused an improvement in the structure of the hepatocytes, but there were still some binucleated cells present.

Immune system

14. Zhu et al. (2012) examined the potential effect of aluminium chloride on the immune function of male rats. Male Wistar rats were given 0, 64.18, 128.36, 256.76 mg/kg bw/d $AlCl_3$ in drinking water for 120 days. Serum levels of T lymphocyte subpopulations ($CD3^+$, $CD4^+$, $CD8^{+)}$, acid non-specific activity esterase ($ANAE^+$) as a measure of active lymphocytes, and cytokines (interleukin-2 (IL-2) and tumour

necrosis factor-α (TNF-α)) were determined following treatment. The levels of ANAE+ decreased in a dose dependent manner in $AlCl_3$ -treated rats. The levels of ANAE+ in the low dose ($P < 0.05$), mid and high dose ($P < 0.01$) were significantly lower compared to controls. The proportions of CD3+ and CD4+ T lymphocytes and the ratio of CD4+/CD8+ decreased significantly ($P < 0.05$), while the proportion of CD8+ T lymphocytes increased in an $AlCl_3$ - dose dependent manner in treated rats ($P < 0.01$). Serum levels of IL-2 and TNF-α decreased in $AlCl_3$-treated rats. They found the levels of IL-2 in low dose rats were significantly lower than the control group ($P < 0.05$) and the levels of IL-2 and TNF-α were significantly lower in the mid and high dose compared to controls ($P < 0.01$).

Developmental/reproductive effects

15. Wang et al. (2012) investigated the effects of aluminium chloride on the reproductive function of female rats. Female Wistar rats were given 0, 64.18, 128.36, 256.72 mg/kg bw/d $AlCl_3$ in drinking water for 120 days. They examined the effect of Al on oestrogen (E2), progestogen (P), testosterone (T), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels as well as aluminium concentrations in the serum and ovaries. Ovary weights were significantly lower in the mid and high dose group compared to controls ($P < 0.01$). The levels of E2, P, LH and FSH were lower in all Al treated rats when compared to control group levels, with statistically significant differences observed for the mid and high dose compared to controls ($P < 0.01$). The level of T was significantly higher in the low and mid dose groups ($P < 0.05$) but there was no significant change in T levels between the high dose and control group. The Al concentration in the sera and ovaries was significantly higher in all the treated groups compared to the control group ($P < 0.01$).

16. Moselhy et al. (2012) evaluated the effects of aluminium chloride on the reproductive system in male rats. Albino Male rats were given 34 mg/kg bw/d $AlCl_3$ orally for up to 60 days. The effect of ginger on the Al induced reproductive toxicity was also examined but results will not be discussed here. Serum testosterone levels were significantly decreased following $AlCl_3$ treatment compared to controls at 30, 45 and 60 days. For example, at day 60, serum testosterone levels were 5.20 ± 0.73 ng/ml in control rats and 1.71 ± 0.24 ng/ml in Al-treated rats. They also observed that Al treatment caused a significant increase in testicular malondialdehyde (MDA) levels as compared to controls at day 60 (62.78 ± 12.50 nmol/g in testicular homogenates of control rats compared to 102.81 ± 10.81 nmol/g in testicular homogenates from treated rats). Treatment with Al also had an effect on epididymal spermatozoa, causing a significant decrease in both sperm motility and live/dead ratio and significant increases in total sperm abnormalities. A cytotoxic effect was also observed following Al treatment, with a significant elevation in DNA fragmentation observed compared with control levels. Histopathological examinations revealed a number of degenerative changes in the rat testes following $AlCl_3$ treatment. Effects were observed in the spermatogenic cells, epididymis and prostate following treatment.

17. Previously we reviewed a two-generation reproductive study by Hirata-Koizumi et al. (2011a) where rats were exposed to aluminium sulfate. In a subsequent two generation reproductive study Hirata-Koizumi et al. (2011b), 5 week old F0 Crl:CD(SD) rats were exposed to aluminium ammonium sulfate (AAS) in drinking water at 0, 50, 500 and 5000 ppm (Calculated average intake of AAS during the

whole period was 3.78, 33.5 and 305 mg/kg bw in F0 males, 6.52, 58.6 and 500 mg/kg bw in F0 females, 4.59, 41.8 and 372 mg/kg bw in F1 males, and 6.65, 61.9 and 517 mg/kg bw in F1 females for the 50, 500 and 5000 ppm groups, respectively). After 10 weeks of AAS administration, each female rat was mated with a male rat of the same dosage group and pregnant females were allowed to deliver spontaneously and nurse their pups. AAS dosing was continued throughout the mating, gestation and lactation period. F0 parental male rats were necropsied after the parturition of paired females, and F0 females were necropsied after weaning of their pups. For the second (F1) generation study, male and female weanlings in each group were selected as parents on PNDs 21-25. F1-selected rats were given drinking water with the respective formulation of AS and were mated, allowed to deliver and nurse their F2 pups and necropsied in the same manner as F0 rats.

18. Water consumption was decreased compared with controls in males and females of all treatment groups in a concentration-dependent manner and the body weight of parental animals transiently decreased in the 5000 ppm group. There were no significant differences in birth weight of F1 and F2 pups between the control and AAS-treated groups. However, the body weight of F1 males on PND 21 and of F1 females on PNDs 14 and 21 was significantly lower in the 5000 ppm group than in the control. A similar decreasing trend was found in the body weight of male and female F2 pups around the time of weaning in the highest dose group, although no statistical significance was found.

19. In their analysis of reproductive effects, they found no significant differences in the estrous cycle between control and AAS treated groups and no significant changes in the copulation, fertility or gestation index between controls and AAS-treated groups in F0 and F1 generations. They also observed no significant differences in precoital interval, gestation length in either generation, number of implantations, number of pups delivered or delivery index. Also, they also did not observe any significant differences between control and AAS-treated groups for sperm parameters (number of testis sperm and cauda epididymal sperm, the percentage of motile sperm and progressively motile sperm, the swimming speed and pattern, and the percentage of morphologically abnormal sperm). In F1 female animals, vaginal opening was significantly delayed at 5000 ppm (32.3 ± 1.8 days of age, compared with 30.2 ± 2.1 days of age in controls, $P \leq 0.01$), although body weights were not significantly different at the time of vaginal opening.

20. For all F0 and F1 adults, they found no treatment related macroscopic observations at sacrifice. In F0 females, relative kidney weights were increased significantly at 500 and 5000ppm, with a significant decrease in the absolute weight of the pituitary gland. There was a significant decrease in the absolute weight of the pituitary gland and thymus in the 5000ppm treated F1 female group and in the absolute brain weight in the 500ppm treated F1 females. For males, they found a significant increase in relative kidney weight in the 5000ppm treated F1 males and a significant decrease in the relative weight of the seminal vesicle in 50ppm treated F1 males. They found no treatment-related alterations in the histopathology of male or female reproductive organs. In F1 and F2 weanlings, males and females had significantly lower body weights, and the absolute and relative weights of the spleen in both sexes and of the thymus in males were significantly decreased in this 5000 ppm group. A decrease in the absolute thymus weight was also observed in F1 females given 500 and 5000 ppm and in F2 females given 5000 ppm, but there were

no significant changes in relative weight in F1 or F2 females. For both F1 and F2 weanlings, they found that the weight of the liver and spleen decreased at 5000 ppm, but no histopathological changes were found in these organs. In the behavioural tests in the F1 generation, no differences were observed between AAS-treated animals and controls in conducting a spontaneous locomotor activity or their performance in a water-filled multiple T-maze. They report a NOAEL of 500 ppm for AAS in this two-generation reproductive/developmental toxicity, based on the retardation of sexual development in the F1 females, attributed to inhibition of growth, and decreased body weight gain and liver, spleen and thymus weights in the F1 and F2 offspring (Hirata-Koizumi et al., 2011b).

21. Ali et al. (2008) investigated the effect of Aluminium Chloride ($AlCl_3$) supplementation during lactation on the memory on the offspring of Wistar rats. Female Wistar rats were given 0, 200, 400, 600 or 800 mg/kg/d $AlCl_3$ in their drinking water for two weeks of lactation. Memory was tested using a shuttle box apparatus assessing passive avoidance response. They found that maternal $AlCl_3$ consumption (200, 400, 600 mg/kg/d) for two weeks at the lactation stage, did not significant effect short term (2 days) or long term (30 days) memory in their offspring. However, maternal consumption of 800 mg/kg/d $AlCl_3$ significantly impaired short term memory ($p<0.001$) and long term memory ($p<0.05$) in their offspring compared to controls.

Conclusions

22. In conclusion, the French TDS study indicated that EFSA TWI of 1 mg Al/kg bw/week was exceeded by only 0.2% of adults and 1.6% of children.

23. There have been a number of studies published which evaluate the effects of oral aluminium dosing in animal models. The studies have mainly focussed on neurological effects but reproductive, immunological and hepatological end points have also been examined. It is not possible to draw many particular conclusions from the studies presented as it is difficult to compare the studies from different laboratories. Differences in study design and protocols adopted by the different groups or even the same groups for that matter make comparison difficult.

Reference list to Appendix 27

Abu-Taweel GM, Ajarem JS, Ahmad M. Neurobehavioral toxic effects of perinatal oral exposure to aluminium on the developmental motor reflexes, learning, memory and brain neurotransmitters of mice offspring. Pharmacol Biochem Behav. 2012;101(1):49-56.

Ali MA, Vostacolaee E, Rahim C (2008). Effect of oral aluminum chloride administration during lactation on short and long-term memory of their offspring. *Journal of Biological Sciences*, 8(4):767–772.

Arnich N, Sirot V, Riviere G, Jean J, Noel L, Guerin T, Leblanc JC. Dietary exposure to trace elements and health risk assessment in the 2nd French Total Diet Study.Food Chem Toxicol. 2012 Apr 20.

Bhasin P, Singla N, Dhawan DK.Protective role of zinc during aluminum-induced hepatotoxicity. Environ Toxicol. 2012 Mar 16.

Cui X, Wang B, Zong Z, Liu S, Xing W. The effects of chronic aluminum exposure on learning and memory of rats by observing the changes of Ras/Raf/ERK signal transduction pathway. Food Chem Toxicol. 2012;50(2):315-9.

Hirata-Koizumi, M., Fujii, S., Ono, A., Hirose, A., Imai, T., Ogawa, K., Ema, M., Nishikawa, A., (2011a). Two-generation reproductive toxicity study of aluminium sulfate in rats. Reprod. Toxicol. 31, 219–230.

Hirata-Koizumi M et al. (2011b). Evaluation of the reproductive and developmental toxicity of aluminium ammonium sulfate in a two-generation study in rats. *Food and Chemical Toxicology*, 49(9):1948–1959.

Kakkar V, Kaur IP. Evaluating potential of curcumin loaded solid lipid nanoparticles in aluminium induced behavioural, biochemical and histopathological alterations in mice brain. Food Chem Toxicol. 2011;49(11):2906-13.

Khanna Sood P, Nahar U, Nehru B. Curcumin attenuates aluminum-induced oxidative stress and mitochondrial dysfunction in rat brain. Neurotox Res. 2011;20(4):351-61.

Khanna Sood P, Nahar U, Nehru B. Stress proteins and glial cell functions during chronic aluminium exposures: protective role of curcumin. Neurochem Res. 2012;37(3):639-46.

Moselhy WA, Helmy NA, Abdel-Halim BR, Nabil TM, Abdel-Hamid MI.Role of ginger against the reproductive toxicity of aluminium chloride in albino male rats. Reprod Domest Anim. 2012;47(2):335-43.

Ribes D, Torrente M, Vicens P, Colomina MT, Gómez M, Domingo JL. Recognition Memory and β-amyloid Plaques in Adult Tg2576 Mice are not Modified After Oral Exposure to Aluminum. Alzheimer Dis Assoc Disord. 2012;26(2):179-85.

Ribes D, Colomina MT, Vicens P, Domingo JL. Effects of oral aluminum exposure on behavior and neurogenesis in a transgenic mouse model of Alzheimer's disease. Exp Neurol. 2008;214(2):293-300.

Thirunavukkarasu SV, Venkataraman S, Raja S, Upadhyay L. Neuroprotective effect of Manasamitra vatakam against aluminium induced cognitive impairment and oxidative damage in the cortex and hippocampus of rat brain. Drug Chem Toxicol. 2012;35(1):104-15. (abstract only).

Tomljenovic L. Aluminum and Alzheimer's disease: after a century of controversy, is there a plausible link? J Alzheimers Dis. 2011;23(4):567-98.

Wang B, Xing W, Zhao Y, Deng X. Effects of chronic aluminum exposure on memory through multiple signal transduction pathways. Environ Toxicol Pharmacol. 2010;29(3):308-13.

Wang N, She Y, Zhu Y, Zhao H, Shao B, Sun H, Hu C, Li Y. Effects of subchronic aluminum exposure on the reproductive function in female rats. Biol Trace Elem Res. 2012;145(3):382-7.

Zhu Y, Hu C, Li X, Shao B, Sun H, Zhao H, Li Y. Suppressive effects of aluminum trichloride on the T lymphocyte immune function of rats. Food Chem Toxicol. 2012;50(3-4):532-5.

Annex to Appendix 27

FAO/WHO Unpublished Bioavailability Studies on Aluminium in animals

1. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has just published a monograph in the WHO Additives Series (no. 65) on the Safety evaluation of certain food additives and contaminants which includes a summary of the data on aluminium-containing food additives. The monograph was prepared at the seventy-fourth meeting of the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA), in Rome, Italy, in June 2011. The seventy-fourth report of JECFA has been published by the World Health Organization as WHO Technical Report No. 966.

2. During the review process of the scientific data for this latest monograph, the JECFA committee had access to a number of unpublished reports on the bioavailability of aluminium (Al) submitted by Sunaga of the Safety Research Institute for Chemical Compounds Co in Japan (2010). These data was presented as part of a paper at a COT meeting in June 2012 (COT/2012/21). The data on the bioavailability of Al is new and unpublished at present, but available in part in the FAO/WHO report. It should be noted that it was not possible for the secretariat to obtain access to these original reports. We have taken the relevant paragraphs from the report and presented them below (in italics). The data has also been summarised in the attached table, modified from the version in COT/2012/21.

Taken from FAO/WHO
2.1.1 Absorption, distribution and excretion
(a) Absorption

3. The bioavailability of a single dose of aluminium ammonium sulfate was assessed in groups of four male (302–379 g) and four female (236–265 g) fasted Crl:CD (SD) rats in a study that was compliant with good laboratory practice (GLP). Aluminium ammonium sulfate dissolved in physiological saline was administered by oral gavage at 300 and 1000 mg/kg bw and intravenously at 2 mg/kg bw. Blood samples were taken from the jugular vein at intervals up to 24 hours, and serum aluminium was measured by fluorescence detection liquid chromatography. Four of the top-dose animals (one male and three females) died and were replaced by additional animals. The cause of death in these animals is unclear. The bioavailability was calculated from the 24-hour area under the concentration versus time curve (AUC) values to be 0.039% in males and 0.061% in females dosed with aluminium ammonium sulfate at 300 mg/kg bw and 0.048% in males and 0.067% in females dosed at 1000 mg/kg bw (Sunaga, 2010a). If it is assumed that these doses were expressed as aluminium ammonium sulfate, the oral doses of aluminium would be 33 and 110 mg/kg bw, respectively.

4. The repeated-dose bioavailability of aluminium ammonium sulfate was assessed in groups of four male (267–293 g) and four female (183–198 g) Crl:CD (SD) rats in a study that was compliant with GLP. Aluminium ammonium sulphate dissolved in physiological saline was administered by oral gavage at 300 and 1000 mg/kg bw or

intravenously at 2 mg/kg bw once daily for 14 days. Blood samples were taken from the jugular vein at intervals up to 24 hours after the final dosing, and serum aluminium was measured by fluorescence detection liquid chromatography. The bioavailability was calculated from the 24-hour AUC values to be 0.008% in males and 0.003% in females dosed with aluminium ammonium sulfate at 300 mg/ kg bw and 0.006% in males and 0.023% in females dosed at 1000 mg/kg bw. The maximum concentration (Cmax) and AUC values increased in a dose-related manner between groups. There was no indication of accumulation. Comparison with the results of the single-dose study (Sunaga, 2010a) led the author to conclude that repeated administration resulted in decreased absorption of aluminium ammonium sulfate (Sunaga, 2010b). If it is assumed that these doses were expressed as aluminium ammonium sulfate, the oral doses of aluminium would be 33 and 110 mg/kg bw, respectively.

5. The bioavailability of a single dose of aluminium lactate was assessed in groups of four male (296–330 g) and four female (190–217 g) fasted Crl:CD (SD) rats in a study that was compliant with GLP. Aluminium lactate dissolved in physiological saline was administered by oral gavage at 300 and 1000 mg/kg bw or intravenously at 2 mg/kg bw. Blood samples were taken from the jugular vein at intervals up to 24 hours, and serum aluminium was measured by fluorescence detection liquid chromatography. The bioavailability was calculated from the 24-hour AUC values to be 0.067% in males and 0.164% in females dosed with aluminium lactate at 300 mg/kg bw and 0.161% in males and 0.175% in females dosed at 1000 mg/kg bw (Sunaga, 2010c). If it is assumed that these doses were expressed as aluminium lactate, the oral doses of aluminium would be 27 and 91 mg/kg bw, respectively.

6. The repeated-dose bioavailability of aluminium lactate was assessed in groups of four male (253–272 g) and four female (187–211 g) Crl:CD (SD) rats in a study that was compliant with GLP. Aluminium lactate dissolved in physiological saline was administered by oral gavage at 300 and 1000 mg/kg bw or intravenously at 2 mg/kg bw once daily for 14 days. Blood samples were taken from the jugular vein at intervals up to 24 hours after the final dosing, and serum aluminium was measured by fluorescence detection liquid chromatography. The bioavailability was calculated from the 24-hour AUC values to be 0.009% in males and 0.007% in females dosed with aluminium lactate at 300 mg/kg bw and 0.043% in males and 0.044% in females dosed at 1000 mg/kg bw. There was no indication of accumulation. Comparison with the results of the single-dose study (Sunaga, 2010c) led the author to conclude that repeated administration resulted in decreased absorption of aluminium lactate. The AUCs for the high-dose group were about 10–15 times greater than those for the low-dose group. The author considered the exceedance of the dose ratio to be due to disappearance of aluminium in blood at an early stage in the low-dose group and bimodal transition of serum aluminium concentrations in the high-dose group (Sunaga, 2010d). If it is assumed that these doses were expressed as aluminium lactate, the oral doses of aluminium would be 27 and 91 mg/kg bw, respectively.

7. The bioavailability of a single dose of aluminium sulfate was assessed in groups of four male (297–335 g) and four female (195–224 g) fasted Crl:CD (SD) rats in a study that was compliant with GLP. Aluminium sulfate dissolved in physiological saline was administered by oral gavage at 600, 1000 and 2000 mg/kg bw and intravenously at 1 mg/kg bw. Blood samples were taken from the jugular vein at intervals up to 24 hours, and serum aluminium was measured by fluorescence

detection liquid chromatography. All of the top-dose animals, except for one female, died. The bioavailability was calculated from the 24-hour AUC values to be 0.046% in males and 0.064% in females dosed with aluminium sulfate at 600 mg/kg bw and 0.053% in males and 0.069% in females dosed at 1000 mg/kg bw (Sunaga, 2010e). If it is assumed that these doses were expressed as aluminium sulfate, the oral doses of aluminium would be 95 and 158 mg/kg bw, respectively.

8. The repeated-dose bioavailability of aluminium sulfate was assessed in groups of four male (247–270 g) and four female (184–213 g) Crl:CD (SD) rats in a study that was compliant with GLP. Aluminium sulfate dissolved in physiological saline was administered by oral gavage at 600, 1000 and 2000 mg/kg bw or intravenously at 1 mg/kg bw once daily for 14 days. Blood samples were taken from the jugular vein at intervals up to 24 hours after the final dosing, and serum aluminium was measured by fluorescence detection liquid chromatography. Dosing at 2000 mg/kg bw was discontinued as a result of deaths and loss of body weight. The bioavailability was calculated from the 24-hour AUC values to be 0.012% in males and 0.035% in females dosed with aluminium sulfate at 600 mg/kg bw and 0.012% in males and 0.052% in females dosed at 1000 mg/kg bw. The Cmax and AUC values increased in a dose-related manner between groups. There was no indication of accumulation. Comparison with the results of the single-dose study (Sunaga, 2010e) led the author to conclude that repeated administration resulted in decreased absorption of aluminium sulfate in male rats. The Cmax and AUC values increased in a dose related manner between groups (Sunaga, 2010f). If it is assumed that these doses were expressed as aluminium sulfate, the oral doses of aluminium would be 95 and 158 mg/kg bw, respectively.

Comments from JECFA on the Sunaga studies

9. The new data indicated that absorption of aluminium following the ingestion of various aluminium compounds by rats is generally in the region of 0.01–0.3% and support the assumption that the more water-soluble aluminium compounds are generally more bioavailable. As a result of limitations in the sensitivity of the analytical methods, inter-animal variation and methodological differences between studies, including the administered doses, it is not possible to draw firm conclusions on quantitative differences in absorption between different compounds. There are indications that there are sex differences in absorption in rats and that the proportion of the dose absorbed is lower following repeated administration than following single administration.

Comments on Sunaga studies and the summary in the final report

10. In addition to the JECFA comments above, it should be noted that there was no indication of accumulation of Al from the repeat dose studies for the three Al compounds tested. In the Subgroup's final report, the bioavailability data is summarised as "*Although, in general, studies indicate that absorption of aluminium is low across the gut following ingestion or across the skin, the chemistry of aluminium and the complex interactions that it may undergo make the precise quantification of absorption and the underlying mechanisms involved difficult to determine. There is thus a considerable potential for variability in the extent of absorption in humans. This is usually around 0.2–0.4% in healthy young adults but has been shown to be 10 times higher in one case in a young adult (Taylor et al, 1992) and may also be*

enhanced during fasting". Comparing the results from the above animal studies with human studies, which this Committee has previously reviewed, the absorption of aluminium in human volunteers was within the same range as that seen in the rats.

References

Sunaga M (2010a). *Single dose bioavailability study of aluminium ammonium sulfate in rats.* Sapporo, Japan, Safety Research Institute for Chemical Compounds Co., Ltd (Study No. SR07178). Submitted to FAO/WHO by the Ministry of Health, Labour and Welfare, Japan.

Sunaga M (2010b). *Repeated dose bioavailability study of aluminium ammonium sulfate in rats.* Sapporo, Japan, Safety Research Institute for Chemical Compounds Co., Ltd (Study No. SR07179). Submitted to FAO/WHO by the Ministry of Health, Labour and Welfare, Japan.

Sunaga M (2010c). *Single dose bioavailability study of aluminium lactate in rats.* Sapporo, Japan, Safety Research Institute for Chemical Compounds Co., Ltd (Study No. SR07176). Submitted to FAO/WHO by the Ministry of Health, Labour and Welfare, Japan.

Sunaga M (2010d). *Repeated dose bioavailability study of aluminium lactate in rats.* Sapporo, Japan, Safety Research Institute for Chemical Compounds Co., Ltd (Study No. SR07177). Submitted to FAO/WHO by the Ministry of Health, Labour and Welfare, Japan.

Sunaga M (2010e). *Single dose bioavailability study of aluminium sulfate in rats.* Sapporo, Japan, Safety Research Institute for Chemical Compounds Co., Ltd (Study No. SR07174). Submitted to FAO/WHO by the Ministry of Health, Labour and Welfare, Japan.

Sunaga M (2010f). *Repeated dose bioavailability study of aluminium sulfate in rats.* Sapporo, Japan, Safety Research Institute for Chemical Compounds Co., Ltd (Study No. SR07175). Submitted to FAO/WHO by the Ministry of Health, Labour and Welfare, Japan.

