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

Preface

In 2003 the Committee took another major step forward in improving the openness and transparency of its working by permitting observers to attend committee meetings. So far, the numbers attending have been very small, but an important principle has been established. I welcome this decision, which has allowed interested parties to more fully understand the Committee's deliberations. More information on this process is described elsewhere in this report.

The Committee has provided advice on a number of chemicals that may be present in various foods, including metals such as arsenic, mercury and nickel, fluorine, iodine, brominated flame retardants, terphthalic acid, the enzyme chymosin and the bulk sweetener erythritol. The Committee published its Report on Phytoestrogens and Health and established a new working group to consider Variability and Uncertainty in Toxicology. Other generic issues discussed include guidelines for exposure assessment and the use of physiologically-based pharmacokinetic models.

The Food Standards Agency has occasionally needed to seek urgent advice on a food safety issue. These related to the use of 2,4-dinitrophenol as a dietary supplement, detection of fumonisins in maize meal, use of an unauthorised dye in chilli powder, and preliminary data on nickel leaching from kettles. Advice given between meetings is followed by a paper to the full committee at the subsequent meeting and is described in a separate section of this annual report.

This is my second annual report as COT chairman. I was sorry to lose the wisdom and accumulated experience of a number of members who completed their terms of office, but also pleased to welcome new members bringing new perspectives and expertise to the committee. I am grateful to Professor Rowlands for agreeing to take on the position of vice-chairman after Professor Aggett retired from the committee.

Finally, I would like to add my sincere thanks and appreciation of the work of the administrative and scientific secretariats without whose excellent work the Committee would not be able to function.

Professor I A Hughes (Chairman)
MA MD FRCP FRCP(C) FRCPH F Med Sci.

COT evaluations

Arsenic in food: results of the 1999 Total Diet Study

1.1 In 2002 the Food Standards Agency completed a survey of the total and inorganic arsenic levels in samples from the 1999 Total Diet Survey (TDS), which was carried out between 1999 and 2002. The COT was asked to comment on the survey and assess if the levels of arsenic in the diet posed a risk to human health.

1.2 The COT noted that inorganic arsenic is genotoxic and a known human carcinogen and therefore exposure should be as low as reasonably practicable (ALARP). The COT also noted the limited evidence to support the commonly held assumption that organic arsenic is less toxic than inorganic arsenic. Overall, the COT concluded that there are no relevant tolerable intakes or reference doses by which to assess safety of either inorganic or organic arsenic. The low concentrations of inorganic arsenic appeared to be consistent with dietary exposure being ALARP, but refinements to increase the sensitivity of the analysis would be welcome.

1.3 Fish was the major contributor to dietary exposure to arsenic, and the predominant form of arsenic in fish is organic. The COT considered that the limited evidence indicated that the dietary exposure to organic arsenic identified in this survey was unlikely to constitute a hazard to health. The average population dietary exposure to total arsenic was lower than that estimated for previous years, providing reassurance that exposure to total arsenic through food is not increasing.

1.4 The COT statement is included at the end of this report.

Brominated flame retardants in fish from the Skerne-Tees rivers system

1.5 In 2003, the COT considered the results of a survey investigating the concentrations of brominated flame retardants (BFRs) in brown trout and eels from the Skerne-Tees river system. The Committee was asked to assess the toxicological properties of selected BFRs in order to advise on any health implications of the estimates of dietary exposure.

1.6 BFRs are structurally diverse chemicals used in plastics and other materials to enhance their flame retardant properties. The chemicals that were analysed for in the survey were those considered to be representative of the polybrominated biphenyl ethers (PBDEs) congeners used and produced in the Skerne-Tees area and hexabromocyclododecane (HBCD).

1.7 The COT concluded that the toxicological databases for the PBDEs and HBCD were insufficient to allow establishment of tolerable daily intakes. A Margin of Exposure (MoE) approach was therefore used in the risk assessment.

1.8 Members considered that comparison of the worst case estimated intakes from consumption of a single portion of eels or trout per week from the Skerne Tees with the available toxicological data indicated that these intakes were unlikely to represent a risk to health. However, in view of the uncertainties surrounding the toxicological database and exposure assessments, this conclusion was considered tentative.