Taylor GA, Ferrier IN, McLoughlin IJ, Fairbairn AF, McKeith IG, Lett D and Edwardson JA (1992). Gastrointestinal absorption of aluminium in Alzheimer's disease: response to aluminium citrate. Age and Ageing **21**(2): 81-90.

Bioavailability of aluminium compounds in single-dose or repeat-dose studies (tabulated from data from FAO/WHO, 2012, modified from COT/2012/21).

	Dose of Compound (mg/kg/d)	Bioavailability (%)[a]		Oral Dose of Al (mg/kg/d) [b]	Reference
		Male	Female		
Aluminium ammonium sulphate	300 (single dose)	0.039	0.061	33	Sunaga, (2010a)
	1000 (single dose)	0.048	0.067	110	
	300 (repeat dose)[c]	0.008	0.003	33	Sunaga, (2010b)
	1000 (repeat dose)[c]	0.006	0.023	110	
Aluminium lactate	300 (single dose)	0.067	0.164	27	Sunaga, (2010c)
	1000 (single dose)	0.161	0.175	91	
	300 (repeat dose)[c]	0.009	0.007	27	Sunaga, (2010d)
	1000 (repeat dose)[c]	0.043	0.044	91	
Aluminium sulphate	600 (single dose)	0.046	0.064	95	Sunaga, (2010e)
	1000 (single dose)	0.053	0.069	158	
	2000 (single dose)	All animals in group died, except one female			
	600 (repeat dose)[c]	0.012	0.035	95	Sunaga, (2010f)
	1000 (repeat dose)[c]	0.012	0.052	158	
	2000 (repeat dose)[c]	Dosing discontinued due to death and weight loss of animals			

[a] Bioavailability was calculated from the 24-hour area under the concentration versus time curve (AUC). [b] If assumed that doses stated in Column 2 were expressed as aluminium ammonium sulphate, aluminium lactate or aluminium sulphate, respectively. [c] Repeat dose =14 days

Appendix 28: Review paper on metal-metal interactions prepared for the Lowermoor subgroup by the Department of Health Toxicology Unit, Imperial College, London (January 1970 to February 2003)

Note: this was a paper prepared for discussion by the Lowermoor Subgroup. It does not necessarily represent the views of the subgroup.

Introduction

1. As a result of the Lowermoor water contamination incident in July 1988, water supplies to the Camelford area were contaminated with aluminium (Al[105]). A maximum estimated concentration of 620 mg/l Al in the water supply has been cited (Lowermoor Incident Health Advisory Group (LIHAG 1989, 1991). Increased concentrations of other metals in the water supply were also noted: copper (Cu, 8.8 mg/l), zinc (Zn, up to 9 mg/l), lead (Pb, 0.35 mg/l), iron (Fe) and manganese (Mn) (40-fold max EU regulations[106], no specific values available) (figures in brackets indicate the highest estimated cold-water-supply concentration, data from LIHAG reports and LSG/02/8). Based on these values, maximum theoretical daily intakes of each metal, per kg body weight, for an individual consuming ~ 2 l/day of this water are shown in Table 17a. This review, prepared for the COT subgroup on the Lowermoor water contamination incident by the Department of Health Toxicology Unit at Imperial College London, is concerned with biological interactions which may occur between these 6 metals, with relevance to potential effects in humans exposed orally.

2. Al and Pb are nonessential metals. Fe, Cu, Zn and Mn are essential micronutrients, the major source in humans being the diet. Interactions between a number of essential and non-essential metals have been described, in particular where deficiency of an essential metal may predispose to the toxicity of a non-essential metal (Goyer, 1997; Peraza *et al*., 1998). Biological interactions between essential metals have also been reported, often at the level of uptake and/or tissue status.

3. In this report, each pairwise combination of the 6 metals of concern has been considered. As Al was the major pollutant, the main focus is on combinations of Al with each of the other metals. Studies of the interactions of Pb with the essential metals are reviewed more briefly. Data on the interactions of Fe, Cu, Zn and Mn are taken from recent reviews on the toxicities of these metals, which have been prepared for the UK Expert Group on Vitamins and Minerals (EVM). In cases where reviews were used as major information sources, database searches were also carried out to discover additional information of relevance to the subgroup.

4. Data on all types of interactions have been included, but consideration has been given only to studies which have evaluated oral exposure. Some studies have evaluated acute, high dose toxicity, whilst others have reported the chronic effects of high or lower dose levels. A number of studies have indicated inhibitory interactions, often at the level of uptake and/or body status. Few data were identified which suggested potentiative or synergistic toxicity. In the very small number of cases where potentially adverse interactive effects have been reported, these studies have used high doses which exceeded the maximum estimated exposures resulting from the Lowermoor incident by at least several-fold, for periods of several weeks or months.

Results

[105] Throughout the text, chemical symbols, rather than full names, for metallic elements such as Al, Cu, Zn etc. are used in a generic sense to represent these elements.

[106] EC Directive 80/778/EEC set a Maximum Admissible Concentration of 200 μg/l for iron in water intended for human consumption, and 50 μg/l for manganese, at the point of supply.

Aluminium (Al)

5. Al is ubiquitous in food and the environment. An intake of 5-10 mg/day Al, mostly from food, has been estimated for the average western diet (LSG/02/7). The metal is eliminated from the body *via* the urine. Target organs for Al toxicity, in humans and animals, are the lung, bone or CNS (Goyer and Clarkson, 2001). Dietary exposure to Al generally has not been associated with toxicity in healthy subjects. Toxicity has been reported in dialysis patients treated with Al-containing tap water and/or phosphate binders or in cases of industrial exposure to Al *via* inhalation. Data on interactions of Al with Pb, Cu, Zn, Fe and Mn are summarised in the following paragraphs (paragraphs 6-10) and detailed in Appendix 1.

Al & Lead (Pb)

6. Targets for Pb toxicity are the haemopoietic, nervous and renal systems, and Pb poisoning is characterised by anorexia, depressed weight gain, anaemia, nephropathy and encephalopathy. Al is relatively less toxic than Pb, and effects are rare in subjects with normal renal function. Few studies have examined the toxic effects of combined exposure to Pb and Al. One epidemiological study suggested a possible association of combined high (but within accepted limits) levels of Pb and Al in hair with decreased visual-motor performance in children (Marlowe *et al*., 1985b). An experimental (90-day) study in rats showed protective effects of Al against the nephrotoxic effects of Pb (Shakoor *et al*., 2000).

Al & Copper (Cu)

7. Database searches revealed few *in vivo* data on biological interactions of Al and Cu. There is little evidence to suggest that Al affects Cu kinetics or metabolism to an appreciable extent. A case-report described severe Cu deficiency in a woman who had taken massive doses of Al-containing antacids for several years (Nutrition Reviews, 1984). One small study showed no effect of low-level (~ 2 mg/kg bw/day) Al supplementation, for 20 days, on Cu retention in healthy adult men (Greger and Baier, 1983). Stemmer and colleagues reported that chronic dietary Al supplementation (~ 50 mg/kg bw/day) to animals that were substantially deficient in Cu had varying effects on levels of sex hormones and catecholamines (Wenk and Stemmer, 1981; Liu and Stemmer 1990a). Chronic treatment of rats with moderate levels (~ 6 mg/kg bw/day + standard dietary intake) of Al in drinking water led to increased Al and decreased Cu levels in the intestine, but concentrations in other tissues were not affected (Fulton *et al*., 1989).

Al & Zinc (Zn)

8. The group of Stemmer and colleagues have suggested various interactions of chronic dietary Al supplementation (~ 50 mg/kg bw/day) with low Zn status in rats; that Al supplementation can redress some of the adverse consequences of low Zn status, but also that low Zn status potentiates Al uptake into the brain (Wenk and Stemmer, 1981; Wenk and Stemmer, 1982; Wenk and Stemmer, 1983; Liu and Stemmer, 1990a; Liu and Stemmer, 1990b). However, McNall & Fosmire (1996) reported no effect of Zn status on tissue Al concentrations in rats given dietary Al supplementation (~ 25 mg/kg bw/day) for a 28-day period. A small number of studies using rats or mice have shown that dietary Al supplementation (50 - 600 mg/kg

bw/day) for periods of several weeks may reduce Zn absorption and/or serum levels (Sugawara *et al*., 1987; Ecelbarger and Greger, 1991). However, one small study in humans showed no effect of low-level (~ 2 mg/kg bw/day) dietary Al supplementation, for 20 days, on Zn retention in healthy adult men (Greger and Baier, 1983). There does not appear to be any evidence to suggest an adverse interaction of increased Zn and Al intake.

Al & Iron (Fe)

9. There is evidence for a metabolic relationship between Fe and Al metabolism, including intestinal absorption and plasma transport of the metals, perturbation of cellular Fe metabolism, and modulation of the toxic effects of Fe, by Al.

9.1 Within the plasma, the majority of Al is bound to the Fe binding protein Tf, which has a lower affinity for Al than for Fe (Trapp, 1983; Cochran *et al*., 1984).

9.2 Cellular uptake of Tf-bound Al *via* Tf-receptors on cell surfaces and *via* subsequent internalisation by receptor-mediated endocytosis has been shown in a variety of cell lines, including neuroblastoma cells, erythroleukaemia cells, haematopoietic progenitor cells, osteosarcoma cells, hepatocytes and lymphocytes (Ittel *et al*., 1996) and refs therein).

9.3 High concentrations of Al may interfere with cellular Fe uptake and metabolism, including ferritin regulation by Fe, utilisation of Fe for the synthesis of haem and expression of the Tf receptor. In vitro studies have shown that Al can enhance cellular Fe uptake, potentially by Tf-dependent or independent mechanisms (Abreo *et al*., 1994; Oshiro *et al*., 1998; Abreo *et al*., 1999), and Al has been shown to bind and stabilise IRP2, a key regulator of intracellular Fe metabolism (Yamanaka *et al*., 1999; Ward *et al*., 2001). In conditions of overload, Fe exhibits strong pro-oxidative capabilities, and Al has been shown to accentuate the degree of peroxidation that is mediated by Fe (Gutteridge *et al*., 1985; Quinlan *et al*., 1988; Xie *et al*., 1996; Bondy *et al*., 1998). It has been suggested that the toxic effects of Al in the brain may, in part, be due to disruption of normal Fe homeostasis and cellular metabolism.

9.4 Fe/Al ratios vary widely in different organs, being high in the spleen, liver and kidneys (due to high Fe) and heart, brain and muscle (due to low Al), low in intestine, lungs, skin and hair (due to relatively high Al) (cited by (Goyer, 1997). It has been stated that Al, as well as Fe, is accumulated in subjects with hereditary Fe-overload disorders such haemochromatosis and thalassaemia major (cited by (Goyer, 1997), although no reference was given). (Iancu *et al*., 1996) observed prominant Al, as well as Fe, accumulation in some animal models of Fe-overload.

9.5 Al has been reported to have a negative effect on Fe uptake in dialysis patients treated with EPO (Donnelly *et al*., 1990; Kooistra *et al*. 1998). Oral administration of ~ 2 mg/kg bw/day Al for 20 days did not affect Fe retention in 8 healthy adult volunteers.

9.6 Oral administration of moderate to high levels of Al (~ 10 - 600 mg/kg bw/day) to experimental animals for periods of several weeks has been observed to reduce intestinal uptake of Fe in some studies, but generally has not shown effects on serum or tissue Fe levels (Greger *et al*., 1985; Sugawara *et al*., 1987; Fulton *et al*.,

1989; Fulton and Jeffrey, 1990; Ecelbarger and Greger, 1991; Morgan and Redgrave, 1998). Administration of 100 mg/kg bw/day Al to rats for 35 days was associated with reduced spleen Fe levels (Nasiadek and Chmielnicka, 2000). Golub *et al*. (1996) reported that high dietary maternal Al (~ 50 mg/kg bw/day) during gestation and lactation did not affect milk Fe concentrations, nor Fe absorption or tissue distribution in nursing mouse pups, but was associated with ~ 10% reduction in the ability of pups to retain absorbed Fe. One study showed that co-administration of Al (~ 160 mg/kg bw/day, for ~ 10 weeks) exacerbated the suppression of growth rate associated with severe Fe-overload (~ 1000 mg/kg bw/day) in young rats (Morgan and Redgrave, 1998).

9.7 Fe deficiency has been suggested to promote the intestinal absorption of Al (Cannata *et al*., 1991; Cannata and Diaz Lopez, 1991), although it has also been reported that that co-administration of Fe may increase Al uptake (Ittel *et al*., 1996). Some authors claim that Fe and Al share a common, Tf-dependent, uptake mechanism, and that Fe deficiency may increase Al absorption due to increased Tf receptor expression (Cannata and Diaz Lopez, 1991; Fernandez Menendez *et al*., 1991), but this is disputed by others (Ittel *et al*., 1996). Some clinical studies have shown a negative relationship between serum ferritin, Fe or Tf saturation and serum Al concentrations in dialysis patients (Cannata *et al*., 1985; D'Haese *et al*., 1990; Huang *et al*., 1992; Cannata *et al*., 1993). One report described increased Al excretion rates in renal failure patients with low serum ferritin, suggesting increased intestinal Al absorption (Lin *et al*., 1995). Conversely, (Blaehr *et al*., 1986) reported that dialysis patients given Al-containing phosphate binders with ~ 60 mg/day Fe (as Ferrofumarate solution) for 3 months tended to show higher serum Al levels than patients not receiving Fe (although the difference was not statistically significant).

9.8 Recent studies have shown that Tf is unlikely to be the direct mucosal regulator of Fe absorption. Dietary Fe is absorbed as Fe(II), after reduction from Fe(III) (the predominant form in the diet). The DMT1 (divalent metal transporter) protein has been identified recently as the likely transporter of Fe(II) (and other divalent cations) into the enterocyte (see reviews by (Crichton *et al*., 2002; Philpott, 2002).

Al & Manganese (Mn)

10. Al and Mn are both neurotoxicants with the potential to contribute to neurodegenerative disorders. Mn can produce a Parkinsonism-like syndrome. Al can contribute to dialysis encephalopathy syndrome. In contrast to Al, for which no mammalian essentiality has been shown, Mn is essential, required for brain development and function.

10.1 A combination of low dietary intake of Ca+Mg with high concentrations of Al+Mn has been suggested as a factor in the incidence of amyotrophic lateral sclerosis and Parkinsonian dementia (ALS-PD) in specific areas of the western Pacific. (Garruto *et al*., 1984) noted that the volcanic soils of the regions of Guam with a high incidence of ALS-PD contained high concentrations of Al and Mn and were low in Ca and Mg. They postulated that low Ca and Mg intake induced secondary hyperparathyroidism, resulting in an increase in Ca, Al and other toxic metals, and leading to neuronal injury and death. It has been suggested that the diet of the inhabitants of Guam may be the source of the Al, perhaps *via* the respiratory tract,

and Al uptake through nasal-olfactory pathways has been demonstrated (Perl and Good, 1987). It has also been suggested that consumption of the neurotoxic seed of the false sago palm tree (*Cycas circinalis*) may play a role in the prevalence of ALS-PD in these areas, and a genetic component is also possible (Plato *et al.*, 2002).

10.2 Supplementation of the diets of cynomolgus monkeys maintained on a low calcium diet, with Al (150 mg/day) and Mn (50 mg/day), with or without flour prepared from unwashed seed of *Cycas circinalis*, for 41-46 months, was not associated with behavioural changes or neurological deficits. Histological abnormalities of motor neurons of the spinal cord, brain stem, substantia nigra and motor cortex were associated with the low Ca diet, and the authors noted that these lesions appeared to be most abundant in animals on the low Ca/high Al+Mn diet, although differences were not statistically significant. One monkey given the low Ca/high Mn+Al diet showed Al deposition in the spinal cord (Garruto *et al.*, 1989).

10.3 A small number of studies have indicated that Al or Mn supplementation may affect uptake/retention or tissue levels of the other metal. Rats fed a low Ca/Mg diet with supplemental Al (~ 97 mg/kg bw/day) for 90 days showed significantly increased bone Al and Mn levels (Yasui *et al.*, 1995). Al supplementation (~ 50 mg/kg bw/day) during gestation and lactation lowered the ability of nursing mouse pups to retain absorbed Mn by ~ 10% as compared with controls (Golub *et al.*, 1996). Nielsen *et al.* (1988) reported that the effects of Al supplementation (~ 50 mg/kg bw/day) for 7 weeks to rats varied depending on the level of Mn supplementation in the diet (1 or 2.5 mg/kg bw/day).

Lead (Pb)

11. Lead toxicity affects several organ systems, including the nervous, haematopoietic, renal, endocrine and skeletal, depending on the age of the subject and the size of the dose. The CNS is the primary target organ, and an effect which is of prime concern is the impairment of cognitive and behavioural development in infants and young children exposed to Pb in the environment. Pb in water is more efficiently absorbed than Pb in food, and so Pb in tap water contaminated by solder and Pb-containing fittings in residential plumbing is a matter of particular concern. Nutritional deficiencies of essential metals can increase the hazard from Pb exposure by enhancing absorption and toxicity of dietary Pb. The essential metals with the most marked influence on blood levels and toxic effects of Pb are Ca, Fe and Zn (cited by (Goyer, 1997)). The interaction of Pb and Ca is the most well defined. Ca deficiency potentiates the absorption and retention of Pb, and Pb interacts to disrupt Ca homeostasis and functioning in the nervous system (see reviews by (Goyer, 1997), (Peraza *et al.*, 1998)). Fe deficiency increases Pb uptake by an unknown mechanism. Zn deficiency also potentiates Pb uptake, whilst Pb increases Zn excretion and inhibits Zn-dependent enzymes. Tissue Cu and Pb levels have been shown to be inversely related and Cu deficiency potentiates Pb-associated depression of growth rate in animals. Administration of both Zn and Cu have been shown to ameliorate the toxic effects of Pb. No data were identified regarding interactions of Pb and Mn (given orally). As previously described (see paragraph 6, interactions of Al & Pb), one study reported a possible association of upper normal hair-content levels of the Al+Pb combination with reduced visual motor performance in children (Marlowe *et al.*, 1985b). However, a study in rats showed that co-administration of Al reduced the

nephrotoxic effects of Pb (Shakoor *et al.*, 2000). More detailed information regarding interactions of Pb with other metals is given in Appendix 2.

Essential metals – Copper (Cu), Zinc (Zn), Iron (Fe), Manganese (Mn)

12. The estimated average daily intake of Cu from dietary sources in the UK is ~ 1.8 mg. Food is the major source, but drinking water can make an important contribution in some circumstances. Cu may be included in products for general sale to a maximum daily dose of 1 mg. For products sold under the supervision of a pharmacist, daily doses up to 4 mg are specified. Cu-containing preparations are also available as food supplements in the form of multivitamin and mineral preparations; the use of these supplements at the recommended dosage would produce daily intakes of up to 2 mg/day. Concentrations > 3 mg/l in drinking water have been reported to produce gastrointestinal effects such as nausea, vomiting and diarrhoea. Severe acute toxic effects (hepatic necrosis and death) have been reported following massive ingestion (eg, 100 g copper sulphate). Chronic dietary Cu overload appears to be related to genetic predisposition to increased absorption, either when dietary intakes are normal (eg, Wilson disease) or high (eg, Indian childhood cirrhosis, idiopathic copper toxicosis). Toxicity is thought to occur as a result of free radical damage.

13. Human exposure to Zn is largely through food. In the UK, the population average intake from food is 10-12 mg/day, excluding dietary supplements. Products containing Zn at a maximum daily dose of 5 mg may be sold over the counter, whilst doses up to 150 mg/day are permitted under the supervision of a pharmacist. The current UK regulatory limit for Zn in drinking water is 5 mg/l, based only on aesthetic criteria. Zn has generally been considered to be relatively non-toxic. Homeostatic mechanisms regulate the Zn body burden and it does not appear to accumulate in the body except within bone. In humans, the acute toxic effects seen at very high intakes, include abdominal pain, nausea and vomiting. Prolonged use of high doses of Zn can result in secondary deficiency of Cu, leading to the development of sideroblastic anaemia. Zn therapy may be used to treat the Cu overload associated with Wilson disease.

14. Fe intake in humans is mainly from foods, as either the haem or non-haem form. In the UK there is mandatory fortification of white and brown flour at a level of not less than 1.65 mg Fe/100 g flour, whilst many other foods are fortified on a voluntary basis. Average dietary Fe intakes for men and women in Great Britain are 14.0 mg and 12.3 mg, respectively. The maximum permitted level in UK water supplies is 0.2 mg/l. Over-the-counter Fe-containing supplements may contain doses up to 72 mg elemental Fe per day (24 mg, 3x per day). Doses up to 400 mg/day (commonly ~ 60 mg/day) may be used medically for the treatment of Fe deficiency. Many of the key biological functions of Fe in living systems rely on the high redox potential, enabling it to switch rapidly between the Fe^{2+} and Fe^{3+} forms. The high oxidative potential is, however, also potentially very harmful in terms of the capacity for damage to cellular components. Thus Fe within the body, whether it is being stored, transported or as a component of various catalytic pathways, is bound to carrier proteins and/or molecules with antioxidant properties, which abrogate the capacity of the free ion to cause oxidative stress. Furthermore, Fe uptake by the gut is highly regulated dependent on body status and requirements. For these reasons, increased oral Fe intake rarely results in Fe overload or related toxicity in normal, healthy adults. Rather, chronic (dietary) Fe overload usually occurs as the result of

genetic predisposition to unregulated (or increased) Fe uptake from the gut, either with normal Fe intake levels, as in hereditary haemochromatosis (HHC) or hereditary anaemia syndromes, or in combination with high dietary intake (eg, Bantu siderosis). Pathologic consequences of chronic severe Fe overload (excess total body Fe > 10 g in adult) are Fe-induced tissue damage, including cirrhosis of the liver and impaired heart and endocrine function. High normal levels of dietary Fe intake over several years have been associated with adverse effects (eg, cardiovascular disease) in some epidemiological studies, although these claims are not proven.

15. The 1994 Total Diet Study showed that the estimated population average intake of Mn in the UK in 1994 was 4.9 mg/day, the majority of which was from drinking tea. The limit for Mn in the water supply is 50 µg/l, although "relaxation" of this limit is allowed up to 2000 µg/l. A health-based guideline of 500 µg/l has been suggested. Mn-containing supplements may be sold over-the-counter (up to 1 mg/day) or under pharamacist supervision (up to 5 mg/day). Mn toxicity from oral ingestion is rare, due to homeostatic regulation of body burden. The most common form of Mn toxicity occurs as a result of inhalation. Acute inhalation can cause Mn pneumonitis. Chronic Mn poisoning (manganism) from inhalation produces neuropsychiatric effects leading to a Parkinson-like syndrome, as well as liver cirrhosis.

16. It is possible that Fe and other similar cations are taken up by common pathways in the gut and so competition for uptake may occur. Binding to common binding proteins (eg, Tf) may also be associated with effects of one metal on the tissue or cellular uptake or homeostasis of another.

17. Data relevant to interactions of Fe, Cu, Zn and Mn have been reviewed extensively in recent reports prepared for the Food Standards Agency's Expert Committee on Vitamins and Minerals (EVM) (Cu, 1999 ; Mn, 1999; Zn, 1999; Fe, 2000, full reports available at http://www.foodstandards.gov.uk/). Relevant sections are reproduced in Appendix 3. In addition, database searches were carried out and studies relevant to this report which were not described in the EVM reports are detailed separately in Appendix 3.

18. In general Fe, Cu, Zn and Mn appear to show inhibitory effects on each other's uptake. In particular, excessive Zn intake can have an inhibitory effect on Cu balance. It has been reported that intestinal metallothionein, which is induced by Zn, may act as a "trap" for absorbed Cu. It was suggested that Zn absorption is increased in individuals homozygous for hereditary haemochromatosis (HHC) and that these individuals would be particularly vulnerable to Zn-induced Cu deficiency. High concentrations of Cu may inhibit the absorption of Zn. Animal studies suggest that Fe has an inhibitory effect on Cu absorption when Cu status is low or marginal. High levels of (non-haem) Fe may inhibit Zn absorption, although the magnitude of this effect appears to be greater in rats than in humans. It is also possible that Zn supplementation may have an inhibitory effect on Fe uptake and status. Interactions may occur at the level of plasma transport, as both metals are transported by Tf. However, the effect of Zn on indices of Fe status may also result as a secondary effect of Zn-induced Cu deficiency. Few data were identified regarding interactions of Cu or Zn with Mn. One study showed that co-administration (30 days) of Mn (~ 160 mg/kg bw/day, in drinking water) potentiated Cu accumulation in the brains of rats treated with Cu (~ 83 mg/kg bw/day, in the diet) (Murthy *et al.*, 1981). Co-administration of Zn increased plasma uptake of Mn (single oral dose) in 4 healthy adult volunteers

(Freeland-Graves and Lin, 1991). Fe and Mn may inhibit the absorption of each other and Fe deficiency may predispose to Mn toxicity. One report described some interactions between Fe and Mn at the level of tissue uptake in rats when these metals were give orally at very high doses during days 18-19 of pregnancy, suckling and weaning (Chua and Morgan, 1996).

Summary and conclusions

19. As a result of the Lowermoor water contamination incident in July 1988, water supplies to the Camelford area were contaminated with aluminium sulphate. Increased concentrations of some other metals (copper, zinc, lead, iron, manganese) were also noted. Theoretical maximum intakes of these 6 metals in the water supply are estimated (see Table 1)[107] as:

Al 21 mg/kg bw/day
Cu 0.29 mg/kg bw/day
Zn 0.3 mg/kg bw/day
Pb 0.01 mg/kg bw/day
Fe 0.27 mg/kg bw/day
Mn 0.07 mg/kg bw/day

20. In writing this report, we have been unable to draw any conclusions about the duration of the exposure.

21. This report has considered data on the potential interactions of these metals which may be of relevance to human health. Consideration has been given only to studies which have evaluated oral exposure. Metals have been considered in pairwise combinations, with the major focus on combinations with Al, as this was the main contaminant. Studies relevant to all potential interactions have been included. Some studies have evaluated the acute consequences of high-level exposures, whilst others have investigated chronic exposures to lower doses.

22. A number of studies have indicated inhibitory interactions between these metals, often at the level of uptake and/or body status. Several combinations have shown effects, some of which were inconsistent between studies. The biological significance of these effects often has not been demonstrated and remains unknown.

23. Few data were identified which suggested potentiative or synergistic effects. These studies are summarised below, and in Table 2:

(i) An epidemiological study of hair metal levels in US schoolchildren, reported by Marlowe *et al*. (1985b), suggested a possible association of higher levels (but all within accepted limits) of the Al-Pb combination with reduced visual-motor performance, although this remains to be confirmed.

(ii) An experimental study (Morgan and Redgrave, 1998) showed that severe dietary Fe overload (~ 1000 mg/kg bw/day) was associated with

[107] Note: These estimates were made by the Secretariat when this paper was written in early 2003 as working figures to aid in writing draft conclusions forthe review paper. They may vary from the final exposure estimates made by the Subgroup. Any difference has been taken into account by the Subgroup in writing its report.

impaired growth rate in young male Wistar rats. This effect was potentiated by co-administration of Al (~ 160 mg/kg bw/day) in the diet. These exposure levels were substantially higher than those associated with the Lowermoor incident (~ 8-fold the maximum estimated dose for Al and ~ 3700-fold the maximum estimated dose for Fe, for a period of 9-11 weeks).

(iii) I.T.R.C. male rats fed a standard diet supplemented with Cu (~ 50 mg/kg bw/day in the diet) and Mn (~ 100 mg/kg bw/day in drinking water) for 30 days showed reduced brain 5-HT levels, whilst this effect was only seen for single supplementation groups when a low-protein diet was given. Co-supplementation with Mn was associated with higher brain Cu levels than supplementation with Cu alone (Murthy *et al*., 1981). The doses of Cu and Mn administered in this experiment were more than 100-fold and 1000-fold higher, respectively, than the maximum estimated daily doses associated with the Lowermoor incident.

(iv) A study of the kinetics of a single oral 40 mg Mn load in 4 healthy adult volunteers showed that AUC values were increased by 124% when 50 mg Zn was co-administered (Freeland-Graves & Lin, 1991).

(v) Treatment of Wistar rats with very high levels of Mn (in drinking water) and Fe (in the diet) during days 18-19 of pregnancy and throughout suckling and weaning, resulted in alterations in the level of uptake of these nutrients in some body tissues (Chua and Morgan, 1996). The levels of supplementation for both metals given in this experiment were > 1000-fold the maximum estimated exposures associated with the Lowermoor incident.

24. Of the studies summarised above (paragraph 23) which showed potentiative or synergistic effects of combined oral application of the metals considered in this review, two of these studies (Freeland-Graves & Lin, 1991; Chua & Morgan, 1996) described changes in kinetics, with no biological consequences reported. The report of Marlowe *et al*. (1985b) described an epidemiological association, but the relevance of this association was unclear, and possible confounding factors were not identified. In the study reported by Murthy *et al*. (1981), the only biological consequence of oral doses to rats of Cu and Mn which were, respectively, 100-fold and 1000-fold the maximum estimated intakes resulting from the Lowermoor incident was reduced brain 5-HT levels. One study (Malhotra *et al*., 1982) described impaired growth rate associated with Al supplementation to rats with dietary Fe overload. However, this study used very high doses of Al and extremely high doses of Fe.

25. On the basis of the available data, there is no evidence for biologically significant interactions between any combination of the 6 metals considered here at levels which were encountered as a result of the Lowermoor incident. However, it should be noted that most studies were conducted at relatively high concentrations of metals. The information identified do not support a causal relationship between synergistic effects of the metals and reported ill-health effects in the exposed population.

DH Toxicology Unit
February 2003

Annex 1 - Interactions of Aluminium

Aluminium & Lead

Humans

Sub-chronic/ chronic studies

1. Marlowe and colleagues carried out studies to evaluate potential associations of hair metal levels (all within accepted upper limits) and signs of neuronal damage in schoolchildren in the USA. Assessment of a group of 80 children showed a significant correlation of Pb levels, and to a lesser extent levels of Al and some other metals, with variables of classroom behaviour. Some metal-metal combinations, but not Al-Pb, were also significantly associated with adverse effects on behaviour (Marlowe *et al.*, 1985a). In a separate study, levels of Al, and also the Al-Pb combination, were significantly associated with decreased visual-motor performance in a group of 69 children. The authors suggested that the Al-Pb combination, which accounted for > 8% of the variance over and above other metals and covariates, may have a synergistic negative effect on visual motor performance (Marlowe *et al*., 1985b). However, this remains to be confirmed by further studies.

Animals

Sub-chronic/ chronic studies

2. (Shakoor *et al*., 2000) carried out a study to investigate the possible effects of interactions between Pb and Al on renal function in male albino rats. Test animals were treated for 90 days with Pb acetate and/or Al chloride (probably in deionised drinking water, although this is not clearly stated). Dosage groups and results are shown in Tables 3 and 4. The authors noted that:

2.1 Body weights were suppressed by both single and combined Pb and Al treatments, but that Al provided some dose-dependent protection against the effect of Pb.

2.2 Relative kidney weights in the Pb and Pb+lowAl groups were significantly higher than the mean of the control group. (The results given for Pb+lowAl in the table are not in agreement with this statement – this is possibly a typographical error).

2.3 Plasma creatinine levels were increased at days 30 and 90 in Pb-treated rats, but were not affected by Al treatment (alone). In both groups of rats treated with Pb+Al, plasma creatinine was raised at 30, but not 90, days.

2.4 Kidney Pb concentration (in wet tissue) was significantly lower in Pb+Al treated groups than in Pb-treated animals. (Concentrations in all Pb-treated groups were significantly higher than controls, results for Al-only group were not given).

2.5 No histopathological changes were noted in the kidneys of Al- or Al+Pb-treated animals; those treated with Pb alone showed mild cytomegaly and karyomegaly in renal proximal tubule cells.

3. The authors concluded that Al chloride reduces the nephrotoxic effects of Pb acetate in rats. They suggested that this was the result of decreased absorption of Pb in the presence of Al, and also that depletion of phosphates by prolonged oral exposure to Al might have reduced the net deposition of Pb in the kidneys.

Aluminium and Copper

Humans

Acute/ sub-acute studies

4. Supplementation of 8 healthy adult males for 20 days with 125 mg/day Al (~ 2 mg/kg bw/day, as lactate), described by the authors as representative of the upper limit of Al present in the American diet, had no overall effect on Cu retention by these subjects (Greger and Baier, 1983).

Sub-chronic/ chronic studies

5. A case report described severe Cu deficiency in a patient who had used large amounts of an antacid (up to ~ 7.5 g/day, containing oxides of bismuth, aluminium, silical, magnesium and sodium), for several years. The development of Cu deficiency was ascribed to precipitation of cupric salts by the alkali oxides of the antacid, along with prolonged gastric emptying time in this patient. It was estimated that the level of antacid used would be sufficient to remove completely any soluble Cu from the gastric juice (Nutrition Reviews., 1984).

Animals

Acute/ sub-acute studies

6. When diets were only marginally adequate in Cu (1.9 mg/kg diet, ~ 0.1 mg/kg bw/day), Zn (12.5 mg/kg diet, ~ 0.6 mg/kg bw/day), and Fe (16.2 mg/kg diet, ~ 0.8 mg/kg bw/day), supplementation of the diets of male Sprague-Dawley rats with Al (5-272 mg/kg di*et al*, ~ 0.25-13.6 mg/kg bw/day Al, as the lactate, palmitate, phosphate or hydroxide, for 18 days) was associated with reduced tibial Zn concentrations. However, when diets contained higher levels of Cu (7.1 mg/kg diet, ~ 0.36 mg/kg bw/day), Zn (20.7 mg/kg diet, ~ 1 mg/kg bw/day) and Fe (31 mg/kg diet, ~ 1.6 mg/kg bw/day), Al supplementation was associated with reduced liver Cu levels. The authors remarked that other investigators have also noted that dietary Al sometimes, but not consistently caused alteration in tissue Zn and Cu levels (refs cited by (Greger *et al*., 1985)), but that the reason for these inconsistencies is not known (Greger *et al*., 1985).

Sub-chronic/ chronic studies

7. Feeding diets supplemented with 4000 ppm Al (~ 600 mg/kg bw/day Al, as $AlCl_3.6H_2O$) and ethanol to male ICR mice for 58 days resulted in significantly decreased serum Cu (Sugawara *et al*., 1987).

8. Male Sprague-Dawley rats were maintained on a purified experimental diet containing sub-optimal levels of either Cu (2 ppm, ~ 0.1 mg/kg bw/day), Zn (10 ppm, ~ 0.5 mg/kg bw/day), Fe (5 ppm, ~ 0.25 mg/kg bw/day) or Mg (100 ppm, ~ 5 mg/kg

bw/day), or optimal levels of all these nutrients (Cu, 8 ppm, ~ 0.4 mg/kg bw/day; Zn, 40 ppm, ~ 2 mg/kg bw/day; Fe, 35 ppm, ~ 1.8 mg/kg bw/day; Mg, 400 ppm, ~ 20 mg/kg bw/day), with or without the addition of 0.1% Al (~ 50 mg/kg bw/day Al, as acetate), for 120 days. In animals which were substantially deficient in Zn, Cu, Fe, or Mg the addition of Al had varying effects on catecholamines in some regions of the central nervous system (Wenk and Stemmer, 1981).

9. Male Sprague-Dawley rats were fed semi-purified diets low in Cu (0.5 ppm, ~ 0.03 mg/kg bw/day) or Zn (2 ppm, ~ 0.1 mg/kg bw/day) with or without supplemental Al (1000 ppm, ~ 50 mg/kg bw/day Al, formulation not stated) for 10 weeks. Optimal nutrient groups were fed the semi-purified diet with Cu (7.5 ppm, ~ 0.38 mg/kg bw/day) and Zn (38 ppm, ~ 1.9 mg/kg bw/day) added to the drinking water (optimal nutrient group), with or without supplemental Al (as above). Rats fed a low Cu diet + Al showed increased levels of both Cu and Al in the testes as well as increased Al in the pituitary gland. Rats on the low Zn + Al diet had reduced pituitary gland Zn and Cu. Al supplementation to either the Zn or Cu suboptimal diets was associated with decreased activity of testicular ALP. However, the activities of other testicular enzymes, which were reduced in animals fed low Cu or Zn diets, were normal when Al was also given. Low Cu + Al was associated with an increase in plasma testosterone. The low Cu diet was associated with increased plasma LH levels, but levels were normal when Al was also given (Liu and Stemmer, 1990a).

10. The bioavailability of low levels of Al in drinking water at variable concentration and pH to male Sprague-Dawley rats, and the effects on tissue Cu, Fe and Zn levels were evaluated in a study reported by (Fulton *et al*., 1989). Animals were given free access to drinking water containing $Al(OH)_3$ or $AlCl_3$ dissolved to 0, 0.1, 2.0 or 100 mg/l Al, in either 4 mM acetate, pH 3.2 (A), 4 mM citrate, pH 2.6 (C), 4 mM citrate, pH 7.0 (7C) or distilled water, pH 7.0 (W), for 10 weeks (N.B. there was no 100 mg/l 7C group). The 100 mg/l Al dose was calculated by the authors as equivalent to an intake of 5.5 mg/kg bw/day Al. Intake from food was ~ 6 mg/kg bw/day (thus total Al intake in Al 100 mg/l group would be ~ 12 mg/kg bw/day). Al was significantly increased in intestine in the W, A and C 100 mg/l groups. The increase was Al-dose-dependent in the C group. No consistent differences in Al content were seen in other tissues (tibia, liver, brain, kidney, blood). Intestinal Cu levels were significantly reduced in the 100 mg/l W group with a trend to decreased levels in the A and C groups. The authors stated that no effects were seen on Cu levels in other tissues (data not shown).

11. (Fulton and Jeffery, 1990) reported that administration to male New Zealand rabbits of Al in drinking water (100 or 500 mg/l Al, as chloride, with or without 0.11M citrate or 0.11M ascorbate, for 12 weeks did not affect tissue levels of Cu.

Aluminium & Zinc

Humans

Acute/ sub-acute studies

12. Supplementation of the intake of 8 healthy adult men for 20 days with 125 mg/day Al (~ 2 mg/kg bw/day Al, as lactate), described as representative of the upper

limit of Al present in the American diet, had no overall effect on Zn retention by these subjects (Greger and Baier, 1983).

Animals

Effect of Zn status on the effects of Al supplementation

Acute/ sub-acute studies

13. (McNall and Fosmire, 1996) reported that dietary Zn deficiency did not significantly affect Al concentrations in brain or other tissues. Male Sprague-Dawley rats were fed Zn-deficient or Zn-adequate diets (2 or 30 mg/kg diet Zn, ~ 0.1 or 1.5 mg/kg bw/day Zn, respectively, as carbonate) with or without 500 mg/kg di*et al* (~ 25 mg/kg bw/day Al, as hydroxide hydrate) for 28 days. Rats on the low-Zn diet showed overt signs of Zn deficiency. Zn deficiency did not significantly affect Al concentrations in various tissues tested (tibia, liver, kidney, cerebrum, cerebellum, midbrain, hippocampus) and did not result in greater sensitivity to dietary Al exposure. The authors noted that Al supplementation of Zn-adequate diets was associated with decreased Zn concentrations in the cerebella, cerebra and whole brain.

Sub-chronic/ chronic studies

14. Addition of Al to the diet (1000 ppm Al acetate, ~ 50 mg/kg bw/day Al acetate) for 120 days was associated with reduced levels of testicular damage in male Sprague-Dawley rats fed a Zn-deficient (10 ppm) diet. The authors noted that they did not know the mechanistic basis for this effect (Liu and Stemmer, 1990b).

15. Male Sprague-Dawley rats were fed semi-purified diets low in Cu (0.5 ppm, ~ 0.03 mg/kg bw/day) or Zn (2 ppm, ~ 0.1 mg/kg bw/day) with or without supplemental Al (1000 ppm, ~ 50 mg/kg bw/day Al, formulation not stated) for 10 weeks. Optimal nutrient groups were fed the semi-purified diet with Cu (7.5 ppm, ~ 0.38 mg/kg bw/day) and Zn (38 ppm, ~ 1.9 mg/kg bw/day) added to the drinking water, with or without supplemental Al (as above). Rats fed a low Cu diet + Al showed increased levels of both Cu and Al in the testes as well as increased Al in the pituitary gland. Rats on the low Zn + Al diet had reduced pituitary gland Zn and Cu. Al supplementation to either the Zn or Cu suboptimal diets was associated with decreased activity of testicular ALP. However, the activities of other testicular enzymes, which were reduced in animals fed low Cu or Zn diets, were normal when Al was also given. Low Cu + Al was associated with an increase in plasma testosterone. The low Cu diet was associated with increased plasma LH levels, but levels were normal when Al was also given (Liu and Stemmer, 1990a).

16. Male Sprague-Dawley rats were maintained on a purified experimental diet containing sub-optimal levels of either Cu (2 ppm, ~ 0.1 mg/kg bw/day), Zn (10 ppm, ~ 0.5 mg/kg bw/day), Fe (5 ppm, ~ 0.25 mg/kg bw/day) or Mg (100 ppm, ~ 5 mg/kg bw/day), or optimal levels of all these nutrients (Cu, 8 ppm, ~ 0.4 mg/kg bw/day; Zn, 40 ppm, ~ 2 mg/kg bw/day; Fe, 35 ppm, ~ 1.8 mg/kg bw/day; Mg, 400 ppm, ~ 20 mg/kg bw/day), with or without the addition of 0.1% Al (~ 50 mg/kg bw/day Al, as acetate), for 120 days. In animals which were substantially deficient in Zn, Cu, Fe, or Mg the addition of Al had varying effects on catecholamines in some regions of the central nervous system (Wenk and Stemmer, 1981).

17. (Wenk and Stemmer, 1982) reported that Al (0.1% Al in the diet, ~ 50 mg/kg bw/day Al, as acetate, for 120 days) restored activities of the enzymes dopamine-beta-hydroxylase and phenylethanolamine-N-methyltransferase in the brains of male Sprague Dawley rats fed a Zn-deficient (10 ppm, ~ 0.5 mg/kg bw/day Zn) diet. Addition of Al acetate to rat brain homogenate in vitro did not affect the activities of these enzymes.

18. The same authors also examined the relationship between Zn status and Al concentration in brain regions. Male Sprague-Dawley rats were maintained on a purified experimental diet containing sub-optimal levels of either Cu (2 ppm, ~ 0.1 mg/kg bw/day), Zn (10 ppm, ~ 0.5 mg/kg bw/day), Fe (5 ppm, ~ 0.25 mg/kg bw/day) or Mg 100 ppm, ~ 5 mg/kg bw/day), or optimal levels of all these nutrients (Cu, 8 ppm, ~ 0.4 mg/kg bw/day; Zn, 40 ppm, ~ 2 mg/kg bw/day; Fe, 20 ppm, ~ 1 mg/kg bw/day; Mg, 400 ppm, ~ 20 mg/kg bw/day), with or without the addition of 0.1% Al (~ 50 mg/kg bw/day Al, as acetate), for 120 days (Wenk and Stemmer, 1983). Rats fed the low Zn+Al diet showed significant increases in brain Al levels (cortex, hippocampus, cerebellum) compared with rats in the low Zn group. The authors concluded that “these findings suggest that Al may accumulate in the brain, if it is available in elevated levels in the environment, when Zn... intake is compromised”. However, it is not possible to evaluate the effect of low Zn on Al uptake in these studies, as results for optimal diet+Al were not given.

Effects of Al supplementation on Zn uptake/status

Acute/ sub-acute studies

19. (Ecelbarger and Greger, 1991) reported effects of dietary citrate (various levels) and Al (~ 10 or 1000 mg/kg di*et al*, ~ 0.5 or 50 mg/kg bw/day Al, as hydroxide) supplementation for 28 days on male Sprague-Dawley rats. Al had no significant effect on tissue Zn levels, but reduced apparent absorption (intake - faecal loss) of Zn.

20. When diets were only marginally adequate in Cu (1.9 mg/kg diet, ~ 0.1 mg/kg bw/day), Zn (12.5 mg/kg diet, ~ 0.6 mg/kg bw/day), and Fe (16.2 mg/kg diet, ~ 0.8 mg/kg bw/day), supplementation of the diets of male Sprague-Dawley rats with Al (5-272 mg/kg di*et al*, ~ 0.25-13.6 mg/kg bw/day Al, as the lactate, palmitate, phosphate or hydroxide, for 18 days) was associated with reduced tibial Zn concentrations. However, when diets contained higher levels of Cu (7.1 mg/kg diet, ~ 0.36 mg/kg bw/day), Zn (20.7 mg/kg diet, ~ 1 mg/kg bw/day) and Fe (31 mg/kg diet, ~ 1.6 mg/kg bw/day), Al supplementation was associated with reduced liver Cu levels. The authors remarked that other investigators have also noted that dietary Al sometimes, but not consistently caused alteration in tissue Zn and Cu levels (*refs cited* in (Greger *et al*., 1985), but that the reason for these inconsistencies is not known (Greger *et al*., 1985).

Sub-chronic/ chronic studies

21. Feeding diets supplemented with 4000 ppm Al (~ 600 mg/kg bw/day Al, as $AlCl_3.6H_2O$) +/- ethanol to male ICR mice for 58 days resulted in significantly decreased serum Zn (Sugawara *et al*., 1987).

22. Dietary supplementation with Al (up to ~ 6 mg/kg bw/day, in drinking water; maximum total Al in the diet ~ 12 mg/kg bw/day) at variable pH, +/- citrate, for 10 weeks, was reported to have no effect on tissue Zn levels in male Sprague-Dawley rats (although data were not given) (Fulton *et al*., 1989). Further details of this study are described in the section on Al&Cu.

23. (Fulton and Jeffery, 1990) reported that administration to male New Zealand rabbits of Al in drinking water (100 or 500 mg/l Al, as chloride, with or without 0.11M citrate or 0.11M ascorbate, for 12 weeks, did not affect tissue levels of Zn.

Aluminium & Iron

Effects of Al on Fe kinetics and metabolism

Humans

Acute/ sub-acute studies

24. Al has been reported to have a negative effect on Fe uptake or availability in EPO-treated dialysis patients (Kooistra *et al*., 1998; Donnelly *et al*., 1990). In 8 healthy adult males, supplementation for 20 days with 125 mg/day Al (~ 2 mg/kg bw/day Al, as lactate), described as representative of the upper limit of Al present in the American diet, had no overall effect on Fe retention (Greger and Baier, 1983).

Animals

Acute/ sub-acute studies

25. (Ecelbarger and Greger, 1991) reported effects of dietary citrate (various levels) and Al (~ 10 or 1000 mg/kg diet, ~ 0.5 or 50 mg/kg bw/day, as hydroxide) supplementation for 28 days on male Sprague-Dawley rats. Al had no significant effect on tissue Fe levels, but significantly reduced apparent absorption (intake - faecal loss) of Fe.

26. (Greger *et al*., 1985) reported that supplementation of the diets of male Sprague-Dawley rats with Al (5-272 mg /kg di*et al*, ~ 0.3-13.6 mg/kg bw/day Al, as lactate, palmitate, phosphate or hydroxide), for 18 days, did not affect tissue levels of Fe.

27. Groups of White Leghorn cockerels were treated, for 3 weeks, with diets containing Fe (as $Fe_2(SO_4)_3$ – 0.006% Fe [low]; 0.014% Fe [sufficient]; 0.045% Fe [high]) and/or Al (as $AlCl_3$-$6H_2O$, 0.15% or 0.3% Al), as follows:
i. Fe-sufficient (control diet)
ii. 0.15% Al
iii. 0.3% Al
iv. high Fe
v. 0.15% Al + high Fe
vi. 0.3% Al + high Fe
vii. low Fe
Ferritin and non-haem Fe levels were measured in kidney, liver and intestinal mucosa. The high Fe diet resulted in increased levels of non-haem Fe in all 3 organs. There

was no effect of Al on non-haem Fe in the kidney. However, compared with 0 or 0.15% Al, inclusion of 0.3% Al in both the control and high-Fe diets resulted in significantly lower non-haem Fe levels in liver and intestinal mucosa. This effect was greatest in the high-Fe/0.3% Al diet, where intestinal mucosal Fe was reduced by ~ 80% compared with the high-Fe di*et al*one. Ferritin levels were reported to be reduced in all tissues by Al. The authors concluded that dietary Al can inhibit Fe absorption and disrupt the regulation of tissue ferritin levels by Fe in the growing chick (Han *et al*., 2000).