1.9 The COT statement is included at the end of this report.

Enzyme submission – Chymosin preparation derived from GM *Aspergillus niger var. awamori*

1.10 Chymosin is an enzyme preparation that has previously been granted clearance by the COT. In December 2000, the manufacturer sought clearance of a modified purification and recovery procedure for this enzyme preparation. The COT has raised a number of questions relating to the comparison of the product with the material used in the toxicity studies and the purity and specifications of the product (2000 Annual Report, page 16).

1.11 In May 2003, the manufacturer provided additional information in response to the previous COT request intended to demonstrate comparability between the new material and that used in the toxicity studies, the performance of the chromatography process used and product uniformity. A number of concerns were identified: the lack of any direct comparison with the material used in the original toxicity studies, a lack of data demonstrating that no new or potentially hazardous impurities were introduced by the new process, a lack of data on the performance of the column over its full lifetime, the lack of data on epichlorhydrin levels in the final product and information on the current and intended usage of the product. Members considered that the data provided did not adequately address the concerns that had been raised and were therefore unable to give full approval for the new processing procedure.

1.12 In December 2003, the manufacturer submitted further information to the COT to address the points raised. Representatives from the manufacturer were also in attendance at the meeting to answer any additional questions. On this occasion, the COT were satisfied that the company had provided sufficient information to address their concerns and agreed full approval for chymosin as produced by the new process. However, the COT requested information on the effect of column regeneration on the process, in order to determine the lifetime of the column.

Erythritol

1.13 Erythritol is a polyol which has potential uses as a sweetener and as a binding agent, thickener, bulking agent, sequestrant, flavour enhancer and freezing point depressant in a variety of foods and/or beverages. The COT was asked to consider the acceptability of the use of erythritol in beverages. Excessive ingestion of polyols causes laxative effects and for this reason other polyols are not currently authorised for use in beverages as intakes would potentially be much higher than from foods. However, higher intakes of erythritol than other polyols can be ingested before laxation ensues.

1.14 The COT considered laxation to be an unpleasant side effect that should be avoided in adults. Children were of more concern as they are more susceptible to dehydration. The laxation caused was considered to be a local physiological effect caused by excessive bolus ingestion of the polyol. The COT considered that for adults it was not appropriate to express the NOEL for laxative effects on a per kg bodyweight basis as the length of the colon does not vary between adults of different bodyweights. However, children would be expected to be more susceptible due to the shorter length of the GI tract.

1.15 In order for the COT to be able to determine a NOEL the committee would require information on the relative sensitivity of young children to adults. It was suggested that it may be possible to obtain this information from post-market surveillance of foods and beverages (where authorised) containing erythritol or other polyols. The COT concluded that it was not acceptable at present to use erythritol in beverages.

Fluorine in the 1997 Total Diet Study

1.16 Fluorine, bromine and iodine in the 1997 Total Diet Study was originally considered by the COT in 2000. Consideration of any potential effects of dietary fluorine intakes was deferred as fluoride (the ionic form of fluorine found in food) was being considered by the Expert Group on Vitamins and Minerals (EVM). The COT considered the draft EVM review of fluoride in 2001, but agreed that it would be more appropriate to wait until the EVM had finalised its view.

1.17 The EVM subsequently agreed that fluoride was not within its remit and has thus not completed a risk assessment for fluoride. Following the EVM's conclusions the COT considered the available data on fluorine and health outcomes and data on intakes from the 1997 Total Diet Study and from non-dietary sources.

1.18 The COT noted that the most sensitive effect of fluorine (as fluoride) in humans was dental fluorosis, a mottling of the tooth enamel, which occurs in children below the age of 8 years. The COT established a NOAEL for aesthetically significant dental fluorosis of 0.05 mg/kg bw/day. It was noted that the results of the Total Diet Study indicated that a small proportion of children may be at risk of moderate dental fluorosis due to dietary exposure to fluoride. The COT noted that the integrity of teeth with mild or moderate dental fluorosis was not affected, but recommended that more research was needed to determine the impact of the cosmetic effect of dental fluorosis on affected individuals, and on any possible long-term health effects in people with dental fluorosis. No adverse effects other than mild to moderate dental fluorosis were expected to be associated with dietary fluorine intakes in the UK.