Sub-chronic/ chronic studies

28. Feeding diets supplemented with 4000 ppm Al (~ 600 mg/kg bw/day Al, as $AlCl_3.6H_2O$), with or without ethanol, to male ICR mice for 58 days did not affect serum Fe levels (Sugawara *et al*., 1987).

29. (Morgan and Redgrave, 1998) noted that citric acid has been shown to increase the absorption of both Fe and Al and, thus, it is hypothetically possible that the consumption of a diet rich in citric acid, with simultaneous consumption of high amounts of Al and Fe, could lead to a situation with the potential to exacerbate the toxic properties of both metals. Studies were carried out to evaluate whether varying dietary citrate, Al and Fe levels affected Fe uptake and metabolism. Male Wistar rats were fed diets, for 9-11 weeks, which were Fe-deficient (0.15 mmol/kg diet Fe, ~ 0.42 mg/kg bw/day Fe, as ferrous ammonium citrate), Fe-sufficient (1.4 mmol/kg diet Fe, ~ 3.9 mg/kg bw/day Fe, as ferrous ammonium citrate) or Fe-loaded (360 mmol/kg diet Fe, ~ 1001 mg/kg bw/day Fe, as carbonyl Fe), with or without the addition of sodium citrate (120 mmol/kg diet) and/or $AlCl_3.6H_2O$ (120 mmol/kg diet, ~ 162 mg/kg bw/day Al). Al and/or citrate supplementation did not affect nonhaem Fe concentrations in liver, kidney or brain, nor the uptake of i.v. ^{59}Fe or of ^{125}I-Tf by liver, kidney, brain or spleen. Al supplementation was associated with increased ^{59}Fe uptake in femur. Fe-deficient and, to a greater extent, Fe-loaded diets were associated with impaired growth rate, and this effect was exacerbated by supplemental Al (both groups) and/or citrate (Fe-loaded). (Al supplementation of the Fe-sufficient diet was not associated with reduced growth rate). The most marked effect on growth rate occurred when Al was added to the Fe-loaded diet, in the absence of citrate. The authors noted that this could not be explained by variations in the palatability of the diets and that it was more likely due to the toxic effects of Al+Fe, either in the intestine or within the body after absorption. They also suggested that citrate, by chelating Al and/or Fe, may reduce the level of toxic effects produced by these metals.

30. Female Wistar rats were used to study potential adverse effects of Al administration on parameters of Fe status and metabolism and to evaluate whether simultaneous administration of Fe could prevent these effects. For a 35 day period, rats were given (p.o.) 100 mg/kg bw/day Al (as $AlCl_3$, pH 2-3) and/or 4 mg/kg bw/day Fe (as $FeCl_2$). A control group was treated with 0.9% NaCl (pH 2-3). On days 7, 14, 21, 28 and 35, concentrations of Fe in blood, serum, erythrocytes, spleen, liver and kidney, and serum levels of free erythrocyte protoporphyrins (FEP) and Al were determined. Animals treated with Al alone, but not Al+Fe, showed significantly increased serum Al concentrations. Al administration was associated with significantly increased serum FEP and decreased spleen Fe concentrations; these effects were both attenuated by co-administration of Fe. The authors noted a high

correlation between changes in Fe and FEP concentrations in relation to accumulated Al dose (Nasiadek and Chmielnicka, 2000).

31. (Golub *et al*., 1996) reported that high dietary maternal Al (1000 mg/kg di*et al*; ~ 50 mg/kg bw/day Al, formulation not specified) during gestation and lactation did not affect Fe and Mn concentrations in milk, nor the absorption or tissue distribution of these elements in nursing NIH Swiss Webster, Harlan Sprague Dawley [*sic*] mouse pups, but lowered the ability of the pups to retain absorbed Fe and Mn by ~ 10% compared with controls. In their discussion the authors noted that the results of these and other studies did not support the likelihood that this effect was due to either 1] elevated body burden of Al in nursing pups or 2] competition of Al with Fe and Mn for serum Tf transport. They suggested that it is possible that Al-Tf may interfere with cellular Fe and Mn uptake.

32. The bioavailability to male Sprague-Dawley rats of low levels of Al in drinking water at variable concentration and pH, and the effects on tissue Fe, Cu and Zn levels were evaluated in a study reported by (Fulton *et al*., 1989). Animals were given free access to drinking water containing $Al(OH)_3$ or $AlCl_3$ dissolved to 0, 0.1, 2.0 or 100 mg/l Al, in either 4 mM acetate, pH 3.2 (A), 4 mM citrate, pH 2.6 (C), 4 mM citrate, pH 7.0 (7C) or distilled water, pH 7.0 (W), for 10 weeks (there was no 100 mg/l 7C group). 100 mg/l Al was calculated by the authors as equivalent to an intake of 5.5 mg/kg bw/day Al. Intake from food was ~ 6 mg/kg bw/day (thus total Al intake in Al 100 mg/l group would be ~ 12 mg/kg bw/day). Al was significantly increased in intestine in the W, A and C 100 mg/l groups. The increase was Al-dose-dependent in the C group. No consistent differences in Al content were seen in other tissues (tibia, liver, brain, kidney, blood). Intestinal Fe levels were significantly reduced in all 100 mg/l, as compared with 0 mg/l, Al groups. Blood and liver Fe levels reportedly did not vary between treatment groups (data not shown).

33. (Fulton and Jeffery, 1990) reported that administration to male New Zealand rabbits of Al in drinking water (100 or 500 mg Al/l, as chloride, with or without 0.11M citrate or 0.11M ascorbate) for 12 weeks did not affect tissue levels of Fe, or haemoglobin and haematocrit values.

Effects of Fe status and haematological parameters on Al kinetics and metabolism

Humans

34. Some clinical studies have shown a negative relationship between serum ferritin, Fe or Tf saturation and serum Al concentrations in dialysis patients (Cannata *et al*., 1985; D'Haese *et al*., 1990; Huang *et al*., 1992; Cannata *et al*., 1993). One report described increased Al excretion rates in renal failure patients with low serum ferritin, suggesting increased intestinal Al absorption (Lin *et al*., 1995). Conversely, (Blaehr *et al*., 1986) reported that dialysis patients given Al-containing phosphate binders with ~ 60 mg/day Fe (as Ferrofumarate solution) for 3 months tended to show higher serum Al levels than patients not receiving Fe (although the difference was not statistically significant).

Animals

Sub-chronic/ chronic studies

35. (Cannata *et al*., 1991) reported that Fe-deficiency was associated with increased Al absorption in rats. Groups of male Wistar rats were either Fe-loaded (Group 1: i.p. administration of 5 mg Fe dextran/48 hr plus 254 mg/kg diet Fe, ~ 12.7 mg/kg bw/day Fe), untreated (Group 2: 254 mg/kg diet Fe, ~ 12.7 mg/kg bw/day Fe), or Fe-depleted (Group 3: weekly removal of 2.5-3 ml blood, 166 mg/kg diet Fe, ~ 8.3 mg/kg bw/day Fe) (dietary Fe formulation not stated) for 1 month prior to, and continuing through 30 days of Al treatment (13.85 mg/day Al, as $Al(OH)_3$, in drinking water, ~ 34.5 mg/kg bw/day Al). Half (7/14) of the rats in Group 3 died during the last 10 days of the study. Microhaematocrit (Mh), blood and urinary Al concentrations were measured on days 0, 15 and 30, brain Al was measured on day 30. Group 3 showed a decrease in mean Mh during the study period. Urinary Al in Group 3 was increased at all time points, as compared with Groups 1 and 2, but no consistent patterns were seen with serum Al. As compared with control Group 2, brain Al was increased in Group 3, and decreased in Group 1 (which showed similar brain Al levels to untreated laboratory control rats). Single-dose Al absorption studies (50 mg/kg bw Al, as $AlCl_3$) were carried out on rats rendered uraemic by partial nephrectomy and then pretreated as described for Groups 1-3 above. AUC (area under the curve) values were inversely related to Fe-loading status. The authors concluded that Al and Fe "may share common metabolic routes and each may regulate the uptake of the other".

36. (Ittel *et al*., 1996) also carried out studies to evaluate the influence of Fe status on intestinal Al absorption in both normal renal function (NRF) and partially nephrectomised (Nx) rats. Al absorption was evaluated using single-dose studies, and in dietary supplementation and *in situ* organ perfusion studies. Male Sprague-Dawley rats were pre-treated for 4 weeks with diets which were Fe-deficient (6 mg/kg diet Fe, ~ 0.3 mg/kg bw/day Fe) or Fe-sufficient (200 mg/kg diet Fe, ~ 10 mg/kg bw/day Fe). Fe-overload in rats on the standard diet was achieved by i.m. injection of 50 mg Fe (as dextran) every 3-5 days during the pre-treatment period. (Fe formulation in the diet was not specified). Haematological and Fe-status parameters were significantly altered by Fe-loading and depletion. In the first experiment, the kinetics of a single oral (gavage) test dose of 11 mg Al (as $AlCl_3$) were evaluated. Al serum concentrations and excretion rates were higher in Nx than NRF rats, but were not affected by Fe status in either group. Mucosal Al concentrations at 24h post-administration were also not affected by Fe status. In the second experiment, Fe status (achieved as described above, followed by maintenance on the low-Fe diet) did not affect Al concentrations in liver or bone (increased in all Al-loaded groups), following dietary Al loading (8 g/kg di*et al*, ~ 400 mg/kg bw/day Al, as $Al(OH)_3$ plus 1.25 g/l Al, ~ 62.5 mg/kg bw/day Al, as lactate in deionised drinking water; total Al supplement ~ 462.5 mg/kg bw/day) for 41 days. Spleen Al was significantly higher in Fe-loaded than Fe-depleted rats (NRF and Nx groups). Comparable results were obtained with *in situ* intestinal perfusion studies. The authors concluded that the results of these studies refute the hypothesis that Fe deficiency facilitates increased Al uptake. To the contrary, they noted that when they performed a single-dose study on control rats (NRF, normal body Fe stores), co-administration of $AlCl_3$ and $FeCl_3$ resulted in increased Al excretion as compared to administration of $AlCl_3$ (with NaCl).

Aluminium & Manganese

37. Male Wistar rats were fed low Ca or low Ca-Mg diets (low Ca, 30 mg/kg diet, ~ 1.5 mg/kg bw/day; low Mg, 20 mg/kg diet, ~ 1 mg/kg bw/day), with or without added Al (1940 mg/kg di*et al*, ~ 97 mg/kg bw/day Al, as lactate) for 90 days. Al supplementation did not alter serum Al levels. The low Ca-Mg diet with or without Al was associated with increased Al levels in various tissues. The low Ca-Mg + Al diet was associated with significantly increased bone Al and Mn levels. Mn in the frontal cortex increased in the low Ca-Mg groups with or without Al supplementation (Yasui *et al*., 1995).

38. (Golub *et al*., 1996) reported that high dietary maternal Al (1000 mg/kg diet; ~ 50 mg/kg bw/day Al, formulation not stated) during gestation and lactation did not affect Fe and Mn concentrations in milk, nor the absorption or tissue distribution of these elements in nursing NIH Swiss Webster, Harlan Sprague Dawley [*sic*] mouse pups, but lowered the ability of the pups to retain absorbed Fe and Mn, by ~ 10% compared with controls. In their discussion the authors noted that the results of these and other studies did not support the likelihood that this effect was due to either 1] elevated body burden of Al in nursing pups or 2] competition of Al with Fe and Mn for serum Tf transport. They suggested that it is possible that Al-Tf may interfere with cellular Fe and Mn uptake.

39. (Nielsen *et al*., 1988) investigated the effects of diets containing varying levels of Al, B, Mg and Mn, fed to male Sprague-Dawley rats for 7 weeks. These elements were added to the basal diet as follows; Al (0 or 1000 mg/kg diet, ~ 0 or 50 mg/kg bw/day, as chloride), B (0 or 3 mg/kg diet, ~ 0 or 0.15 mg/kg bw/day, as boric acid), Mg (100, 200 or 400 mg/kg diet, ~ 5, 10 or 20 mg/kg bw/day, as acetate), Mn (20 or 50 mg/kg diet, ~ 1 or 2.5 mg/kg bw/day, as manganous acetate). Effects on body and organ weights, haematological parameters and femur mineral contents were determined. With respect to interactive effects of Al and Mn, it was observed that:
i) Plasma Mg was significantly depressed by high dietary Al when the Mn supplement was 50 mg/kg diet, but not when it was 20 mg/kg diet.
ii) Growth was more markedly depressed by high dietary Al in B-supplemented rats when the Mn supplement was 20, rather than 50, mg/kg diet.
The authors concluded that the effect of dietary Mn on the response to high dietary Al was “more than just Al interfering with Mn metabolism or utilisation or vice versa”. They suggested that interactions between the 4 elements tested occur because of changes in membrane or endocrine function, although they noted that this study did not provide any direct evidence for this hypothesis.

40. (Garruto *et al*., 1989) investigated the chronic neurotoxic effects of dietary Al and Mn supplementation in juvenile cynomolgus monkeys. Six animals were maintained on a low calcium (0.32%) diet for 41 to 46 months. Four of these 6 animals were also given supplemental Al (150 mg/day, as chloride) and Mn (50 mg/day, as chloride) in the diet; of these, 2 monkeys were also given diets containing flour prepared from unwashed seed of *Cycas circinalis*. No behavioural changes or neurological deficits were observed during the study period. Histological analysis after killing showed abnormalities in motor neurons of the spinal cord, brain stem, substantia nigra and motor cortex of all monkeys on the low Ca diet, but not in control animals fed a standard diet. The authors noted that lesions appeared to be most abundant in animals on the low Ca/high Al+Mn diet (although differences between the 3 groups were not significant). One of these 2 animals also showed Al deposition

in the spinal cord. The authors concluded that Ca deficiency could potentiate the toxicity of otherwise normal dietary levels of Al and Mn.

Annex 2 - Interactions of Lead

Lead & Aluminium

41. See above.

Lead & Copper

42. Pb and Cu content of human milk appear to be inversely related (Kies and Umoren, 1989). The basis for this interaction has not been established. Experimental studies showed that Pb exposure significantly decreased hepatic Cu in rats (Dhawan *et al*., 1995), that rodents with Pb toxicity showed reduced plasma Cu and caeruloplasmin levels (Petering, 1974, cited by (Goyer, 1997), whilst the addition of dietary Pb to Cu-deficient animals reduced growth rate (Petering, 1978).

43. Haematopoiesis is depressed in animals with low dietary Cu and is further depressed by Pb exposure (Klauder and Petering, 1975). Pb inhibits the activity of ferrochelatase, an Fe-containing enzyme which is necessary for the incorporation of Fe into haemoglobin. Activity can be restored in vitro by the addition of Cu (Tephly *et al*., 1978).

Lead & Zinc

43. Experimental studies in rats showed that Zn deficiency enhances Pb absorption (cited by (Goyer, 1995)) and Pb increases Zn excretion (Victery *et al*., 1987). Blood Pb levels have been inversely correlated with the activity of Zn-dependent haem enzymes, particularly δ-aminolevulinic acid dehydratase (δ-ALAD), suggesting that Pb replaces Zn in these enzymes. In vitro studies have shown that Zn can reverse the inhibition of δ-ALAD by Pb (Border *et al*., 1976) and oral administration of Zn following Pb-chelation therapy can increase δ-ALAD activity significantly (Dutkiewicz *et al*., 1979).

44. Metallothionen may attenuate Pb-induced inhibition of δ-ALAD in rats (Goering and Fowler, 1987), and it has been suggested that a MT-like protein in erythrocytes may bind Pb, protecting against toxicity (Church *et al*., 1993).

Lead & Iron

45. Studies in animals have shown that Fe deficiency is associated with increased Pb absorption from the GI tract (Six and Goyer, 1972; Klauder and Petering, 1975). A study of pre-school children in the USA showed a negative relationship between dietary Fe intake and blood Pb levels (Hammad *et al*., 1996). The mechanism by which Pb and Fe absorption may be interrelated is not known. (Robertson and Worwood, 1978) reported that there appeared to be no direct relationship between the transfer of Fe and Pb across the small intestine of the adult rat. It has been suggested that Pb competes with Fe for intestinal ferritin binding sites (cited by (Goyer, 1997). Evaluation of the inter-relationship between Fe deficiency and Pb toxicity, in terms of

impaired cognitive and behavioural development, is complicated by the fact that both Fe deficiency and excess Pb exposure may impair early mental development.

Lead & Manganese

46. No data were identified regarding interactive effects of orally administrated Pb and Mn.

Annex 3 - Interactions of essential metals – Copper, Zinc, Iron, Manganese

47. Data relevant to interactions of Fe, Cu, Zn and Mn have been reviewed extensively in recent reports prepared for the UK EVM (Cu, 1999 ; Mn, 1999; Zn, 1999; Fe, 2000, full reports available at http://www.foodstandards.gov.uk/). Relevant sections are reproduced below. Titles in italics describe the section of the specific EVM report from which the data are taken. Details of cited references are not included in the reference list of this report, but can be found in the EVM reports. In addition, database searches have been carried out and any relevant data which are not covered in the EVM reports are described separately at the end of each of section.

48. Studies relevant to interactions of Cu, Zn, Fe and Mn with Al and Pb are described in Appendices 1 and 2.

Copper & Zinc

EVM Cu review

Interactions with Zn

49. "Zinc and copper can interact, with high concentrations of one element inhibiting the absorption of the other (Lönnerdahl *et al.*, 1996). Both elements have similar electron configurations and form similar co-ordination complexes in aqueous solution, thereby competing for absorptive pathways (Hill and Matrone, 1970). The mechanism behind the zinc-copper interaction in the small intestine was studied by Hall *et al.*, (1979). They found that high dietary zinc induced intestinal metallothionein and proposed that this metallothionein could act as a "trap" for absorbed copper. This theory has been supported by the findings of Fischer *et al.*, (1983), who found a correlation between the decrease in copper absorption and the appearance of intestinal metallothionein…..

"Several studies in humans have failed to detect a significant effect of increased zinc intake on copper absorption when intakes are within the normal range (August *et al.*, 1989). However, when pharmacological doses of zinc are given, copper absorption is significantly reduced, and such high doses of zinc are often administered in the treatment of Wilson disease (Brewer *et al.*, 1983)…..

"Infants may be more sensitive to changes in the ratio of zinc to copper in their diet. Salim *et al* (1986) found that infants receiving copper-supplemented formula had lower plasma zinc concentrations, although these were still within the normal range."

Absorption and bioavailability

50. " [Cu] Transport across the brush border of the intestine is probably by diffusion, whereas transfer across the basolateral membrane is energy dependent, or carrier mediated, and is a competitive process with other transition metal ions, such as zinc and iron."

Human supplementation studies

51. "As part of a double-blind study of back pain management, 14 adult volunteers received a supplement of 10 mg/day copper as copper gluconate for 12 weeks or a placebo (Pratt *et al.,* 1985). There was no increase in the levels of copper, zinc or magnesium in serum, urine or hair. Haematocrit, triglyceride, SGOT< GGT, LDH and cholesterol levels were no significantly affected by treatment. The side effects of nausea, heartburn and diarrhoea were the same in the treatment and placebo groups. The authors concluded that the results supported the view that excess copper was excreted and homeostasis maintained in non Wilson's disease subjects."

EVM Zn review

Analysis of Zn status

52. "In a study by Davis *et al.* (2000) conducted on a metabolic ward, 25 healthy post menopausal women were fed diets containing low (1 mg/day) or high (10 mg/day) copper for 180 days. For one 90 day period, the women were given a supplement of 50 mg/day zinc, for the other 90 days a placebo. The basal diet contained 3 mg/day zinc. Zinc supplementation significantly increased extracellular but not erythrocyte superoxide dismutase activity. The effect was more apparent when the subjects received the low copper diet. Zinc supplementation of the low copper di*et al*so resulted in an increase in amyloid precursor protein in platelets. Zinc supplementation also resulted in an increase in plasma zinc, free thyroxine and mononuclear 5' nucleotidase activity."

Zn-Cu interaction

53. "A mutual antagonism exists between copper and zinc in terms of uptake. This can be explained by similarities in electronic configuration in that both are *d*10 ions. As a consequence, imbalances may occur because of either deficient or excessive copper intake, or excessive intake of zinc relative to copper. Here, the negative effect of excessive zinc upon copper absorption will be considered….

"Hall *et al.* (1979) found that high levels of dietary zinc in the rat induced the synthesis of intestinal metallothionein. Fischer *et al.* (1983) went on to show that a decrease in copper absorption correlated with the appearance of intestinal metallothionein. Since metallothionein has a greater affinity for copper than zinc, it was suggested that copper could displace zinc and that the metallothionein acted as a trap to sequester copper within the epithelial cell. The entry of copper to the body is therefore controlled, at least in part, by metallothionein. When the mucosal cells are rich in metallothionein, little copper traverses the cells in to the body but is returned to the intestinal lumen with the turnover of mucosa cells…

"Studies in both humans and animals (Sandstead, 1982; Greger *et al.* 1978; Burke *et al.* 1981; Hall *et al.*, 1979) have demonstrated that elevated levels of dietary zinc can have a negative effect upon copper balance. Furthermore, the amount of copper required to maintain balance is directly related to the amount of dietary zinc….

"In a study by Milne *et al.* (2001) 21 healthy post-menopausal women, housed in a metabolic unit, were fed diets containing 2 mg copper and 9 mg zinc for 10 days. They were then divided into two groups, and fed diets containing either 1 or 3 mg copper. After equilibriation, the groups were fed a diet containing 3 mg zinc for 90 days. This was followed by another equilibriation period, following which the dietary zinc content was raised to 53 mg/day. The women were in positive copper status only when the diet contained 53 mg zinc and 3 mg copper. Immunoreactive ceruloplasmin concentrations and platelet cytochrome c oxidase activity on a platelet number basis were significantly lower and the ratio between enzymatic and immunoreactive ceruloplasmin significantly higher when the subjects received low rather than high dietary zinc. The authors concluded that low rather than high dietary zinc was more effective in inducing the changes associated with decreased copper status in postmenopausal women. Whole blood glutathione concentration and erythrocyte glutathione peroxidase activity were lower during the high than during the low zinc intake."

Toxicity following massive ingestion

54. "Several cases of chronic massive zinc supplement abuse have been associated with the development of sideroblastic anaemia... . One case (Simon *et al.*, 1988) reported copper deficiency and sideroblastic anaemia following an ingestion of an alleged 26.6-40 mg zinc per day for 2 years... . Another case reported by Botash *et al.* (1992) concerned a 13 month old girl (body weight 8.6 kg) who had been prescribed zinc (26 mg/day for 7 months) prophylactically from the age of 6 months."

Toxicity – chronic and sub-chronic effects due to zinc-induced copper deficiency

55. "The non-acute effects of zinc are more a consequence of zinc-induced copper deficiency, due to the antagonistic effects of zinc on copper uptake... . Attendant effects of zinc-induced copper deficiency have included hypocupraemia, sideroblastic anaemia, leukopenia, neutropenia, decreased erythrocyte superoxide dismutase (ESOD), decreased ceruloplasmin, decreased cytochrome c oxidase, increased plasma cholesterol, increased LDL:HDL cholesterol, decreased glucose clearance, decreased methionine and leucine enkephalins, abnormal cardiac function and impairment of pancreatic enzymes, amylase and lipase (Walsh *et al.*, 1994; Sandstead 1995 and references there in)."

56. The metabolic consequences of Zn-induced Cu deficiency are discussed in more detail in the EVM report.

LOAELs for Zn-induced Cu deficiency

57. "The studies outlined below demonstrate that relatively modest levels of zinc supplementation can cause adverse effects, primarily due to decreased copper status:

"Twelve healthy men (23-25 years) given 160 mg zinc daily (as sulphate, taken with meals) showed a 25% reduction ($p<0.001$) in HDL-cholesterol levels after 5 weeks, but there was no effect on total cholesterol, LDL-cholesterol, or triglyceride. Near baseline values were restored 11 weeks after the cessation of treatment. Plasma copper was not decreased throughout (Hooper *et al.*, 1980). The amounts of zinc and copper provided by food and beverages were not stated…

"Male subjects (19-29 years) supplemented with 50 or 75 mg zinc daily (as gluconate, consumed after breakfast with water) for 12 weeks, showed decreases in HDL cholesterol (~ 14%, $p=0.04$, n=9-13) at both 6 and 12 weeks in the higher dose group and at week 12 in the lower dose group. However, at week 8, levels of HDL cholesterol in both treated groups were actually higher than those in the placebo control group. Serum copper levels were not altered. The amount of zinc provided by food and beverages ranged between ~ 9-13 mg/day. The amount of copper and zinc provided by food and beverages was 2.1, 1.8 and 1.7 mg/day and 12.6, 14.1 and 9.8 for placebo, 50 mg and 75 mg zinc supplement groups, respectively (Black 1988)…

"Twenty six healthy males, provided with a daily zinc supplement of 50 mg, taken as two doses (as gluconate, morning and night), for 6 weeks, exhibited elevated plasma zinc levels ($p<0.05$) and decreased ESOD activity (maximally ~ 20%, <0.05). Plasma copper and ceruloplasmin activity were not affected (Fischer 1984). The amount of zinc and copper provided by food and beverages was not stated….

"Females (25-40 years) given supplements of zinc gluconate capsules (25 mg zinc twice daily for 10 weeks) developed significant reductions (~50%, 5% and 30%, respectively, compared with pretreatment levels, $p<0.05$, n=18) in ESOD activity, haematocrit, and serum ferritin. Effects on ferritin and haematocrit but not ESOD were ameliorated with equal (mg for mg) iron supplementation (Yadrick 1989). The amount of zinc and copper provided by food and beverages was not stated….

"Zinc capsules (50 mg daily, in the form of sulphate, type available OTC, taken with breakfast) caused a significant 20 % decrease ($p<0.02$) in ESOD in 6 healthy female volunteers (age range 18-36 years), after 12 days. Dietary zinc was estimated as 9-12 mg/day (Abdallah and Samman, 1993). Copper intake was not stated…..

"Cunningham (1994) reported 45% and 20% increases ($p<0.001$) in HbA1c in insulin dependent diabetes mellitus (IDDM) patients (n=14, 18-37 years) and non- DDM individuals (n=15, 23-38 years), respectively, following supplementation with 50 mg/day zinc (as the gluconate) for 28 days, suggesting glycosylation becomes altered in a milieu of zinc excess. In this study, plasma and erythrocyte copper did not differ significantly from baseline levels…..

"Adult women of child bearing age were fed dietary regimes containing 2mg/day copper and 8, 16, or 24 mg/day zinc (as the sulphate) (n=6 or 7) for 18 day. Plasma levels of zinc and copper were increased and decreased, respectively. However, zinc had no effect on copper retention at any dose and the negative copper balance observed in each treatment group was unrelated to zinc dose (Taper *et al.*, 1980). There was no functional assessment of copper status in this study….

"Festa (1985) reported that a total zinc intake of 18.5 mg/day for 2 weeks following on from a week at a lower intake resulted in reduced apparent retention and an

increased excretion of copper. In this study, nine healthy males in their 20s consumed a basal egg-white diet that provided recommended levels of all essential nutrients, with the exceptions of zinc and protein where the diet provided 1.8mg zinc and 16.4g nitrogen daily. Copper intake was 2.63 mg/day, of which 2.5mg was in the form of copper sulphate. Zinc carbonate was added to give a total zinc intake of 20.7 mg/day (week 1), 18.5 mg/day (weeks 3,5,6,8,9), 1.8 mg/day (week 2) 1.8 or 8.0 mg/day (week 4) and 4, 6 or 8 mg/day (week 7). Mean plasma copper concentrations remained within the normal range throughout the study, but mean faecal copper excretion was elevated over copper intake in week 6. The biological significance of this result is uncertain. Negative copper balance was not repeated in week 9 and there was no measurement of any functional index of copper status…..

"However, other studies using similar doses have failed to demonstrate similar effects:

"Women (18-40 years) given 0, 15, 50 or 100 mg zinc supplements as acetate in capsules with water at the evening meal, each day for 8 weeks, showed no change in HDL cholesterol except for transient decrease at 4 weeks in the top dose group. The amounts of zinc and copper provided by food and beverages were 8.5 mg/day and 2.7 mg/day respectively (Freeland-Graves *et al.*, 1982). No functional index of copper status was measured in this study…..

"23 young men given 50 mg zinc per day (as gluconate) for 6 weeks, developed a statistically nonsignificant increase (~16%) in HDL cholesterol and decrease in total cholesterol with a significant decrease in diastolic blood pressure ($p<0.01$). Zn:Cu intake ratio was estimated to be 60:1. Haematocrit, haemoglobin and plasma copper levels were not significantly altered from baseline (Pachotikarn *et al.*, 1985)…..

"As part of a double blind crossover study, healthy females (n=26, mean 27 years) and males (n=21, mean age 28 years) were given 150 mg zinc (as sulphate) per day for 6 weeks. There were no changes in total plasma cholesterol in either males or females. However, in females, LDL cholesterol was decreased by 9% while ESOD and ceruloplasmin activities were reduced. Plasma copper and haematocrit remained unchanged. Differences between the sexes were attributed to females receiving a higher dose on a mg/kg basis (Samman and Roberts 1988). Copper intake was not stated……

"Reasons for the discrepancy are uncertain but may be attributed to differences in experimental design, age and sex of subjects and duration of study. Differences between the studies regarding zinc and copper intakes from food and beverages may have also been influential. Absence of other functional copper index measurements e.g. ESOD, in some studies preclude comparison of copper status."

Chronic toxicity

58. "Zinc-deficient patients (elderly and sickle cell anaemia patients) supplemented with
30-45 mg elemental zinc per day for several months developed neither copper deficiency nor any other observed toxic effects. However, some sickle-cell anaemia patients administered 150 mg/day in divided doses showed signs of copper deficiency (Prasad, 1993 and references therein)….

"Simon *et al.* (1988) reported the case of a 44 year old male who developed copper deficiency and sideroblastic anaemia after ingesting 26.6-40 mg zinc (as gluconate) as a non-prescribed single daily dose, usually after a light breakfast of coffee and juice, for at least two years. This subject was also taking non-prescribed large amounts of other nutrient supplements including vitamins E, A, B1, B2, and B12, niacinamide, biotin, choline, bitartrate, inositol, para-aminobenzoic acid, folic acid and pyridoxine. He was also taking prescribed L-lysine (2 g/day). Details of zinc and copper intakes from food and beverages alone were not reported. The patient had no genetic disorder that might predispose him to copper deficiency……

"Zinc deficient (on the basis of leukocyte zinc concentrations) adult sickle cell patients were supplemented with 50 –75 mg/day zinc (as zinc acetate) for up to 3 years. Following chronic supplementation, there was a significant increase in leukocyte zinc concentrations, a significant increase in IL-2 production and a significant decrease in the number of bacterial infections, hospital admissions and painful crisis (Prasad *et al.*, 1999). Plasma copper levels were unaffected by zinc supplementation. The authors speculate that the observed clinically beneficial effects of zinc supplementation may have been due to a pharmacological action of zinc rather than simply correcting intracellular zinc deficiency as IL-2 production was increased over non zinc deficient SCD controls."

Genetic variation and vulnerable groups

59. “Individuals homozygotic for haemochromatosis have increased gastrointestinal absorption of iron, cobalt and lead and there is some evidence that zinc absorption may also be increased (Adams *et al.*, 1991; Spencer *et al.* 1988). Barton and Bertioli (1997) have suggested that these people, who are largely undiagnosed, may be particularly vulnerable to zinc-induced copper deficiency if they were to take zinc supplements, for example as a cold treatment.”

Summary

60. “Prolonged use of high doses of zinc can result in secondary deficiency of copper. Symptoms of copper deficiency include hypocupraemia, impaired iron mobilisation, anaemia, leukopenia, neutropenia, decreased superoxide dismutase (particularly ESOD), decreased ceruloplasmin, decreased cytochrome c oxidase, increased plasma cholesterol, increased LDL:HDL cholesterol, decreased glucose clearance, decreased methionine and leucine enkephalins, abnormal cardiac function and impairment of pancreatic enzymes, amylase and lipase…..

"Erythrocyte superoxide dismutase (ESOD) activity, one of the most sensitive indices of copper status, has been shown to decrease following supplementation with zinc for 12 days. Longer-term supplementation has resulted in reductions in haematocrit and serum ferritin. Higher doses of zinc have resulted in altered ratios of HDL:LDL cholesterol. One study reported a negative copper balance when a diet deficient in zinc and protein was supplemented with zinc salts, although this effect was not reproduced later on within the same study. Copper deficiency and sideroblastic anaemia, associated with chronic zinc ingestion, was reported in one individual who had taken non-prescribed zinc supplements for at least 2 years.”

Copper & Iron

EVM Cu review

Interactions of Cu

61. "Animal studies suggest that high dietary iron affects copper absorption only when copper status is low or marginal (Cohen *et al.*, 1985a,b; Johnson and Murphy, 1988). Johnson and Murphy (1988) reported that high concentrations of dietary iron and ascorbic acid caused severe anaemia in copper-deficient rats and reduced plasma caeruloplasmin concentrations by 44% in copper-adequate rats, suggesting that ascorbic acid may have a synergistic negative effect with iron on copper levels. Infant foods are frequently fortified with iron and ascorbic acid."

EVM Fe review

Transport of Fe within and from intestinal cells

62. "Following uptake of iron by endothelial cells of the portal capillary system (by an unknown process), oxidation to the ferric form occurs, facilitating binding to transferrin. The copper containing protein, caeruloplasmin, has been implicated in this oxidation (Wollenberg *et al.*, 1990)."

Regulation of Fe uptake by and from tissues

63. "... the mechanism by which apotransferrin mobilises storage iron is not known. It has been suggested that the copper-containing protein, caeruloplasmin, may also be involved in the release of iron from tissues, by acting as a ferroxidase to convert Fe(II) to Fe(III) (Yoshida *et al.*, 1995). This is supported by the observation that iron-loading occurs in various tissues in patients suffering from acaeruloplasminaemia (Harris *et al.*, 1995, Yoshida *et al.*, 1995)"

Interactions of Fe with other transition metals

64. "Studies in experimental animals and humans have shown that iron deficiency can enhance the absorption of lead and metals that lie close to it in the periodic table (this includes cobalt, nickel, copper, manganese, zinc, chromium and cadmium). Enhanced absorption of at least some of these metals in iron deficient rats is inhibited competitively by the provision of iron and *visa versa* (reviewed by Lynch, 1997). Although it may be subject to some dispute (Conrad *et al.*, 1999), it is widely suggested that these metals can share a common uptake mechanism in the gut, competing for the binding ligands that mediate intestinal absorption and subsequent transport into the blood (Lynch, 1997 and references therein). Net uptake of any one of these metals is, therefore, dependent upon its relative binding strengths to the various ion-binding moieties and the concentrations of all the metal ions present in the gut. Consequently, antagonistic interactions between essential trace metals at the level of absorption have the potential to adversely affect overall micronutrient balance. Furthermore, it is possible that the consumption of diets that are deficient in one or more micronutrients could predispose to the toxic effects of nonessential metals…..

"With the exception of the interaction with zinc..., there is, to date, little evidence to suggest that iron supplementation adversely affects micronutrient nutrition in humans."

Interactions of Fe with Cu

65. "Bureau *et al.* (1998) demonstrated that high levels of dietary iron resulted in hypercholesterolaemia and hypertriacylglycerolaemia in a rat model of copper deficiency. The authors suggested that their observation could have implications for those individuals who consume large quantities of iron fortified foods and/or iron supplements but whose intake of copper is sub-optimal."

Iron & Zinc

EVM Fe review

Interactions with other transition metals

66. "Studies in experimental animals and humans have shown that iron deficiency can enhance the absorption of lead and metals that lie close to it in the periodic table (this includes cobalt, nickel, copper, manganese, zinc, chromium and cadmium)……

"With the exception of the interaction with zinc..., there is, to date, little evidence to suggest that iron supplementation adversely affects micronutrient nutrition in humans."

Interactions with Zn

67. "There is some concern regarding the potential adverse effects of iron supplements on zinc nutrition. However, the interaction between iron and zinc in humans appears to be less than it is in rats (Valberg *et al.*, 1984). When administered in the fasting state, a higher zinc-to-iron ratio was required to demonstrate reduced zinc absorption in humans than in rodents (Flanagan & Valberg, 1988)…

"Using radioisotopic technique and whole body counting, Sandstrom *et al.* (1985) reported no inhibition of zinc absorption at a molar ratio of iron to zinc of 2.5:1 when both metals were administered as solutions. When the ratio was increased to 25:1, zinc absorption was reduced significantly. However, when iron and zinc were administered in the same molar ratio but included in a meal, no inhibitory effect was observed. Other investigators have made similar observations (Solomons and Jacob, 1981; Valberg *et al.*, 1984). Consequently, it would appear that the ligands present in food that modify the absorption of both metals lessen any influence that iron may have on the absorption of zinc in the absence of food. Solomons (1986) postulated that it is the total amount of ionic species that affects the absorption of zinc and that 25 mg iron may produce a measurable effect upon zinc absorption. Consequently, to avoid adverse effects on zinc uptake, the author recommended that iron supplements be taken between meals. Lynch (1997) has suggested that even foods that are highly fortified with iron are unlikely to adversely affect zinc nutrition unless zinc intake is very low or the diet is composed of highly purified components….

"A number of human studies have suggested that iron supplementation may inhibit zinc absorption. Meadows *et al.* (1983) demonstrated in 10 healthy subjects that the bioavailability of a single 50 mg dose of zinc (as zinc sulphate) was significantly reduced following supplementation with 100 mg iron (as fumarate) for a period of 14 days. Decreased maternal serum zinc concentrations have been reported after iron supplementation with doses = 60 mg/day during pregnancy (Breskin *et al.*, 1983; Hambidge *et al.*, 1983 1987; Campbell-Brown *et al.*, 1985; Bloxam *et al.*, 1989; O'Brien *et al.*, 1999, 2000). Furthermore, Dawson *et al.* (1989) found that daily supplementation of pregnant women with 18 mg iron, in combination with a multivitamin supplement (on average from 13 weeks' gestation to term), resulted in a significant, 35% decrease in serum zinc levels in the 3rd trimester, compared with women who were given an equivalent multivitamin supplement without iron. Conversely, Sheldon *et al.* (1985) reported no effect of 480 mg/day ferrous fumarate (160 mg/day elemental iron), from the 1st or 2nd trimester of pregnancy to term, on maternal serum zinc concentrations, when compared with women not taking iron supplements. Arnaud *et al.* (1993) found that iron supplementation in Nigerian women during pregnancy (100 mg/day) from 6 months of gestation to 6 months postpartum had no significant effect on the concentrations of iron found in maternal serum or breast milk. Yip *et al.* (1985) reported that administration of 30 mg/day iron to one year old infants had no effect on serum zinc concentrations. In summarising the results of studies examining the effects of iron and zinc interactions in human subjects, Whittaker (1998) noted that, as the plasma zinc concentration is not considered to be a good index of body zinc status, the use of such studies in assessing the effect of iron supplements on zinc status is probably limited…..

"The effect of zinc supplementation on iron status has also been investigated. Sufficiently high zinc: iron ratios have been shown to inhibit iron uptake in animals (Solomons & Ruz, 1997 and references therein). Data from human studies are more scant. Iron and zinc sulphate given in solution in molar ratios of 1:1 and 1:2.5 resulted in significantly reduced plasma iron AUC (area under the curve) in healthy males whereas a ratio of 2.41:1 had no such effect (Crofton *et al.*, 1989). Although increased plasma clearance of iron could not be discounted, the authors also suggested that it as physiologically plausible that zinc could interfere with the intestinal uptake of iron. A five-fold ratio of zinc to iron (15 mg: 3 mg) given in solution resulted in a 56% reduction in iron absorption. However, the same 5:1 excess of zinc given in a hamburger meal had no effect (Rossander-Hulten *et al.*, 1991)……

"Studies in rats have shown that a high level of zinc supplementation can affect iron storage and encourage depletion, interfere with iron uptake in the liver, shorten red blood cell life-span and cause anaemia due to faster iron turnover. (Walsh *et al.*, 1994 and references therein). Since transferrin transports both iron and zinc in plasma, interaction between zinc and iron may be at the transport level. However, these effects may also be secondary to zinc-induced copper deficiency (Linder & Hazegh-Azam, 1996 and references therein). Copper is a component of the ceruloplasmin ferroxidase, a key enzyme involved in the mobilisation of iron and its incorporation into transferrin. Zinc-induced copper deficiency can lead to a reduction in ceruloplasmin activity, which may result in the trapping of iron within the reticuloendothelial system. Consequently, iron is made unavailable for erythropoiesis and anaemia can ensue. In support of this, Yadrick *et al.* (1989) reported significant reductions in haematocrit and serum ferritin in females (n=18) given daily supplements of 50 mg zinc as gluconate for 10 weeks. Levels of copper-dependent erythrocyte superoxide

dismutase (ESOD) activity were also decreased. Effects on ferritin and haematocrit but not ESOD were ameliorated with equal (mg for mg) iron supplementation. However, Pachotikarn *et al.* (1985) saw no changes in haematocrit or haemoglobin levels in 23 young men given 50 mg zinc per day (as gluconate) for 6 weeks. Furthermore, in a double blind crossover study, where healthy females (n=26, mean 27 years) and males (n=21, mean age 28 years) were given 150 mg zinc (as sulphate) per day for 6 weeks, haematocrit remained unchanged (Samman & Roberts, 1988)……

"Although the dietary requirements for iron and zinc in adult males are similar (8.7 and 9.5 mg /day respectively), diet and dietary supplements generally provide greater amounts of iron (Department of Health, 1991). Consequently, issues arising from the interference of iron on zinc uptake are more likely than an effect of zinc on iron."

Human supplementation studies

68. "A few studies have suggested that excess iron intake could result in negative interactions with other trace elements. Decreased maternal serum zinc concentrations have been reported after iron supplementation with doses > 60 mg/day during pregnancy (Breskin *et al.*, 1983; Hambidge *et al.*, 1983, 1987). Furthermore, Dawson *et al.* (1989) found that daily supplementation of pregnant women with 18 mg iron, in combination with a multivitamin supplement (on average from 13 weeks' gestation to term), resulted in a significant, 35 % decrease in serum zinc levels in the 3rd trimester, compared with women who were given an equivalent multivitamin supplement without iron. Conversely, Sheldon *et al.* (1985) reported no effect of 480 mg/day ferrous fumarate (160 mg/day elemental iron), from the 1st or 2nd trimester of pregnancy to term, on maternal serum zinc concentrations, when compared with women not taking iron supplements. Yip *et al.* (1985) reported that administration of 30 mg/day iron to 1 year old infants had no effect on serum zinc concentrations. In summarising the results of studies examining the effects of iron and zinc interactions in human subjects, Whittaker (1998) noted that, as the plasma zinc concentration is not considered to be a good index of body zinc status, the use of such studies in assessing the effect of iron supplements on zinc status is probably limited."

Summary

69. "Interactions may occur between iron and other metals close to iron in the periodic table. Studies in rats have shown that iron supplementation impairs the absorption of zinc, and this has raised concerns that food iron supplements may have adverse effects on zinc nutrition in humans, although the magnitude of such an effect appears to be less in humans than that observed in rats."

<u>EVM Zn review</u>

Zn-Fe interaction

70. "An interaction... arises between zinc and iron due to the similarity of their ionic electronic configuration resulting in mutual competition for common absorption sites. ….

"When given in solution, high levels of iron negatively affect zinc absorption. However, zinc absorption from food is not affected by haem iron (Solomons 1986). Solomons postulated that it is the total amount of ionic species that affects the absorption of zinc and that > 25 mg Fe may produce a measurable effect upon zinc absorption. Consequently, to avoid adverse effects on zinc uptake, the author recommended that iron supplements be taken between meals…..

"The reverse interaction has also been demonstrated. Sufficiently high zinc:iron ratios have been shown to inhibit iron uptake in animals (Solomons and Ruz, 1997 and references therein). Data from human studies are more scant. ... Iron and zinc sulphate given in solution in molar ratios of 1:1 and 1:2.5 resulted in significantly reduced plasma iron AUC (area under the curve) in healthy males whereas a ratio of 2.41:1 had no such effect (Crofton *et al.*, 1989). Although increased plasma clearance of iron could not be discounted, the authors also suggested that it was physiologically reasonable to suppose that zinc could interfere with the intestinal uptake of iron. A five-fold ratio of zinc to iron (15 mg: 3 mg) given in solution resulted in a 56% reduction in iron absorption. However, the same 5:1 excess of zinc given in a hamburger meal had no effect (Rossander-Hulten *et al.*, 1991)…..

"Studies in rats have shown that a high level of zinc supplementation can affect iron storage and encourage depletion, interfere with iron uptake in the liver, shorten red blood cell life-span and cause anaemia due to faster iron turnover. (Walsh *et al.*, 1994 and references therein). Since transferrin transports both iron and zinc in plasma, interaction between zinc and iron may be at the transport level. However, these effects may also be secondary to zinc-induced copper deficiency (Linder and Hazegh-Azam, 1996 and references there in)."

Decreased ceruloplasmin activity, decreased iron mobilisation and anaemia

71. "Copper is a component of the ceruloplasmin (alternatively called ferroxidase), a key enzyme involved in the mobilisation of iron and its incorporation into transferrin. Zinc-induced copper deficiency can lead to a reduction in ceruloplasmin activity, which may result in the trapping of iron within the reticuloendothelial system. Consequently, iron is made unavailable for erythropoiesis and anaemia can ensue."

LOAELs for Zn-induced Cu deficiency

72. "Females (25-40 years) given supplements of zinc gluconate capsules (25 mg zinc twice daily for 10 weeks) developed significant reductions (~50%, 5% and 30%, respectively, compared with pretreatment levels, $p<0.05$, $n=18$) in ESOD activity, haematocrit, and serum ferritin. Effects on ferritin and haematocrit but not ESOD were ameliorated with equal (mg for mg) iron supplementation (Yadrick 1989). The amount of zinc and copper provided by food and beverages was not stated."

Adverse effects of zinc supplementation on functional indices of iron status.

73. "The growth of iron-deficient Iranian school-boys was found to be greater when supplementation was with 20 mg of iron alone rather a combination of 20 mg iron and 20 mg zinc (Mahloudji *et al.*, 1975)….

"Ferritin levels (an index of iron storage) in Jakarta school children responded positively to daily 30 mg iron supplements but not to similar supplements combined with 15 mg of zinc. However, haemoglobin and zinc protoporphyrin levels were increased in both groups (meeting abstract referred to by Solomons and Ruz, 1997)…

"Yadrick *et al.* (1989) reported significant reductions in haematocrit and serum ferritin in females (n=18) given daily supplements of 50 mg zinc as gluconate for 10 weeks. Levels of ESOD were also decreased..

"Although the dietary requirements for iron and zinc in adult males are similar (~10 and 15 mg /day respectively), diet and dietary supplements generally provide greater amounts of iron (Solomons, 1986). Consequently, issues arising from the interference of iron on zinc uptake are more likely than an affect of zinc on iron."