1.19 The COT statement is included at the end of this report.

Hexachlorobutadiene contamination at Weston Quarries

1.20 In 2000 the COT was asked for advice after environmental contamination with hexachloro-1,3-butadiene (HCBD) was found around a disused waste dump in a quarry in Weston, Runcorn (2000 Annual Report, page 20). The COT noted that the target organ for toxicity was the kidney and determined a NOAEL for non-carcinogenic effects of 0.2 mg/kg bw/day from animal studies. This was calculated to correspond to continuous inhalation of air containing 60 ppb HCBD. The COT advised that an air concentration of 0.6 ppb (incorporating an uncertainty factor of 100) would not be expected to cause health risks for non-carcinogenic effects.

1.21 The COM had advised that it would be prudent to consider HCBD to be an *in vivo* mutagen. However, the COT noted that continuous exposure to HCBD at a level of 0.6 ppb resulted in an intake 10,000 times lower than the minimal carcinogenic dose in animals. Therefore 0.6 ppb was recommended as a minimum risk level for risk management purposes.

1.22 In 2003 the COT considered new data, including an assessment of biochemical markers of renal glomerular and tubular toxicity in residents of houses in which HCBD had been detected at average concentrations above 0.6 ppb. The assessments were carried out within 2 months and at least 10 months after the residents were evacuated from their houses. Mean levels of kidney markers had decreased on the second round of testing for all but retinol binding protein. The mean levels of markers were all within the range that is considered normal by the Health and Safety Laboratory in workers. However, the data indicated that 19% of the individuals still had marker levels above the reference range at the second round of testing.

1.23 It was noted that the pattern of changes in individual marker levels was not consistent with the pattern of renal damage seen in animal studies, which could indicate that the apparent decreases were simply due to natural fluctuation. However, the COT considered that the data indicated that any sub-clinical effects on the kidney were now resolving and that this provided reassurance that people had been protected by the risk management action taken.

Iodine in cows' milk

1.24 The COT has reviewed iodine concentrations in cows' milk on a number of occasions since 1989. During these reviews the COT recommended there was a need for additional information on the different chemical forms of iodine which might be present in cows' milk (2000 Annual Report, page 17). In October 2002, the Committee considered the results of a research project on iodine speciation in milk. Following this discussion COT requested further information on possible sources of iodine in milk (2002 Annual Report, page 20).

1.25 Surveys have indicated a seasonal effect on iodine levels in milk. There is very limited information on the species of iodine present in cows' milk although studies have indicated that the predominant form is iodide. A study to determine the species of iodine present in cows' milk indicated that the majority of iodine eluted at a retention time comparable to that of iodide but did not definitively identify the species. Traces of iodine-containing substances with molecular weights ranging from 1 to $\geqslant$ 600 kDa were also detected but not identified. In human breast milk, 80% of the iodine present is reported to be iodide with the remaining 20% as organically bound iodine. There is no information in the literature as to the identification of these organic bound compounds.

1.26 It is generally assumed that following ingestion iodine and iodate are reduced to iodide in the gut. However, much of the toxicological information in the literature does not distinguish between different species.

1.27 Members noted that dietary iodine deficiency had been a significant problem in the recent past and because of this the intake of iodine from milk was generally considered beneficial. Members noted the additional information on iodine species in milk and concluded that there were no health concerns related to presence of iodine in milk at current levels. However, if in the future production methods altered and the iodine content of milk increased this might need to be re-evaluated.

Mercury in fish and shellfish – reconsideration of 2002 COT opinion

1.28 In 2002, the COT had considered the results of a survey of mercury in imported fish and shellfish and UK farmed fish and their products (see 2002 Annual Report, page 16). The COT considered that dietary exposure to mercury resulting from average and high level consumption of fish for which consumption data were available was not likely to result in adverse effects. It also commented on the number of portions of shark, swordfish, marlin or tuna that would not be expected to result in adverse effects on the developing fetus or infant. However, the COT noted uncertainties in the risk assessment and agreed that its conclusions should be reviewed following the JECFA evaluation of methylmercury in 2003.

1.29 In June 2003, JECFA revised the PTWI in order to protect against neurodevelopmental effects, and the COT therefore subsequently reviewed its 2002 statement.