Copper & Manganese

EVM Cu review

74. No data.

EVM Mn review

Interactions

75. "It was reported that calcium and copper may impair the plasma uptake of manganese whilst zinc may increase plasma manganese levels (Freeland-Graves and Lin, 1991)."

Sub-chronic toxicity

76. "Albino rabbits were given oral doses of 60 mg/kg body weight Mn2+ for 6 months (Khandelwal and Tandon, 1981). A variety of blood parameters were measured to identify an early marker of manganese poisoning. Significant increases in blood (but not plasma) manganese, plasma copper and serum total cholesterol were observed compared to the controls throughout the study."

Additional data

77. A sub-chronic study was carried out in which I.T.R.C. male rats (initial weight ~ 60 g) were maintained on a standard- or low-protein synthetic diet for 30 days prior to, and during 30 days of treatment with Mn (1000 mg/l in drinking water, as $MnCl_2.4H_2O$) and/or Cu (250 mg/kg diet, as $CuSO_4.5H_2O$). Supplemental intakes, per rat, were reported as 5 ± 0.5 mg/day Cu and 9.7 ± 1.39 mg/day Mn. Supplementation with Mn, with or without Cu, was associated with altered behavioural parameters, some of which were affected to a greater extent in protein-deficient diets. All supplementation groups, except low-protein+Cu, had increased brain concentrations of DA and NE. 5-HT levels were decreased by combined Mn+Cu supplementation in both dietary groups and by Cu or Mn individually in the low-protein group. Co-supplementation with Cu did not affect the level of accumulation of Mn in the brain. Mn supplementation alone was associated with a small increase in brain Cu levels,

whilst combined supplementation with Cu+Mn was associated with much higher brain Cu levels than supplementation with Cu alone (Murthy *et al*., 1981).

Zinc & Manganese

EVM Zn review

Environmental workplace exposure

78. "Zinc is used extensively in industry and exposure may be particularly high in industrial waste sites. Zinc itself is not considered an industrial health hazard. However, inhalation of dusts containing zinc or zinc compounds, in the presence of metals such as arsenic, cadmium, manganese and lead, can result in metal fume fever."

EVM Mn review

Reported non-nutritional, beneficial effects

79. "Based on the study by Reginster *et al* (1988), the Committee on Medical Aspects of Food and Nutrition Policy (COMA) suggested there might be a plausible biochemical basis for manganese influencing bone health (COMA, 1998). Strause *et al* (1994) found a positive effect on spinal bone density with combined calcium, zinc, manganese and copper supplementation. However, COMA concluded that there is currently insufficient evidence to support dietary recommendations in relation to the effect of manganese on bone health."

Interactions

80. "It was reported that calcium and copper may impair the plasma uptake of manganese whilst zinc may increase plasma manganese levels (Freeland-Graves and Lin, 1991)."

Additional data

81. Freeland-Graves and Lin (1991) reported that plasma AUC values for Mn (40 mg orally, as chloride) were increased by 124% ($p < 0.05$) when given in combination with Zn (50 mg orally, as acetate) to 4 healthy adult volunteers.

Iron & Manganese

EVM Fe review

Transition metals and lead

82. "Studies in experimental animals and humans have shown that iron deficiency can enhance the absorption of lead and metals that lie close to it in the periodic table (this includes cobalt, nickel, copper, manganese, zinc, chromium and cadmium)…..

"With the exception of the interaction with zinc (see below), there is, to date, little evidence to suggest that iron supplementation adversely affects micronutrient nutrition in humans."

EVM Mn review

Chemistry and geochemistry

83. "Manganese can exist in eleven oxidation states from -3 to +7 with the most common valences being +2, +4 and +7. The +2 valence is the predominant form in nature, with the +4 valence occurring in MnO2 and +7 in permanganate. However, the Mn3+ state is critical in nature as this is the oxidative state of manganese in superoxide dismutase, the form in which transferrin binds manganese and probably the form which interacts with iron (ILSI, 1994)."

Analysis of tissue manganese levels and manganese status

84. "The activity of manganese specific enzymes can be used to assess exposure. For example, lymphocyte manganese-dependent superoxide dismutase (MnSOD) activity and serum manganese levels, but not urinary manganese levels, increased compared to controls following 124 days of daily supplementation of female volunteers with 15 mg/day manganese (Davis and Greger, 1992). Similar increases also occurred when 60 mg iron/day was co-administered with the manganese. The authors concluded that the two measures could be used to monitor manganese status. However, use of MnSOD (ILSI, 1994) as a measure is complicated by the number of cytokines and disease states that increase MnSOD expression independently of manganese status."

Interactions with Fe

85. "There is a close relationship between iron and manganese absorption by the intestinal mucosal cells with competition for the available binding sites (cited Carter, 1980). The affinity for manganese is lower than for iron…

"Co-administration of 7.5 or 15 mg manganese (as manganese chloride) with 3 mg iron as ferrous sulphate reduced manganese absorption by 20 and 34% respectively in human volunteers (Rossander-Hultén *et al*., 1991); when higher doses of iron were given, manganese reduced absorption by a similar level. The fraction of iron absorbed from a 3 mg dose was similar to that absorbed from a dose of 0.01 mg iron + 2.99 mg manganese. The authors concluded that competitive inhibition was occurring at the same step of mucosal absorption. When the iron was administered as 3 mg native non-haem iron in a hamburger meal, co-administration of 15 mg manganese reduced iron absorption by 40 % suggesting that other dietary ligands didnot affect the iron-manganese interaction…..

"Chua and Morgan (1996)[108] conducted a number of isotope uptake studies to determine whether manganese uptake and deposition in Wistar rats was affected by iron. They concluded that manganese and iron interacted during transfer from the plasma to the brain and other organs and that the interaction was synergistic rather

[108] The report of Chua and Morgan (1996) is described more fully at the end of Appendix 3.

than competitive. This suggests that excessive intake of both metals may accentuate the risk of tissue damage caused by one metal alone, particularly in the brain……

"Iron-deficient rats absorbed more manganese (24.4 ± 6.6%) than control (12.5 ± 4%) or iron loaded animals (5 ± 2.8%) when measured using an isolated intestinal loop technique (Diez-Ewald *et al*., 1968). Iron deficiency was achieved by prior removal of blood and iron overload by daily inter-muscular injections of iron dextran (total dose 100 mg). However, manganese excretion was also increased in the deficient rats and decreased in the iron-overload animals. It is suggested that this was a compensatory mechanism for the altered absorption. Iron deficiency significantly increased manganese levels in the brain, heart, spleen, kidney, testis, femoral muscle and tibia of rats fed a depleted diet for 3 weeks (Yokoi, 1991). Iron deficiency induced in rats for 8 weeks resulted in an increased in manganese levels in the hypothalamus only (Shukla, 1989). The increase was not abolished by two weeks of iron restoration.

"From day 2 of gestation onwards, pregnant Long Evan rats were fed a low iron (20 mg/kg) or high iron (240 mg/kg) diet (Rehnberg *et al*., 1982). In addition they also received a basal diet containing 50 mg/kg manganese as manganese sulphate, plus 0, 400, 1100 or 3550 mg Mn/kg as manganese oxide (Mn304). When calculated on a body weight basis, this can be estimated to be equivalent to 2.5, 20, 55, 177.5 mg/Mn kg/bw day. The doses for weanling rats would be approximately six times higher for the early part of the study. From weaning, the F1 offspring were given the same diets as the dams. The animals were then mated at day 92-94. The F1 generation was treated until 224 days of age and the F2 offspring until 24 days of age. A manganese-related depression in F1 growth rates was apparent in the low iron groups in the early part of the study. Beyond day 100, no body weight deficits were seen in any group. Mortality was high in the low iron, 3550 mg/kg manganese group, with no animals surviving beyond 50 days. Blood iron levels were severely depressed in these animals. Liver iron levels were lower in the high iron, 3550 mg/kg manganese group than in the low iron controls but this was not significant: liver manganese levels, however, were significantly higher. In the high iron diet a general dose-related increase in liver manganese was apparent. Tissue accumulation of manganese was highest in the weanling rats (where biliary excretion is absent), lactating and term dams and term pups in the iron deficient groups. The levels of manganese in milk and placenta were largely unaffected by treatment. No information is provided on whether manganese treatment affected reproductive or developmental parameters is provided. The authors concluded that the most susceptible animals to tissue manganese accumulation from chronic manganese exposure were those absorbing large amounts of iron, the pre-weanling rat, the lactating dam and the iron deficient rat….

"A study of iron status (as assessed by serum ferritin concentration) and effects on manganese absorption and biological half-life was conducted in 26 women (Finley, 1999). Manganese absorption was highest in subjects on low manganese diets (0.7 mg/day) with low iron status. Absorption was lowest in all subjects on high manganese diets (9.5 mg/day). The half-life was longest in subjects on low manganese diet and high iron status and shortest in all subjects on the high manganese diet. As a result, manganese balance was not affected by iron status at the levels of intake in this study."

Absorption in humans

86. “Absorption of 54Mn from a juice drink was significantly higher in women than in men, but the half-life of the labelled manganese was longer in men compared to women (Finley *et al*., 1994). Half-life and absorption were determined from whole body counts. A significant association was found between manganese absorption and plasma ferritin levels and between manganese absorption and biological half-life. The authors concluded that the differences between men and women might be related to iron status.”

Vulnerable groups

87. “Iron deficient individuals may be at risk of manganese toxicity (ILSI, 1994).”

Toxicity in laboratory animals – haematology

88. “A number of effects on haematological parameters have been reported following administration of manganese compounds, probably as result of interference with iron. Additional work has been conducted using diets with variable iron levels in addition to the manganese……

"Groups of 10 male or female F344 rats were fed diet containing control (92 mg/kg manganese), 1,600, 3,130. 6,250, 12,500 or 25,000 mg/kg manganese sulphate (NTP, 1993) for 13 weeks. Mean daily intake ranged from 110 to 1700 mg/kg bw in the males and 115 to 2000 mg/kg bw in the females. Food consumption and body weights were not significantly affected by treatment. Absolute and relative liver weights were reduced in all treated males and the top dose females. Absolute and relative lung weights were also reduced in all treated females. Neutrophil counts were significantly higher in treated males, but lymphocyte counts significantly lower in the males receiving 6,250 mg/kg or above manganese sulphate. In the females the total leukocyte was significantly reduced in the 6,250 mg/kg or above groups, largely as a result of reduced lymphocyte numbers. A small but significant increase in haematocrit and erythrocyte count was measured in the 6,250 mg/kg or above males. No clinical or histopathological findings were attributed to treatment….

"Groups of 10 male or female B6C3F1 mice were fed a diet containing control (92 mg/kg manganese), 3,130. 6,250, 12,500, 25,000 or 50,000 mg/kg manganese sulphate (NTP, 1993) for 13 weeks. Mean daily intake ranged from 330 to 7400 mg/kg bw in the males and 390 to 6900 mg/kg bw in the females. Absolute and relative liver weights were reduced in the top dose males only. Haematocrit, haemoglobin concentrations and mean erythrocyte volume were reduced in the top dose groups compared to the controls. The findings were thought to suggest microcytic anaemia possibly related to sequestration or deficiency of iron. Total leukocyte counts in the males of the top two dose groups were reduced but it was uncertain whether this was due to treatment. It was reported that a few animals in the treated groups had fight wounds and that mild epithelial hyperplasia was observed in 3 of the 10 males in the top does group. No other treatment related effects were reported…..

"Long Evans rats were exposed *in utero* to normal or iron deficient (240 and 20 mg/kg respectively) diet, which was supplemented with manganese oxide (Carter *et al*., 1980). The males of the F1 generation were then exposed to the same diet until day 224. Both types of diet contained 50 mg/kg manganese sulphate initially and after

supplementation contained a total of 50, 400, 1100 or 3550 mg/kg manganese. Due to excessive mortality, the animals in the low iron/3550 mg/kg manganese group were killed at day 40. The achieved doses are not given. However, these can be estimated from control data, to be approximately 2.3, 18.4 or 50.6 mg Mn /kg bw/day for the control, 400 and 1100 mg/kg and normal iron groups and 2.7, 21.6 and 63.8 mg Mn /kg bw/day in the control, 400 and 1100 mg/kg and low iron groups. Differences in red cell count and mean cell volume (MCV) were apparent between the low and normal iron groups. In the normal iron group, a slight manganese doserelated increase in RBC count was apparent at days 60 and 224 but this was not significant. No effects due to manganese were apparent on MCV or, on the level of serum proteins (albumin and globulins), glucose or enzymes (alkaline phosphatase, lactate dehydrogenase or glutamic-oxaloacetic transaminase). In the low iron group, manganese treatment was associated with a dose-related decrease in RBC count and MCV; the differences lessened during the study and had disappeared by the end of the study (day 100 for MCV). Treatment with 400 and 1100 mg/kg manganese reduced serum creatinine levels and treatment with 1100 mg/kg manganese increased serum phosphate and calcium levels at day 100 in both iron groups…

"In a second study conducted by the same authors, the dams received the normal iron diet. From day 10 after gestation, groups of 9-11 male offspring received low or high iron diet, or low iron diet with 400 or 1100 mg/kg manganese for a further 30 days. While RBC count, MCV, haematocrit and haemoglobins were reduced in the low iron groups compared to the controls, there was no additional effect attributable to manganese. The authors concluded that the rats given normal iron diets were largely unaffected by manganese treatment, but those on the low iron diet in the pre and post natal period developed microcytic anaemia. The young animals were considered to be more sensitive to manganese treatment."

Summary

89. "Manganese absorption occurs in the small intestine. It is relatively low but is dependent on the chemical form of the element. Absorption is thought to be higher in infants or young animals. It has been suggested that variable manganese absorption helps to maintain homeostasis. Iron and manganese compete for binding site and thus can interfere with each others' absorption. This can result in adverse effects in laboratory animals."

90. "No genetic variants with increased susceptibility to manganese toxicity have been identified. It has been suggested that elderly people, infants, individuals with liver disease and individuals that are iron deficient may be vulnerable to manganese accumulation and toxicity".

Additional data

91. Chua & Morgan (1996) described interactions between Mn and Fe with regard to tissue uptake in sub-chronic studies in rats. Wistar rats (sex not specified) were fed diets containing low Fe (5-10 mg/kg diet Fe, ~ 0.25-0.5 mg/kg bw/day Fe, as ferrous ammonium sulphate), standard Fe (70 mg/kg diet Fe, ~ 3.5 mg/kg bw/day Fe, as ferrous ammonium sulphate) or high Fe (20 g/kg diet Fe, ~ 1000 mg/kg bw/day Fe, as carbonyl Fe). Each Fe group was divided into standard (36 mg/kg in the basal diet) or high (2 g/l, ~ 100 mg/kg bw/day, as acetate in drinking water) Mn groups. (The 6

diets were represented as C, CMn+, Fe-, Fe-Mn+, Fe+, Fe+Mn+). Dosing was carried out during days 18-19 of pregnancy, and continued throughout suckling and after weaning. Animals were killed at 15 or 63 days of age. Reduced body weights were noted in groups CMn+, Fe-Mn+, Fe+ (15 days) and Fe+ (63 days). Mn supplementation was associated with increased Mn concentrations in brain, liver and kidney at 15 and 63 days (except CMn+, 15 days); the magnitude of increase was greater for Fe-Mn+ and Fe+Mn+ than CMn+. In addition, Fe- (15 days) and Fe+ (15 and 63 days) diets were associated with increased brain Mn. Tissue (brain, liver, kidney) Fe levels were significantly correlated with dietary Fe. As compared with C, the CMn+ groups showed increased brain and kidney Fe (15 days). As compared with Fe-, the Fe-Mn+ group showed increased kidney Fe (63 days). As compared with Fe+, the Fe+Mn+ group showed decreased kidney Fe (63 days). Isotope uptake studies showed that Fe deficiency did not affect ^{54}Mn uptake. However, Fe overload was associated with significantly increased ^{54}Mn uptake (brain, liver, kidney, femur) at 15 days (but not 63 days). Fe deficiency increased ^{59}Fe uptake in brain (63 days), liver (15 and 63 days) and kidney (15 days). Mn increased ^{59}Fe uptake at 15 days in brain, liver and kidney of Fe deficient and control animals, whilst the opposite effect was observed in liver and kidney of Fe loaded animals. The authors concluded that Fe status may affect Mn transport into the brain and that Mn status can affect Fe metabolism.

Reference List to Appendix 28

Abreo,K., Abreo,F., Sella,M.L., and Jain,S. (1999). Aluminum enhances iron uptake and expression of neurofibrillary tangle protein in neuroblastoma cells. J. Neurochem. *72*, 2059-2064.

Abreo,K., Glass,J., Jain,S., and Sella,M. (1994). Aluminum alters the compartmentalization of iron in Friend erythroleukemia cells. Kidney Int. *45*, 636-641.

Blaehr, H., Madsen, S., and Andersen, J. R. Effect of iron-loading on intestinal aluminium absorption in chronic renal insufficiency. Taylor, A. Aluminium and other trace elements in renal disease. 71-75. 1986. Eastbourne, Bailliere Tindall. 16-9-0085.
Ref Type: Conference Proceeding

Bondy,S.C., Guo-Ross,S.X., and Truong,A.T. (1998). Promotion of transition metal-induced reactive oxygen species formation by beta-amyloid. Brain Res. *799*, 91-96.

Border,E.A., Cantrell,A.C., and Kilroe-Smith,T.A. (1976). The in vitro effect of zinc on the inhibition of human delta-aminolevulinic acid dehydratase by lead. Br. J. Ind. Med. *33*, 85-87.

Cannata,J.B. and Diaz Lopez,J.B. (1991). Insights into the complex aluminium and iron relationship. Nephrol. Dial. Transplant *6*, 605-607.

Cannata,J.B., Fernandez-Soto,I., Fernandez-Menendez,M.J., Fernandez-Martin,J.L., McGregor,S.J., Brock,J.H., and Halls,D. (1991). Role of iron metabolism in absorption and cellular uptake of aluminum. Kidney Int. *39*, 799-803.

Cannata,J.B., Olaizola,I.R., Gomez-Alonso,C., Menendez-Fraga,P., Alonso-Suarez,M., and Diaz-Lopez,J.B. (1993). Serum aluminum transport and aluminum uptake in chronic renal failure: role of iron and aluminum metabolism. Nephron *65*, 141-146.

Cannata,J.B., Suarez,S.C., Cuesta,V., Rodriguez,R.R., Allende,M.T., Herrera,J., and Perez,L.J. (1985). Gastrointestinal aluminium absorption: is it modulated by the iron-absorptive mechanism? Proceedings of the European Dialysis & Transplant Association - European Renal Association *21*, 354-359.

Chua,A.C. and Morgan,E.H. (1996). Effects of iron deficiency and iron overload on manganese uptake and deposition in the brain and other organs of the rat. Biol. Trace Elem. Res. *55*, 39-54.

Church,H.J., Day,J.P., Braithwaite,R.A., and Brown,S.S. (1993). Binding of lead to a metallothionein-like protein in human erythrocytes. J. Inorg. Biochem. *49*, 55-68.

Cochran,M., Coates,J., and Neoh,S. (1984). The competitive equilibrium between aluminium and ferric ions for the binding sites of transferrin. FEBS Lett. *176*, 129-132.

Crichton,R.R., Wilmet,S., Legssyer,R., and Ward,R.J. (2002). Molecular and cellular mechanisms of iron homeostasis and toxicity in mammalian cells. J. Inorg. Biochem. *91*, 9-18.

D'Haese,P.C., Clement,J.P., Elseviers,M.M., Lamberts,L.V., Van de Vyver,F.L., Visser,W.J., and De Broe,M.E. (1990). Value of serum aluminium monitoring in dialysis patients: a multicentre study. Nephrol. Dial. Transplant *5*, 45-53.

Dhawan,D., Singh,B., Chand,B., Singh,N., Mangal,P.C., and Trehan,P.N. (1995). X-ray fluorescence in the assessment of inter-elemental interactions in rat liver following lead treatment. Biometals *8*, 105-110.

Donnelly,S.M., Ali,M.A., and Churchill,D.N. (1990). Bioavailability of iron in hemodialysis patients treated with erythropoietin: evidence for the inhibitory role of aluminum. American Journal of Kidney Diseases *16*, 447-451.

Dutkiewicz,B., Dutkiewicz,T., and Milkowska,G. (1979). The effect of mixed exposure to lead and zinc on ALA level in urine. Int. Arch. Occup. Environ. Health *42*, 341-348.

Ecelbarger,C.A. and Greger,J.L. (1991). Dietary citrate and kidney function affect aluminum, zinc and iron utilization in rats. J. Nutr. *121*, 1755-1762.

Fernandez Menendez,M.J., Fell,G.S., Brock,J.H., and Cannata,J.B. (1991). Aluminium uptake by intestinal cells: effect of iron status and precomplexation. Nephrology Dialysis Transplantation *6*, 672-674.

Freeland-Graves,J.H. and Lin,P.H. (1991). Plasma uptake of manganese as affected by oral loads of manganese, calcium, milk, phosphorus, copper, and zinc. J.Am.Coll.Nutr. *10*, 38-43.

Fulton,B., Jaw,S., and Jeffery,E.H. (1989). Bioavailability of aluminum from drinking water. Fundam. Appl. Toxicol. *12*, 144-150.

Fulton,B. and Jeffery,E.H. (1990). Absorption and retention of aluminum from drinking water. 1. Effect of citric and ascorbic acids on aluminum tissue levels in rabbits. Fundamental & Applied Toxicology *14*, 788-796.

Garruto,R.M., Fukatsu,R., Yanagihara,R., Gajdusek,D.C., Hook,G., and Fiori,C.E. (1984). Imaging of calcium and aluminum in neurofibrillary tangle-bearing neurons in parkinsonism-dementia of Guam. Proc. Natl. Acad. Sci. U. S. A *81*, 1875-1879.

Garruto,R.M., Shankar,S.K., Yanagihara,R., Salazar,A.M., Amyx,H.L., and Gajdusek,D.C. (1989). Low-calcium, high-aluminum diet-induced motor neuron pathology in cynomolgus monkeys. Acta Neuropathol. (Berl) *78*, 210-219.

Goering,P.L. and Fowler,B.A. (1987). Metal constitution of metallothionein influences inhibition of delta-aminolaevulinic acid dehydratase (porphobilinogen synthase) by lead. Biochem. J. *245*, 339-345.

Golub,M.S., Han,B., and Keen,C.L. (1996). Iron and manganese uptake by offspring of lactating mice fed a high aluminum diet. Toxicology *109*, 111-118.

Goyer,R.A. (1995). Nutrition and metal toxicity. Am. J. Clin. Nutr. *61 Suppl.*, 646S-650S.

Goyer,R.A. (1997). Toxic and essential metal interactions. Annu. Rev. Nutr. *17*, 37-50.

Goyer,R.A. and Clarkson,T.W. (2001). Toxic effects of metals. In Cassarett & Doull's Toxicology: the basic science of poisons., C.D.Klaassen, ed. McGraw-Hill), pp. 811-867.

Greger,J.L. and Baier,M.J. (1983). Effect of dietary aluminum on mineral metabolism of adult males. Am. J. Clin. Nutr. *38*, 411-419.

Greger,J.L., Bula,E.N., and Gum,E.T. (1985). Mineral metabolism of rats fed moderate levels of various aluminum compounds for short periods of time. J. Nutr. *115*, 1708-1716.

Gutteridge,J.M., Quinlan,G.J., Clark,I., and Halliwell,B. (1985). Aluminium salts accelerate peroxidation of membrane lipids stimulated by iron salts. Biochim. Biophys. Acta *835*, 441-447.

Hammad,T.A., Sexton,M., and Langenberg,P. (1996). Relationship between blood lead and dietary iron intake in preschool children. A cross-sectional study. Ann. Epidemiol. *6*, 30-33.

Han,J., Han,J., and Dunn,M.A. (2000). Effect of dietary aluminum on tissue nonheme iron and ferritin levels in the chick. Toxicology *142*, 97-109.