1.30 The COT agreed that the 2003 JECFA PTWI of 1.6 μg /kg bw/week was sufficient to protect against neurodevelopmental effects in the fetus. The COT noted the lack of information on susceptibility of infants to methylmercury and agreed that, as a precautionary measure, the 2003 JECFA PTWI of 1.6 μg /kg bw/week should also be applied to infants. The Committee noted that there was no new evidence to indicate health risks other than neurodevelopmental effects at the 2000 JECFA PTWI of 3.3 μg /kg bw/week, and therefore this guideline could be applied to protect against non-developmental adverse effects in the general population.

1.31 The COT also considered research needs and noted the difficulty in extrapolating possible effects from methylmercury exposure associated with regular consumption of fish in the Seychelles Islands, to occasional consumption of fish containing higher concentrations of methylmercury in the UK. However, conduct of meaningful epidemiological studies, with adequate sized populations, would be difficult in the UK. Mechanistic studies could help to elucidate population groups more at risk. Development of analytical methodology to allow direct measurement of methylmercury would help to identify whether exceedances of the guidelines are of concern. Members also suggested that research integrating the risks with nutritional benefits could be of value. This could be considered further by the joint COT/SACN subgroup reviewing the risks and benefits of fish consumption.

1.32 The COT statement was revised to take into account the new PTWI, and is included at the end of this report. This 2003 COT statement supersedes the version in the 2002 Annual Report.

Metals and other elements in infant foods

1.33 The COT was informed of the results of a Food Standards Agency survey of metals in infant food. This survey was carried out to establish the concentrations of aluminium, antimony, arsenic, cadmium, chromium, copper, lead, mercury, nickel, selenium, tin and zinc in a representative range of commercial infant foods and formulae. Estimates of dietary exposure were calculated for each of the 12 elements using three different approaches to allow an assessment of the dietary exposure to each metal by infants aged 0-12 months.

1.34 The COT considered that consumption data based on the 1986 survey of British infants was likely to result in an underestimation of dietary exposure, but was useful as it allowed comparison with the previous survey of elements in infant foods. An approach based on manufacturers' feeding recommendations was probably an over estimate of dietary exposure and could be considered to be a worst case scenario. Members agreed that these two approaches should be used in assessing the results of the survey, however new studies to determine the patterns of consumption of foodstuffs in infants would be welcomed.

1.35 Members reviewed the concentrations of elements in the infant foods, and considered the potential toxicological effects of the estimated dietary exposures. Overall, Members agreed that the consumption of infant foods sampled in the survey would not result in the intake of such quantities of any of the analysed elements such as would give concern for the health of the infants. Future assessments would be more robust if information was made available on the actual species of metal present in the food and on the contribution of the metal concentrations in water used to reconstitute formula and dried foods.

1.36 The COT statement is included at the end of this report.

Metals and other elements in the 2000 Total Diet Study

1.37 The COT was also informed of the results of a Food Standards Agency survey of aluminium, arsenic, cadmium, chromium, copper, lead, manganese, mercury, nickel, selenium, tin and zinc in the 2000 Total Diet Study (TDS). Estimates of dietary exposure had been calculated for each of the 12 elements using food consumption data taken from the National Food Survey and the National Diet and Nutrition Surveys (NDNS).

1.38 The COT reviewed the concentrations of elements in the food samples, and considered the potential health effects of the estimated dietary exposures. Whilst there were no specific concerns related to the estimated dietary exposures, Members agreed that in future surveys of elements in food, priority should be given to those of greatest toxicological concern such as arsenic, mercury and lead, and that speciation of metals such as mercury, arsenic and chromium would be helpful for the risk assessment.

1.39 The COT statement is included at the end of this report.

Nickel leaching from kettle elements into boiled water

1.40 In January 2003, COT Members were asked to provide urgent advice on the health implications of a report on nickel leaching from kettle elements into boiled water, based upon results of a study commissioned by the Drinking Water Inspectorate (DWI). The study reported that more nickel leached into water boiled in kettles with exposed nickel-plated copper heating elements than when the water was boiled in kettles with exposed stainless steel elements or concealed elements. The study also reported that filtering the water in commercially available filter jugs increased the amount of nickel leaching from exposed nickel-plated copper heating elements.

1.41 Members were provided with the full DWI study report, a summary of the data drafted by the Secretariat, the draft risk assessment of nickel from the Expert Group on Vitamins and Minerals (EVM) and an opinion previously provided by a COT expert to support the EVM evaluation. Seven Members were able to provide written comments in the time available. A summary of the COT comments, drafted by the Secretariat and approved by the Chairman, is included at the end of this report.