Huang,J.Y., Huang,C.C., Lim,P.S., Wu,M.S., and Leu,M.L. (1992). Effect of body iron stores on serum aluminum level in hemodialysis patients. Nephron *61*, 158-162.

Iancu,T.C., Perl,D.P., Sternlieb,I., Lerner,A., Leshinsky,E., Kolodny,E.H., Hsu,A., and Good,P.F. (1996). The application of laser microprobe mass analysis to the study of biological material. Biometals *9*, 57-65.

Ittel,T.H., Kinzel,S., Ortmanns,A., and Sieberth,H.G. (1996). Effect of iron status on the intestinal absorption of aluminum: a reappraisal. Kidney International *50*, 1879-1888.

Kies,C. and Umoren,J. (1989). Inhibitors of copper bioutilization: fiber, lead, phytate and tannins. Adv. Exp. Med. Biol. *258*, 81-93.

Klauder,D.S. and Petering,H.G. (1975). Protective value of dietary copper and iron against some toxic effects of lead in rats. Environ. Health Perspect. *12*, 77-80.

Kooistra,M.P., Niemantsverdriet,E.C., van Es,A., Mol-Beermann,N.M., Struyvenberg,A., and Marx,J.J. (1998). Iron absorption in erythropoietin-treated haemodialysis patients: effects of iron availability, inflammation and aluminium. Nephrology Dialysis Transplantation *13*, 82-88.

Lin,J.L., Lim,P.S., and Leu,M.L. (1995). Relationship of body iron status and serum aluminum in chronic renal insufficiency patients not taking any aluminum-containing drugs. Am. J. Nephrol. *15*, 118-122.

Liu,J.Y. and Stemmer,K.L. (1990a). Interaction between aluminum and zinc or copper and its effects on the pituitary-testicular axis. II. Testicular enzyme and serum gonadotropin assay. Biomedical & Environmental Sciences *3*, 11-19.

Liu,J.Y. and Stemmer,K.L. (1990b). Interaction of aluminum with zinc and copper and its effects on pituitary-testicular axis: a histological study. Biomedical & Environmental Sciences *3*, 1-10.

Lowermoor Incident Health Advisory Group. Water pollution at Lowermoor, North Cornwall. Report of the Lowermoor Incident Health Advisory Group. Chairman: Professor Dame Barbara Clayton. Truro: Cornwall and Isles of Scilly Health Authority, 1989.

Lowermoor Incident Health Advisory Group. Water pollution at Lowermoor, North Cornwall. Second report of the Lowermoor Incident Health Advisory Group. Chairman: Professor Dame Barbara Clayton. HMSO, London, 1991.

LSG/02/7 Aluminium.

Malhotra,K.M., Shukla,G.S., and Chandra,S.V. (1982). Neurochemical changes in rats coexposed to lead and copper. Arch. Toxicol. *49*, 331-336.

Marlowe,M., Cossairt,A., Moon,C., Errera,J., MacNeel,A., Peak,R., Ray,J., and Schroeder,C. (1985a). Main and interaction effects of metallic toxins on classroom behavior. Journal of Abnormal Child Psychology *13*, 185-198.

Marlowe,M., Stellern,J., Errera,J., and Moon,C. (1985b). Main and interaction effects of metal pollutants on visual-motor performance. Arch. Environ. Health *40*, 221-225.

McNall,A.D. and Fosmire,G.J. (1996). Zinc status does not affect aluminum deposition in tissues of rats. Biol. Trace Elem. Res. *53*, 7-18.

Morgan,E.H. and Redgrave,T.G. (1998). Effects of dietary supplementation with aluminum and citrate on iron metabolism in the rat. Biological Trace Element Research *65*, 117-131.

Murthy,R.C., Lal,S., Saxena,D.K., Shukla,G.S., Ali,M.M., and Chandra,S.V. (1981). Effect of manganese and copper interaction on behavior and biogenic amines in rats fed a 10% casein diet. Chem. Biol. Interact. *37*, 299-308.

Nasiadek,M. and Chmielnicka,J. (2000). Interaction of aluminum with exogenous and endogenous iron in the organism of rats. Ecotoxicology & Environmental Safety *45*, 284-290.

Nielsen,F.H., Shuler,T.R., Zimmerman,T.J., and Uthus,E.O. (1988). Dietary magnesium, manganese and boron affect the response of rats to high dietary aluminum. Magnesium *7*, 133-147.

Nutrition Reviews. (1984). Conditioned copper deficiency due to antacids. Nutr. Rev. *42*, 319-321.

Oshiro,S., Kawahara,M., Mika,S., Muramoto,K., Kobayashi,K., Ishige,R., Nozawa,K., Hori,M., Yung,C., Kitajima,S., and Kuroda,Y. (1998). Aluminum taken up by transferrin-independent iron uptake affects the iron metabolism in rat cortical cells. Journal of Biochemistry *123*, 42-46.

Peraza,M.A., Ayala-Fierro,F., Barber,D.S., Casarez,E., and Rael,L.T. (1998). Effects of micronutrients on metal toxicity. Environ. Health Perspect. *106 Suppl 1*, 203-216.

Perl,D.P. and Good,P.F. (1987). Uptake of aluminium into central nervous system along nasal-olfactory pathways. Lancet *1*, 1028.

Petering,H.G. (1978). Some observations on the interaction of zinc, copper, and iron metabolism in lead and cadmium toxicity. Environmental Health Perspectives. *25*, 141-145.

Philpott,C.C. (2002). Molecular aspects of iron absorption: Insights into the role of HFE in hemochromatosis. Hepatology *35*, 993-1001.

Plato,C.C., Galasko,D., Garruto,R.M., Plato,M., Gamst,A., Craig,U.K., Torres,J.M., and Wiederholt,W. (2002). ALS and PDC of Guam: forty-year follow-up. Neurology *58*, 765-773.

Quinlan,G.J., Halliwell,B., Moorhouse,C.P., and Gutteridge,J.M. (1988). Action of lead(II) and aluminium (III) ions on iron-stimulated lipid peroxidation in liposomes, erythrocytes and rat liver microsomal fractions. Biochim. Biophys. Acta *962*, 196-200.

Robertson,I.K. and Worwood,M. (1978). Lead and iron absorption from rat small intestine: the effect of dietary Fe deficiency. Br. J. Nutr. *40*, 253-260.

Shakoor,A., Gupta,P.K., Singh,Y.P., and Kataria,M. (2000). Beneficial effects of aluminum on the progression of lead-induced nephropathy in rats. Pharmacol. Toxicol. *87*, 258-260.

Six,K.M. and Goyer,R.A. (1972). The influence of iron deficiency on tissue content and toxicity of ingested lead in the rat. Journal of Laboratory. & Clinical Medicine *79*, 128-136.

Sugawara,C., Sugawara,N., Ikeda,N., Okawa,H., Okazaki,T., Otaki,J., Taguchi,K., Yokokawa,K., and Miyake,H. (1987). Effects of ingested 4000ppm aluminum on the essential metals, especially zinc, in intact and ethanol treated mice. Drug Chem. Toxicol. *10*, 195-207.

Tephly,T.R., Wagner,G., Sedman,R., and Piper,W. (1978). Effects of metals on heme biosynthesis and metabolism. Fed. Proc. *37*, 35-39.

Trapp,G.A. (1983). Plasma aluminum is bound to transferrin. Life Sci. *33*, 311-316.

Victery,W., Miller,C.R., Zhu,S.Y., and Goyer,R.A. (1987). Effect of different levels and periods of lead exposure on tissue levels and excretion of lead, zinc, and calcium in the rat. Fundam. Appl. Toxicol. *8*, 506-516.

Ward,R.J., Zhang,Y., and Crichton,R.R. (2001). Aluminium toxicity and iron homeostasis. J. Inorg. Biochem. *87*, 9-14.

Wenk,G.L. and Stemmer,K.L. (1981). The influence of ingested aluminum upon norepinephrine and dopamine levels in the rat brain. Neurotoxicology *2*, 347-353.

Wenk,G.L. and Stemmer,K.L. (1982). Activity of the enzymes dopamine-beta-hydroxylase and phenylethanolamine-N-methyltransferase in discrete brain regions of the copper-zinc deficient rat following aluminum ingestion. Neurotoxicology *3*, 93-99.

Wenk,G.L. and Stemmer,K.L. (1983). Suboptimal dietary zinc intake increases aluminum accumulation into the rat brain. Brain Res. *288*, 393-395.

Xie,C.X., Mattson,M.P., Lovell,M.A., and Yokel,R.A. (1996). Intraneuronal aluminum potentiates iron-induced oxidative stress in cultured rat hippocampal neurons. Brain Res. *743*, 271-277.

Yamanaka,K., Minato,N., and Iwai,K. (1999). Stabilization of iron regulatory protein 2, IRP2, by aluminum. FEBS Lett. *462*, 216-220.

Yasui,M., Ota,K., and Garruto,R.M. (1995). Effects of calcium-deficient diets on manganese deposition in the central nervous system and bones of rats. Neurotoxicology *16*, 511-517.

Table 1: Biological effects of metal-metal combinations *in vivo*

Metal combin-ation	**Subjects/ species**	**Dose, duration and route of administration**	Dose (-fold) relative to estimated maximum exposure at Lowermoor	**Toxic/biological effect**	**Reference**
Al, Pb	School-children in the US	Hair metal levels in the upper range of accepted limits	NA	Possible association of high normal levels of Al/Pb combination with reduced visual-motor performance	Marlowe *et al*. (1985b)
Al, Fe	Male Wistar rats	Al - 120 mmol/kg diet, ~ 162 mg/kg bw/day, as chloride hydrate, and/or Fe - 360 mmol/kg diet, ~ 1000 mg/kg bw/day, as carbonyl Fe, ± citrate, 9-11 weeks	Al 7.7 Fe 3704	Supplemental Al and/or citrate exacerbated impaired growth rate associated with Fe-overload. Effect greatest in Fe-loaded + Al (no citrate). No association of Al supplementation alone with reduced growth rate.	Morgan & Redgrave (1998)
Cu, Mn	I.T.R.C. male rats	Cu - 250 mg/kg diet, as sulphate, ~ 50 mg/kg bw/day, and/or Mn - 1000 mg/l in drinking water, as chloride, ~ 100 mg/kg bw/day), normal or reduced protein diet, 30 days	Cu 172 Mn 1430	Co-supplementation with Cu+Mn was associated with; 1. Reduced levels of 5-HT in the brains of animals fed diets with a standard protein content (for single-supplement groups this effect was only seen in animals on the reduced-protein diet) 2. Much higher brain Cu levels compared with Cu-only supplementation	Murthy *et al*. (1981)
Mn, Zn	Healthy adult volunteers (n = 4)	Mn - 40 mg oral load, ~ 0.67 mg/kg bw, as chloride, with or without, Zn - 50 mg, ~ 0.83 mg/kg bw, as acetate, single dose	Mn 10 Zn 2.8	Co-administration of Zn increased AUC values for Mn by 124%	Freeland-Graves & Lin (1991)
Mn, Fe	Wistar rats	Mn - 2 g/l, ~ 100 mg/kg bw/day, as acetate in drinking water), and/or Fe - 20 g/kg diet Fe, ~ 1000 mg/kg bw/day Fe, as carbonyl Fe, during days 18-19 of pregnancy and throughout suckling and after weaning	Mn 1493 Fe 3703	Some interactions observed between Mn and Fe with respect to uptake into various tissues.	Chua & Morgan (1996)

Appendix 29: Second review paper on metal-metal interactions prepared for the Lowermoor subgroup by the Department of Health Toxicology Unit, Imperial College, London (March 2003 to April 2012)

Note: this was a paper prepared for discussion by the Lowermoor Subgroup. It does not necessarily represent the views of the subgroup.

1. Metal-Metal interactions were reviewed in detail and prepared for the COT Lowermoor Subgroup in 2003. This current paper covers the period up to May 2012. The previous review provides a background to each of the metals including information on their dietary sources, the targets in the body for acute and chronic toxicity and data on human exposure. Members are asked to consider the paper and to advise on whether any of the new data should be discussed in the text of the report.

2. Following the Lowermoor water contamination incident in July 1988, water supplies to the Camelford area were contaminated with aluminium (Al). Increased concentrations of other metals such as lead (Pb), iron (Fe), copper (Cu), zinc (Zn) and manganese (Mn) in the water supply were also noted. Al and Pb are nonessential metals. Fe, Cu, Zn and Mn are essential micronutrients, the major source in humans being the diet. This update review is concerned with biological interactions which may occur between these 6 metals, with relevance to potential effects in humans exposed orally. Pairwise combinations of the 6 metals of concern have been considered. As Al was the major pollutant, the main focus is on combinations of Al with each of the other metals.

Reviews on metal-metal interactions

3. A number of reviews have been published in this area since 2003. A series of reviews on the effect of metals ions on the various systems in the body was recently published in a book entitled "Metal Ions in Life Science" by the Royal Society of Chemistry in the UK in 2010. Metals and their interactions were addressed for the neurological system (Pohl et al., 2010), the haematological system (Roney et al., 2010), eyes and skin (Lansdon, 2010), the pulmonary and cardiovascular system (Corradi and Mutti, 2010), the reproductive and developmental system (Apostoli and Catalani, 2010), the immune system (Lehmann et al., 2010), the kidney system (Fowler, 2010) and the gastrointestinal system including the liver (Naughton et al, 2010).

4. Huang et al. (2004) reviewed the involvement of Zn, Cu and Fe in oxidative stress and discussed how this could be linked to Alzheimer's Disease (AD) pathology. Verstraeten et al. (2008) provided a review of the molecular mechanisms of brain toxicity involving Al and Pb neurotoxic effects. They reviewed data that investigated oxidative stress, deregulation of cell signalling and impairment of neurotransmission.

5. Yokel (2006) provided a very detailed review of the contribution of the blood-brain barrier flux of Al, Mn, Zn, Fe, Cu and other metals to metal-induced neurodegeneration. Shcherbatykh and Carpenter (2007) reviewed studies which implicated a role for metals such as Al, Cu, Zn, Mn and Fe in contributing to or causing AD. Zatta et al. (2003) reviewed the role of Al, Zn and Mn in neurodegenerative processes. In another review Zatta et al. (2011) discussed the most recent evidence linking metal ion imbalance and beta-amyloid (Aβ) aggregation. They also examined the participation of the Al – Aβ complex as a cofactor in the pathogenesis of AD.

6. Maynard et al. (2005) reviewed the role played by metals such as Cu, Zn and Fe in AD pathogenesis. The main focus of the paper was to review evidence for roles of amyloid precursor protein (APP) and Aβ in copper homeostasis and how this relates to metal imbalances in AD brains. The review also discusses the importance of brain

metal homeostasis in Aβ accumulation and amyloid formation. Roberts et al. (2012) reviewed the role of metal ions in Alzheimer's disease and discussed the involvement of iron, copper and zinc through the interactions with amyloid precursor protein, the proteolytically cleaved peptide Aβ, and other related metalloproteins.

Human Studies

7. Strozyk et al. (2009) investigated the association between cerebrospinal fluid (CSF) Cu, Zn, Fe, Al, Mn and CSF Aβ42 in ventricular fluid autopsy samples taken from a cohort of Japanese-American men participating in a population based Honolulu Asia Aging Study (HANS). This paper was previously discussed in LSG/11/1 but is discussed in more detail here. They found the relative abundances in the CSF were Fe> Zn> Cu> Se>Al>Mn>Cr. They also found that increasing biometal concentrations were associated with a decrease in Aβ42 concentration in the post-mortem CSF after adjusting for all covariates. The association was strongest for Cu (β coefficient = -1.30, 95% CI [-1.78,-0.8], p trend = <0.0001) and zinc in the highest tertile (β coefficient = -1.26, 95% CI [-1.70, -0.8], p trend = <0.0001), when compared to the lowest tertile. Fe and Mn were also significantly inversely associated with CSF Aβ42. The authors did not find any relationship between CSF Aβ42 and Al. Cu and Zn were synergistically associated with CSF Aβ42 levels. Combined high Zn and high Cu levels were associated with lower levels of CSF Aβ42 (β coefficient = -1.16, 95% CI [-1.60, -0.7], p trend = <0.0001) compared to the low levels of both metals. However, there was no association with CSF Aβ42 if only one metal was elevated, i.e. highest tertile of Zn combined with the lowest tertile of Cu or vice versa. The study found that the prevalence of ante-mortem dementia diagnosis did not vary between post-mortem CSF Cu, CSF Zn, or the other metals. They did find a trend of higher CSF Cu and Zn levels with fewer neuritic plaque counts in either the neocortex or the hippocampus. They found no relationship with the other metals and neuropathology.

Animal studies

Al and interaction with/effect on Fe, Zn, Cu, and/or Mn

8. The Tg2576 AD mouse model, which carries a transgene coding for the 695- amino acid isoform of the human Alzheimer Aβ precursor protein (ABPP), derived from a Swedish family with early-onset Alzheimer's disease. The Tg2576 mouse expresses high levels of the mutant ABPP in the cell body of neurons. They exhibit neuronal loss, synaptic alterations, inflammation and gliosis and dendritic alterations, and have a phenotype characterised by memory deficits after 9-10 months of life.

9. Using this AD model, Gomez et al. (2008) evaluated the concentration of metals hypothetically implicated in neurodegenerative diseases, such as Al, Fe, Cu, Mn and Zn, in the cerebral regions of the brain, the liver, kidney and bone following chronic exposure to Aluminium lactate. The authors had intended to give female mice 1 mg/g of diet for 6 months but, due to manufacturer error, the dose given to the animals was 370 µg of Al/g of diet, which they calculated to be equivalent to approximately 54 mg/kg bw/day. The results for Al were discussed in LSG/11/2. Briefly, the authors did not find any significant differences in Al levels in the different brain regions, liver or kidneys of control wild-type (WT) or in control transgenic (TG) animals. Al was not detected in bone tissue of either control WT or TG animals. Following exposure of both wild-type and TG animals to Al, the highest levels of Al were found in the hippocampus, followed by those in cerebellum and cortex[109]. However, there were no significant differences in Al concentrations in any of the brain regions between genotypes. In the other tissues, higher Al levels were detected in the kidney of the wild-type animals following treatment but no significant differences were observed when these animals were compared with the homonymous TG exposed group.

10. For the different metals, Gomez et al. (2008) report that control wild-type (WT) and control transgenic (TG) animals did not show significant differences in Cu, Fe, Mn and Zn levels in the brain regions analysed at the end of the experimental period. Copper, zinc, manganese and iron in liver, kidney and bone did not show significant differences between genotypes. Following treatment of both wild-type and TG animals to Al, iron levels decreased in the cerebellum of TG animals, while the concentration of Zn significantly increased in the cerebellum of the same genotype. However, Cu and Mn levels did not show significant differences. The levels of Cu were similar in the liver and kidney of both wildtype and TG animals, whereas Fe concentrations were higher in livers of wild-type animals than in those of TG 2576 animals. Iron levels also increased in bone and kidney of the wild-type exposed groups. They also observed an increase in Mn concentrations in the liver of TG animals and the bone of wild-type animals. With respect to Zn, lower levels were observed in the bone of TG animals following Al exposure (Gomez et al, 2008).

11. Fattoretti et al. (2003 and 2004) investigated the effect of administering 2 g/L of Al chloride $AlCl_3$ x $6H_2O$ in drinking water for 6 months on the brain levels of Al, Cu, Zn and Mn in 22 month old male Wistar rats. Three areas of the brain were analysed for metal content namely a) prosencephalon and mesencephalon (PME), b) pons medulla (PMD) and c) cerebellum. PME ($p< 0.1$) and PMD ($p< 0.05$) showed a significant increase in Al concentration in treated animals compared to controls. No significant change was observed in the cerebellum. In the PME, there was a non-significant increase ($p<0.5$) in Cu, Zn and Mn concentration following Al administration. In the PMD, a significant increase was observed for Cu ($p< 0.05$) in Al treated rats, while a non-significant increase ($p<0.5$) was observed for Zn and Mn. In the cerebellum, Cu concentration was decreased non-significantly in treated rats, while a small but significant increase ($p< 0.01$) was observed for Zn. No significant change was observed in Mn concentration between Al treated and control rats.

12. Li et al. (2011) investigated the effects of aluminium chloride (430 mg/L) in drinking water (approx. 50 mg/kg bw/day) for up to 150 days on bone minerals, trace elements and bone mineral density (BMD) of the femur in male Wistar rats. The Al level increased gradually in the bone of Al treated group and this was significantly

[109] Data presented graphically, therefore not possible to present actual values.

higher than the levels in control groups. The levels of Zn, Fe, Cu and Mn in bone of Al treated rats decreased gradually and were statistically significantly lower than in control groups from day 60.

13. Golub et al. (2003) investigated the effect of a diet low in Fe, Zn, phosporous (P), Ca and Mg, to which Al was added, on developmental toxicity in female Swiss Webster mice, from conception to weaning. Control basal diets contained 7 µg Al/kg diet compared to 1000 µg Al/kg diet in Al exposed diets. Only metals of relevance are discussed here. Fe and Zn levels in the control diet were 75 mg/kg and 25 mg/kg diet compared to the deficient diet which contained 8 mg/kg Fe and 15 mg/kg Zn. A number of effects were observed. Pregnancy completion, as determined by ratio of deliveries to pregnancies in each group, was not affected by the different marginal diets. However, this ratio was influenced by Al in mice fed the marginal Zn basal diet. They found that deficiencies in the basal diet to which Al was added, had a significant effect on at least one of the end points examined (pregnancy weight gain and pup weight at weaning) with the exception of litter size. The marginal Fe diet resulted in less pregnancy weight gain and lower birth weights than in the other diets. Compared to control basal diet, all of the marginally deficient diets led to smaller litter size. However, a statistically significant Al effect on litter size occurred only with the marginal Fe diet (P=0.032). An index of postnatal mortality was constructed (the number of litters with 8 or more pups at birth but with less than 6 pups at weaning). An Al effect was observed for the marginal Zn basal diet. In the control diet with marginal Zn, 42 % of the litter were reduced to less than 6 pups compared to 8 % in the Al condition.

Al & Lead (Pb)

14. Shakoor et al. (2003) examined the influence of Al chloride, if any, on the neurotoxic effects of Pb acetate in male albino rats. Rats were exposed to Al (2% $AlCl_3$ in water, equivalent to 50 mg/kg bw) and/or Pb (lead acetate 2.5 % in water, equivalent to 125 mg/kg bw) for up to 90 days. On day 45 of the study, only rats treated with both Al and Pb exhibited a significant reduction ($p<0.01$) in the Forced Locomotor Activity (FLA) test. On day 90, rats treated with Al alone, Pb alone or both Al and Pb exhibited a significant reduction in FLA ($p<0.001$, $p<0.05$, $p<0.01$, respectively). A significant reduction in traction performance was observed in rats treated with both Al and Pb after 90 days. Reaction times to tail immersion tests found Al and Pb treated rats exhibited a significant increase on day 45. At 90 days, rats treated with Pb only, as well as those fed Al and Pb, exhibited an increase in reaction time to tail immersion. Significantly higher levels of Pb were observed in the brains of animals that received both Al and Pb over the 90 day period compared to controls (5.32 ± 1.0 µg/g nervous tissue of treated animals compared to 2.16 ± 0.29 µg/g nervous tissue of control animals). No effect was observed on relative brain weights of treated rats compared to controls. They also observed higher levels of malondialdehyde (MDA) and lower levels of acetylcholinesterase (AChE) enzyme in the brain homogenates of rats treated with both Al and Pb as compared to Pb only.

Al & Iron (Fe)

15. Turgut et al. (2004) investigated the effects of chronically administrated Al sulphate on iron metabolism-related parameters in the liver and blood of female adult Balb-C mice. The study also determined the effects of co-administration of Al with

vitamin E on the above mentioned parameters but the results will not be discussed here. Mice, aged 16 - 20 weeks were given 877 µmol $Al_2(SO_4)_3$/kg bw/d (equivalent to 300 mg/kg/d) in drinking water for 3 months. Serum and liver tissue levels of iron and ferritin were determined as well as serum levels of haemoglobin, haematocrit and Total Iron binding Capacity (TIBC). Turgut et al. found a decrease in serum haemoglobin and haematocrit levels in Al treated mice compared to controls. They did not find a statistically significant change in transferrin levels in the Al treated mice compared to controls. Chronic administration of Al did not cause any changes in serum iron, TIBC and ferritin levels compared to control animals. However, they did find that the levels of liver iron and ferritin increased following Al exposure. Ward et al. (2001) similarly found liver iron increased with Al exposure.