1.42 The COT concluded that the results of the DWI report supported previous observations that boiling water in some types of kettle may result in elevated levels of nickel in the water. No other conclusions could be reached in the absence of statistical analysis of the data. In order to assess the risks associated with nickel in boiled water, more information was needed to derive exposure data based on water boiled under conditions similar to those used in homes, the work-place and catering establishments.

1.43 Following this assessment, the FSA advised people with nickel allergic dermatitis who were considering buying a new kettle, that they should either choose a flat-bed kettle or seek advice from retailers on which kettles have stainless steel elements.

1.44 In December 2003, the COT reviewed the results of an additional study commissioned by the Scottish Executive. Members noted that the statistical concerns in the earlier study were addressed in the new study. However the extreme differences between the results of the laboratory and consumer phases of the study, and the uncertainty regarding the reasons for these differences, meant that it was not possible to estimate potential levels of dietary exposure. The COT therefore again could not conduct a risk assessment and considered it would be beneficial if the Secretariat met with the study sponsors to discuss the information required.

Terephthalic acid

1.45 In 2000, the Committee reviewed the health implications of the results of a survey of terephthalic acid (TPA) migration from can coatings into food (2000 Annual Report, page 24). In particular, the Committee was asked to give its views on the possibility that TPA might have endocrine disrupting activity. The Committee considered that the available toxicity studies were inadequate to exclude this possibility. It was therefore recommended that appropriate studies should be carried out to determine

whether TPA possesses endocrine disruptor activity. The Food Standards Agency directed industry to carry out this further toxicological work and to keep migration of TPA and isophthalic acid, from can coatings into food, to a minimum.

1.46 In June 2003, BP Chemicals Ltd submitted the report of a full multigeneration reproduction toxicity study on terephthalic acid. Members considered that the information provided in the report was sufficient to demonstrate that TPA does not have endocrine disrupting effects at 20000 ppm in the diet, the highest dose tested.

1.47 However, Members noted that reductions in kidney weights occurred at all doses of TPA. Therefore, the dose resulting from administration of 1000 ppm TPA in the diet appeared to be the lowest observable effect level (LOEL) for effects on the kidney. This LOEL was in the region of 100 mg/kg bw/day, which appears to be lower than the dose used by the Scientific Committee on Food in deriving the temporary TDI of 0.125 mg/kg bw/day. Histopathological changes in the urinary bladder and the kidney were reported at the highest dose (20000 ppm) but these organs had not been examined in the mid- and low dose groups (5000 and 1000 ppm respectively).

1.48 The COT considered that it was important to follow up the effects observed in the urinary bladder and the kidney and asked for information on the histopathology of these organs if they are available.

Urgent advice provided by COT

2,4-Dinitrophenol

1.49 The Food Standards Agency (FSA) was notified via the European Commission Rapid Alert System for Food and Feed that a Finnish body builder became seriously ill after taking some capsules purchased from a website, apparently based in the UK. Further information indicated that the individual had purchased 'fat-burner' capsules containing 2,4-dinitrophenol (2,4-DNP). This website marketed a variety of products aimed primarily at the bodybuilding community and 2,4-DNP was portrayed as a way of losing excess fat. 2,4-DNP is an industrial chemical with no approved human uses.

1.50 The Medicines and Healthcare products Regulatory Agency (MHRA) considered that 2,4-DNP was not a medicinal product. The MHRA identified other items on the website that would be a cause for concern and would require further investigations.

1.51 A risk assessment was undertaken based on literature searches identifying observed human effects and information provided by the Finnish authorities on levels of 2,4-DNP in the capsules.

1.52 DNP is a metabolic poison. Signs of acute poisoning include nausea, vomiting, restlessness, flushed skin, sweating, dizziness, headaches, rapid respiration, tachycardia, fever and cyanosis, possibly leading to coma and death. The lethal oral dose in humans is 1 to 3 g.

1.53 The capsules were advertised on the website as containing 200 mg DNP, but Finnish authorities have reported about 380 mg/capsule. There appears to be significant variability in the amount contained in the capsules. Based on the reported analytical findings taking 3 or 4 of these capsules at once could be lethal. Apparently, the toxicity runs a rapid course, such that death or recovery occurs within 24 to 48 hours of ingestion.

1.54 DNP is also associated with chronic effects; these include formation of cataracts and skin lesions, weight loss, cardiovascular effects and effects on bone marrow and the CNS. The US EPA has established a Reference Dose for chronic oral exposure for DNP of 0.002 mg/kg bw/day. This was based on reports of cataract formation when DNP was used medicinally (as a slimming pill), with a LOAEL of 2 mg/kg bw/day and a total uncertainty factor of 1000. This indicates that repeated consumption of just 140 mg/day in an average 70 kg man, i.e. less than half of one capsule, could result in harmful effects.

1.55 The COT Chairman was consulted on the risk assessment and agreed with the conclusion that there were both short and long term health risks associated with 2,4-DNP.

1.56 The FSA considered that 2,4-DNP was not suitable for human consumption and advised consumers not to take any product containing 2,4-DNP at any level. This advice was issued without compromising further investigations or prosecutions by other bodies.

Fumonisins in maize meal

1.57 In 2003, the Food Standards Agency requested advice on a risk assessment on fumonisins in maize meal. This was produced by the Secretariat in consultation with the COT chairman, and is included at the end of this report.

1.58 Fumonisins are mycotoxins produced by the fungi *Fusarium verticilloides* and *Fusarium proliferatum*. The three most common fumonisins, B1, B2 and B3 usually occur together, with the fumonisin B1 generally found in the highest amount and fumonisin B3 present in small amounts, if at all. The toxins are predominantly found as contaminants of maize and maize products, although they have, on occasions, been found in other cereals and cereal products albeit at low levels. Fumonisins have been shown to be both hepatotoxic and nephrotoxic in rodents after short term exposure and there is evidence for carcinogenicity in the liver and kidney after long term exposure. Fumonisins have been implicated as a possible factor in the increased incidence of oesophageal cancer in some populations.

1.59 The Agency is conducting an on-going survey of mycotoxins in maize-based foodstuffs. During this survey two maize meal products were found to contain fumonisins that exceed the proposed European maximum level of 500 μg/kg for fumonisin B1 + fumonisin B2. The affected products were withdrawn from sale.

1.60 The risk assessment, as agreed by the COT chairman, concluded:

- *The levels of fumonisins found were not a concern for the health of those consuming the affected products already sold, given the low levels of consumption of maize meal. However, if consumers were concerned they were advised to dispose of the affected products.*

Sudan I found in chilli powder

1.61 Sudan I, a dye that is not permitted for use in food, was found in some food products manufactured in the UK that contain chilli powder imported from India. The source of the Sudan I was determined to be adulterated chilli powder.

1.62 There is evidence that Sudan I is carcinogenic in rodents and genotoxic *in vitro* and *in vivo*. Following consultation with the chairmen of the COT, COC and COM, it was agreed that, although there are some incomplete and possibly equivocal results, it is prudent to assume that Sudan I is a genotoxic carcinogen and that dietary exposure should be as low as reasonably practicable (ALARP).

1.63 Based on this risk assessment and the fact that Sudan I is not a permitted food additive, the Agency has been working with the local authorities and industry to ensure that products containing Sudan I do not enter or are removed from the food chain. The Agency has also issued press releases informing consumers of the products contaminated with Sudan I, and advising people who have bought any of these products not to eat them.

1.64 The companies originally identified as being responsible for supplying the contaminated chilli have had their licences to trade suspended. In addition, new legislation has been introduced within the European Community (2003/460/EC). It states that all hot chilli and hot chilli products imported into the Community in whatever form, intended for human consumption, should be accompanied by an analytical report provided by the importer or food business operator concerned demonstrating that the consignment does not contain Sudan I. The legislation also states that Member States shall carry out random sampling and analysis of hot chilli and hot chilli products at import or already on the market.

1.65 The risk assessment, agreed in consultation with the COT, COM and COC chairmen, is at the end of this report.

Committee procedures and working groups

Horizon scanning

1.66 Most of the Committee's work is based on the need for advice from Government Departments, particularly the Food Standards Agency and Department of Health, and thus tends to be reactive. Members have agreed that they wish to have an annual horizon scanning agenda item to discuss topics that are likely to be of interest/concern in the future. A list of future topics is displayed on the COT website, allowing interested parties an opportunity to provide additional information.