16. Farina et al. (2005) investigated the effect of long term exposure (18 months) to a low dose of Al sulphate (30 mM), diluted in a sodium citrate solution (35 mM) on haematological parameters in female Wistar rats, ad libitum. No. of red blood cells, haematocrit, haemoglobin concentrations were evaluated. Also iron status in liver and bone marrow, δ-ALA-D activity, erythrocyte TBARS, non protein thiols and osmotic fragility were analysed. Statistical analysis indicated significant decreases in the number of red blood cells, haemoglobin concentration and haematocrit in the Al exposed rats compared to controls. They found that serum Fe concentration was significantly lower in Al-treated rats. However, Al treatment did not change TIBC.

Al & Copper (Cu)

17. Becaria et al. (2006) evaluated the potential synergistic effects of a 12 week exposure on promoting inflammatory and oxidative events in B6C3F1 mice brains to Al lactate (10 or 100 µM, equivalent to 0.44 and 4.4 mg/kg bw/d, respectively), copper sulphate (8 µM (2 ppm)) or a combination of Al and Cu in drinking water. For oxidative and inflammatory markers they observed elevated levels of the cytokine TNF-α in the brains of animals exposed to Al (100 µM) or combined Al (100 µM) and Cu (8 µM) but there was no significant difference between the two treatment groups. Systemic changes in serum and spleen were also determined. In the serum, TNF-α level decreased in all metal-exposed groups compared to the control animals. Following Al treatment, levels of TNF-α in the spleen decreased in a dose dependent manner. Exposure to Al together with Cu further enhanced the decrease in TNF-α in the spleen. For IL-1α, the response was similar in the brain to the TNF-α response. However, the levels of IL-1α dose dependently increased in the serum of Al treated animals and co-exposure to Cu did not modulate this effect. Basal IL-1α levels were greater in the spleen than serum or brain and exposure to Cu, Al (10 µM) or Al (100 µM) did not affect the level of IL-1α in this tissue. However, co-exposure to Al and Cu increased the levels of IL-1α at both concentrations of Al. Exposure to Al (10 µM), Al (10 µM) and Cu, or Al (100 µM) and Cu significantly increased brain IL-4 levels compared to controls. IL-4 was undetectable in the serum. In the spleen, IL-4 levels decreased after Al exposure and this response was not modulated further by further addition of Cu.

18. Becaria et al. also examined oxidative markers and found that the lipid peroxidation product malondialdehyde (MDA) was significantly elevated in the brain tissue after exposure to Cu (8 µM) or Al (100 µM) or both. For nNOS immunoreactivity, the number of nNOS-immuno neurons increased in the frontal

cortex of mice exposed to Cu, Al (100 µM) or Al (100 µM) and Cu (8 µM). Co-treatment with Al and Cu decreased the response relative to Al (100 µM) alone. Individually or combined Al (100 µM) and Cu did not increase levels of Ab1-40 or Ab1-42. However, levels of APP were significantly increased after exposure to Al (100 µM) and Cu co-exposure further enhanced this effect.

Other Studies on metal interaction, but not Al

19. Maynard et al. (2002) investigated the effect of aging and APP and /or Aβ over-expression on Cu, Zn, Fe, and Mn levels in the brains of normal (BL6/SJL and BL6/DBA) and transgenic mice lines (TG2576, TgC100.wt and TgC100.V717F) across the majority of their lifespan. In both the non-transgenic stains, two way anova analyses, with age and sex as independent variables, revealed marked and significant increases in Cu and Fe levels. No significant age-sex interaction was observed in the BL6/SJL. Zinc levels showed no significant alteration with age but a significant age-sex interaction was found ($p<0.01$). When analysed separately, males displayed a relatively small increase (10%, $p<0.01$) in brain Zn levels across the age groups while female Zn levels remained relatively constant in all age groups. Mn levels showed no significant overall change with age and no significant age-sex interaction. In the BL6/DBA line, Mn levels, compared to BL6/SJL strain, showed a significant decrease with age ($p<0.01$) but no age-sex interaction was observed. For Zn, no significant overall change occurred with age in the BL6/DBA line. However, a significant age-sex interaction was found ($p<0.05$). The three transgenic mouse lines (TG2576, TgC100.wt and TgC100.V717F) displayed the same direction of age-related changes in Cu, Fe and Mn levels as their corresponding non transgenic background controls.

20. Maynard et al. (2002) also determined the effect of APP over-expression on brain homeostasis by comparing brain metal levels of TG2576 and BL6/SJL with age. Cu and Zn levels were decreased in TG2576 compared with BL6/SJL brains. However, Mn was significantly increased in TG2576 compared to BL6/SJL brains with no significant difference observed in Fe levels between the two groups of mice. They also determined the effect of Aβ over-expression on metal levels in the TgC100 mouse brain compared to BL6/DBA controls with age. They found a significant overall reduction in Cu and Fe levels in the TgC100.V717F line compared to BL6/DBA ($p<0.0010$, a small but significant overall increase in Zn levels and a significant increase in Mn levels in TgC100.V717F ($p<0.001$) compared to BL6/DBA controls. TGC100.WT showed similar results for Cu, Fe, Mn when compared to BL6/DBA. However, no significant difference was observed for Zn.

21. Maynard et al. (2009) examined the effect of chronic high intake of dietary Cu and Zn in drinking water on brain metal levels and the accumulation and solubility of Aβ in vivo in the transgenic TgC100 mouse model. A pilot feeding experiment established the maximum tolerable level of Zn in drinking water 1000 ppm and 150 ppm for Cu for these mice. The experiment fed mice a diet high in Zn (1000 ppm, 500ppm or 300 ppm, equivalent to 150, 75 and 45 mg/kg bw/d, respectively) or Cu (150 ppm and 100 ppm, equivalent to 22.5 and 15 mg/kg bw/d, respectively) and euthanatised at 5, 7, 11 or 17 months of age. A significant overall increase in brain Zn levels ($p = 0.001$) was found in high Zn fed mice, with no significant effect of mouse strain. Cu levels in the brain were not significantly altered by high Zn feeding with no statistical significant mouse strain effect on Cu level alterations due to high Zn feeding. The Cu/Zn ratio in brains of mice fed a high Zn diet was decreased compared to water controls but only reached statistically significance in the TgC100 line. High Cu feeding resulted in elevated Cu levels in both TgC100 and non transgenic mice. These non significant Cu elevations were accompanied by similar elevations in brain Zn levels, resulting in an unchanged Cu/Z ratio.

22. They also examined the ability of high Zn and high Cu diets to alter brain Aβ40 levels and solubility in TgC100 mice. Aβ40 levels in total homogenates showed no significant alterations due to the high Zn or Cu feeding, whereas soluble Aβ40 levels tended to decrease in Zn and Cu fed groups. No significant effect on protein markers of cellular stress or neuronal loss (NF200, GFAP, SOD1, APP and C100) were observed in brain homogenates of TgC100 mice fed high Zn (500ppm) or Cu (100 ppm) diets compared to controls. No marked differences were observed in the intensity or distribution of Aβ40 staining in mice fed diets high in Zn or Cu or in GFAP staining.

Summary

23. Water supplies to the Camelford area were contaminated with aluminium sulphate as a result of the Lowermoor water contamination incident. Increased concentrations of other metals such as copper, zinc, lead, iron and manganese also occurred. This update considered data on the potential interactions of these metals which may be of relevance to human health. As before, only studies using oral or dermal exposure were identified and obtained. Metals have been considered in pairwise combinations, with the major focus on combinations with Al, as this was the main contaminant. Consideration was also given to studies relevant to all potential interactions.

24. It is difficult to draw any particular conclusions from the studies presented here. Several combinations have shown effects but the biological significance of these effects remains unclear or unknown. It should be noted also that most studies were conducted at high concentrations of metals administered for prolonged periods.

Reference list to Appendix 29

Apostoli, P and Catalani, S. (2010). Metal Ions Affecting Reproduction and Development. Metal Ions in Toxicology: Effects, Interactions, Interdependencies. Metal Ions in Life Science, RCS, 8, 263-303.

Becaria A, Lahiri DK, Bondy SC, Chen D, Hamadeh A, Li H, Taylor R, Campbell A. (2006). Aluminum and copper in drinking water enhance inflammatory or oxidative events specifically in the brain. J Neuroimmunol. 176(1-2):16-23

Corradi, M and Mutti, A. (2010). Metal Ions Affecting the Pulmonary and Cardiovascular Systems. Metal Ions in Toxicology: Effects, Interactions, Interdependencies. Metal Ions in Life Science, RCS, 8, 81-105.

Farina M, Rotta LN, Soares FA, Jardim F, Jacques R, Souza DO, Rocha JB. (2005). Hematological changes in rats chronically exposed to oral aluminum. Toxicology, 209(1):29-37.

Fattoretti P, Bertoni-Freddari C, Balietti M, Mocchegiani E, Scancar J, Zambenedetti P, Zatta P. (2003). The effect of chronic aluminum(III) administration on the nervous system of aged rats: clues to understand its suggested role in Alzheimer's disease. J Alzheimers Dis. 2003 Dec;5(6):437-44.

Fattoretti P, Bertoni-Freddari C, Balietti M, Giorgetti B, Solazzi M, Zatta P. (2004). Chronic aluminum administration to old rats results in increased levels of brain metal ions and enlarged hippocampal mossy fibers. Ann N Y Acad Sci., 1019:44-7.

Fowler, B. (2010). Metal Ions Affecting the Kidneys. Metal Ions in Toxicology: Effects, Interactions, Interdependencies. Metal Ions in Life Science, RCS, 8, 133-141.

Golub MS, Germann SL, Keen CL. (2003). Developmental aluminum toxicity in mice can be modulated by low concentrations of minerals (Fe, Zn, P, Ca, Mg) in the diet. Biol Trace Elem Res., 93(1-3):213-26.

Gómez M, Esparza JL, Cabré M, García T, Domingo JL.(2008). Aluminum exposure through the diet: metal levels in AbetaPP transgenic mice, a model for Alzheimer's disease. Toxicology, 249(2-3):214-9.

Huang X, Moir RD, Tanzi RE, Bush AI, Rogers JT. (2004). Redox-active metals, oxidative stress, and Alzheimer's disease pathology. Ann N Y Acad Sci. 1012:153-63.

Lansdown, ABG. (2010). Metal Ions Affecting the Skin and Eyes. Metal Ions in Toxicology: Effects, Interactions, Interdependencies. Metal Ions in Life Science, RCS, 8, 187-246.

Lehmann, I, Sack, U and Lehmann, J. (2010). Metal Ions Affecting the Immune System. Metal Ions in Toxicology: Effects, Interactions, Interdependencies. Metal Ions in Life Science, RCS, 8, 157-185.

Li X, Hu C, Zhu Y, Sun H, Li Y, Zhang Z. (2011). Effects of aluminum exposure on bone mineral density, mineral, and trace elements in rats. Biol Trace Elem Res., 143(1):378-85.

Lowermoor Incident Health Advisory Group. Water pollution at Lowermoor, North Cornwall. Report of the Lowermoor Incident Health Advisory Group. Chairman: Professor Dame Barbara Clayton. Truro: Cornwall and Isles of Scilly Health Authority, 1989.

Lowermoor Incident Health Advisory Group. Water pollution at Lowermoor, North Cornwall. Second report of the Lowermoor Incident Health Advisory Group. Chairman: Professor Dame Barbara Clayton. HMSO, London, 1991.

Maynard CJ, Cappai R, Volitakis I, Laughton KM, Masters CL, Bush AI, Li QX. (2009). Chronic exposure to high levels of zinc or copper has little effect on brain metal homeostasis or Abeta accumulation in transgenic APP-C100 mice. Cell Mol Neurobiol. 29(5):757-67.

Maynard CJ, Bush AI, Masters CL, Cappai R, Li QX.(2005). Metals and amyloid-beta in Alzheimer's disease. Int J Exp Pathol. 86(3):147-59.

Naughton, DP., Nepusz, T and Petroczi, A. (2010). Metal Ions Affecting the Gastrointestinal System Including the Liver. Metal Ions in Toxicology: Effects, Interactions, Interdependencies. Metal Ions in Life Science, RCS, 8, 107-132.

Pohl, HR., Roney, N, and Abadin, HG. (2010). Metal Ions Affecting the Neurological System. Metal Ions in Toxicology: Effects, Interactions, Interdependencies. Metal Ions in Life Science, RCS, 8, 247-262.

Roberts BR, Ryan TM, Bush AI, Masters CL, Duce JA. (2012). The role of metallobiology and amyloid-β peptides in Alzheimer's disease. J Neurochem. 120(1), 149-66.

Roney, N, Abadin, HG., Fowler, B and Pohl, HR. (2010). Metal Ions Affecting the Hematological System. Metal Ions in Toxicology: Effects, Interactions, Interdependencies. Metal Ions in Life Science, RCS, 8, 143-156.

Shakoor A, Gupta PK, Kataria M. (2003). Influence of aluminium on neurotoxicity of lead in adult male albino rats. Indian J Exp Biol. 41(6):587-91.

Shcherbatykh I, Carpenter DO. (2007). The role of metals in the etiology of Alzheimer's disease. J Alzheimers Dis. 11(2):191-205.

Strozyk D, Launer LJ, Adlard PA, Cherny RA, Tsatsanis A, Volitakis I, Blennow K, Petrovitch H, White LR, Bush AI. (2009). Zinc and copper modulate Alzheimer Abeta levels in human cerebrospinal fluid. Neurobiol Aging., 30(7):1069-77.

Turgut G, Kaptanoğlu B, Turgut S, Enli Y, Genç O. (2004). Effects of chronic aluminum administration on blood and liver iron-related parameters in mice. Yonsei Med J., 45(1):135-9.

Ward RJ, Zhang Y, Crichton RR. (2001). Aluminium toxicity and iron homeostasis. J Inorg Biochem., 87(1-2):9-14.

Yokel R.A. (2006). Blood-brain barrier flux of aluminum, manganese, iron and other metals suspected to contribute to metal-induced neurodegeneration. J Alzheimers Dis.10(2-3):223-53.

Zatta P, Lucchini R, van Rensburg SJ, Taylor A. (2003). The role of metals in neurodegenerative processes: aluminum, manganese, and zinc. Brain Res Bull. 62(1):15-28

Zatta P, Drago D, Bolognin S, Sensi SL. (2009). Alzheimer's disease, metal ions and metal homeostatic therapy. Trends Pharmacol Sci. 30(7), 346-55.

Appendix 30: Potential study designs to address recommendations for neuropsychological and neurological investigations

Neuropsychological studies

1. Adult study

The purpose of this study would be to assess whether exposure to the contaminated water in the 1988 contamination incident is associated with an increased risk of abnormal neuropsychological status.

This study would examine two groups of individuals:

i. Randomly selected adults aged 42 years or over[110] who were living in 1988 in an area supplied with contaminated water and who drank the water.
ii. A reference group of matched individuals who were living in 1988 in an area not supplied with contaminated water and who did not drink the contaminated water.

The subjects would undergo an appropriate assessment of pre-morbid IQ and a battery of neuropsychological tests to assess neuropsychological status. These should address factors such as attention, memory, learning and information processing speed, and the potential moderating influences of depression and anxiety.

2. Developmental study

The purpose of this study would be to assess whether exposure to the contaminated water in the 1988 contamination incident has affected the cognitive development of children who were under 1 year of age at the time of the incident and children who were *in utero* at the time of the incident.

This study would examine the following groups of individuals:

i. Randomly selected individuals who were *in utero* during the period 7 to 10 July 1988, inclusive, and whose mothers were living in an area supplied with contaminated water and drank the water.
ii. A reference group of matched individuals whose mothers were living during the period 7 to 10 July 1988 in an area not supplied with contaminated water and who did not drink the contaminated water.
iii. Randomly selected individuals who were children under one year of age at the time of the contamination incident, were living in an area supplied with contaminated water and who drank the water.
iv. A reference group of matched individuals who were living in an area not supplied with contaminated water and who did not drink the water.

Sufficient individuals should be recruited to inclusion of subjects potentially exposed to the contaminated water during the first, second, and third trimesters and throughout to first postnatal year.

[110] This is to ensure that the individuals were adults ($\geq$ 18 years) at the time of exposure.

The subjects would be tested 1) with a broad neuropsychological test battery which addresses factors such as attention, memory, learning and information processing speed, and the potential moderating influences of depression and anxiety; 2) with an appropriate estimate of pre-morbid IQ, and 3) with questionnaires which assess implications in daily life, such as a quality of life questionnaire.

In both the adult study and the developmental study, applicants should provide the following:

i. Evidence that they are experienced in the administration and interpretation of the neuropsychological tests described in the tender.
ii. Details of how the tests will be analysed and interpreted.
iii. Justification of the group sizes to be used with power calculations.
iv. A consideration of whether it is possible to incorporate a dose-response assessment into the study design.
v. Information on how results will be fed back to individual subjects.
vi. Full costings.

Neuropathological studies

1. Long-term study

This study would use an enhanced protocol from the Medical Research Council (MRC) study on Cognitive Function and Aging (CFAS) and would recruit a random sample from GP practices in Cornwall, including the area which received contaminated water following the 1988 incident. Participants would be invited to donate their brains when they die.

If the study was to determine and compare the emerging incidence of dementia in different regions of Cornwall, a large sample size would be needed to account for attrition. Follow-up would be required every 2 years. To assess whether any higher incidence in the contaminated area was due to aluminium exposure, the study would need to include a detailed lifestyle questionnaire with relevant questions to determine total exposure to aluminium and, if possible, an assessment of body burden of aluminium.

Donated brains would undergo neuropathological examination and aluminium estimation on frozen brain samples. In order to diagnose CAA, the whole brain would be required.

This study was considered to be most likely to produce valuable results. It could produce incidence rates within 4 years to compare with the rest of the country but any work relying on accrued brain donation could take up to 20 years.

The questions which could be answered by such a study are:

- Does the incidence of different types of dementias in individuals living in the area which received contaminated water differ from those in other parts of Cornwall and England and Wales?

- Is any higher incidence in individuals in the contaminated area associated with either a higher past or current intake of aluminium, or with a higher body burden of aluminium?

2. Shorter term study

This would only be appropriate for individuals developing dementia before the age of 65 as health service records are poor for assessing the prevalence of dementia cases in older patients.

The study would use existing data from clinics, GP practices and other sources to draw up a register of early-onset dementia cases. Where possible, cases with CAA should also be included, although these may not present as dementia but with other symptoms. Those whose next-of-kin have symptoms would be invited to donate the brains of the individuals on the register at the time of death for full neuropathological examination and aluminium estimation on frozen brain samples.

The register could then be used to compare early-onset dementia prevalence in the area receiving the contaminated water with that in other parts of Cornwall and, if sufficient brains samples were donated, to compare the incidence of neuropathological diagnoses in different areas and the aluminium concentrations in individuals with the same neuropathology from different areas.

This study would indicate whether the prevalence of early-onset dementia in individuals living in the area which received contaminated water differed from those in other parts of Cornwall.

Appendix 31: Current procedures for the management of chemical incidents

1. At the time of the Lowermoor incident, there were essentially no structures in place to deal with chemical incidents such as pollution of the water supply. Following the incident, a number of new procedures and organisations were established by the Department of Health to improve the arrangements within the NHS for the investigation and public health management of chemical incidents. Together with other major chemical incidents, such as the Bhopal disaster of 1985 and the deliberate release of the organo-phosphate nerve agent sarin on the Tokyo underground in 1995, the Lowermoor incident provided a major impetus to the development of local, regional and national structures for the management of the public health consequences of chemical incidents in the UK.

3. In the mid 1990s, regional service provider units (RSPUs) were established in England, Wales and Scotland, providing advice and support in the event of a chemical incident across the whole of the UK, as well as Eire. Health authorities were required to contract with one of the four RSPUs, which were in Birmingham, Cardiff, London and Newcastle. As a consequence of the "internal market" and the "purchaser-provider" split of the time, the provision of advice to health authorities by RSPUs was geographically diverse, with neighbouring areas frequently receiving support from different RSPUs. The Scottish Centre for Infection and Health (SCIEH) served as the RSPU in Scotland.

4. The establishment of RSPUs was further supplemented by the formation of the National Focus for Chemical Incidents in 1997. Funded by the Department of Health and devolved administrations, the National Focus for Chemical Incidents served to co-ordinate the activities of the RSPUs and collected, integrated and collated information from all agencies and organisations involved in management of incidents, providing timely advice to the DH and/or devolved administrations. All these organisations were consolidated in April 2003 when the Health Protection Agency (HPA) was established.

5. In the event of a chemical contamination of the water supply, there is now a statutory requirement for water companies to inform the Director of Public Health in the primary care trust[111] covering the affected area. The primary care trust would seek support from the local Health Protection Unit (HPU). HPUs are part of the Local and Regional Services Division of the HPA (LARS) and there are about 100 serving the 301 primary care trusts in England, giving support in the event of chemical, biological or radiological incidents.

6. In Wales, the infrastructure is slightly different, with the formation of 23 local health boards instead of primary care trusts. These are supported by the National Public Health Service for Wales, which is composed of consultants in communicable disease control, support staff and the former Public Health Laboratory Services in Wales. Although not a part of the HPA *per se*, the National Public Health Service for Wales has functions analogous to LARS.

[111] Primary Care Trusts have taken over most of the duties of district health authorities. They cover a smaller area and population size than the old health authorities

7. The model, therefore, is for local expertise, whether in LARS or the National Public Health Service for Wales, to provide the initial management of chemical, biological and radiation events.

8. To support the HPUs and National Public Health Service for Wales in the management of chemical incidents, the HPA has 4 regional centres of chemical expertise in its Radiation, Chemicals and Environmental Hazards Directorate (CRCE), which has a headquarters in Harwell, Oxon. CRCE provides 24 hour, 365-day/year support and advice to first line responders, the NHS, local authorities, the HPA and other agencies, and government departments on the likely public health consequences of exposure to environmental chemicals. Advice provided encompasses the principal areas of environmental risk assessment and decontamination, modelling and sampling, clinical management and biological sampling, public health consequences, risk communication and epidemiological follow up.

9. The local structures, whether primary care trusts and HPU or local health boards and National Public Health Service for Wales, would decide, in discussion with other relevant bodies, what action was necessary to ensure protection of public health, and whether any follow-up action should be taken and, if so, what the action should be.

The Water Industry

10. Changes in the organisation and regulation of the water industry were already planned at the time of the incident. The legal framework before and after 1989 is outlined in Appendix 7 of this report. The incident itself led to at least three changes: immediate new procedures by water companies to prevent such an incident happening again (eg stringent procedures for checking and supervision of chemical deliveries, improved monitoring of the water treatment process and of the finished water); a new criminal offence of supplying water unfit for human consumption; and, as mentioned above, a statutory requirement for water companies to inform the NHS in the event of an incident.

11. Also, with the privatisation of the water industry, the Drinking Water Inspectorate (DWI) was established. This body acts as a technical auditor. It has three main functions: assessment of compliance data against statutory standards; inspection of sites, procedures and policies in relation to the supply and treatment of drinking water; and assessment of water quality incidents. In the event of an incident, it can take enforcement action and initiate prosecutions under Section 70 of the Water Industry Act 1991. DWI is notified of all events and, where appropriate, notifies the HPA and other stakeholders based on an assessment of the individual circumstances. In the case of major incidents (not just pollution incidents but, for example, plane crashes which might affect the water supply) the water company must also notify the Department of the Environment, Food and Rural Affairs (Defra) which oversees water-related major emergencies. Water companies must have contingency plans in place in the event of an emergency eg provision of alternative supplies to the public.