1.67 Members were provided with an update on the literature relating to toxicogenomics and proteomics, subsequent to the COT/COC/COM joint symposium in October 2001. Members commented that a considerable amount of data is being generated, and although these may be of value in hazard identification, the relevance to risk assessment is still uncertain. The data therefore did not warrant revision of the conclusions reached at the joint meeting. However, Members found the paper a useful means of keeping track of current data and methodology and considered that an annual update of the advances reported in the literature, especially with regard to validation of techniques and bioinformatics, would be helpful.

1.68 Other topics suggested under horizon scanning were:

- Adverse trends in the development of the male reproductive system;
- Proposal for a working group on uncertainty factors in toxicology.

1.69 These topics were taken forward in subsequent discussions and are discussed in more detail elsewhere in this report. In addition, Members were reminded that they may inform the Secretariat at any time of any substances for which the toxicological data require evaluation, or of other topics of emerging importance.

Phytoestrogens and health

1.70 In 1999, the COT established a Working Group to advise on the health implications of dietary phytoestrogens through review of published scientific research and the Food Standards Agency phytoestrogen research programme.

1.71 The COT had discussed the Working Group's draft report at its meetings in February and July 2002 and the report had been issued for public consultation between October and December 2002. The Working Group had received 47 submissions, which included a comprehensive review by an independent expert in the field. Additionally, at the request of the Working Group, the Scientific Committee on Nutrition (SACN) had provided an opinion on the sections of the report relating to soy-based infant formula. The Working Group on Phytoestrogens met in January 2003 to consider the submissions and as a result the report had been modified.

1.72 In February 2003, the Committee endorsed the report, subject to agreed changes. The final report was published in May 2003 and is available at http://www.food.gov.uk/multimedia/pdfs/phytoreport0503.

Procedure for holding COT meetings in open session

1.73 In December 2002, the COT agreed in principle to move to open meetings during 2003 but wished to discuss and agree a more detailed protocol for holding meetings in open session. This protocol

was intended to minimise adverse impacts on the ability of the Committee to function effectively and to provide adequate security for members and officials. The protocol was produced in line with the Committee's existing Code of Practice on openness. It covers all aspects of the advertising of meetings and the application process, any restrictions on attendees and limitations on attendance. The protocol describes the circumstances where discussion is not possible in public and arrangements to discuss these in closed session. Members specified that every agenda should include an opportunity for observers to ask questions. The protocol was agreed by COT in February and all COT meetings since April have been held in open session.

1.74 The protocol is intended to be adjusted in light of experience and to be rapidly modified to adopt best practice. There have already been minor amendments in regard to attendance by the media to allow these arrangements to better fit their time-scales.

1.75 The draft protocol is being discussed by COM and COC with a view to those committees following the same procedures for holding meetings in open session. Following discussion and agreement by COT, COM and COC, an appendix summarising the protocol would be added to the Code of Practice on Openness and publication in a future Annual Report.

Variability and uncertainty in toxicology

1.76 The COT agreed to establish a new Working Group to consider variability and uncertainty in toxicology, and alternative approaches to dealing with these in the risk assessment process. The Food Standards Agency will find the considerations of the Working Group helpful in allowing it to interpret the health implications of exceedances of safety guidelines by particular subsets of the population.

1.77 The terms of reference of the Working Group are:

- To review the evidence of the bases and range of variability in adverse response to chemicals.
- To consider sources of uncertainty in hazard characterisation.
- To consider the appropriateness of uncertainty factors customarily used to extrapolate toxicological data from animals to humans.
- To consider the appropriateness of uncertainty factors customarily used to allow for variation within the human population, including specific subgroups such as children.
- To consider other methods which might be used in setting acceptable or tolerable intakes for food chemicals.
- To consider how to express the level of confidence in the risk assessment.

Risk assessment strategies

Guidelines for Exposure Assessment Practice for Human Health

1.78 The Interdepartmental Group on Health Risks from Chemicals (IGHRC) is an informal group of representatives of UK government departments, agencies and research councils (see http://www.le.ac.uk/ieh/ighrc/ighrc.html). One aim of the IGHRC is to produce guidance documents on the approaches of different government departments and agencies to risk assessment (see also paragraph 1.87). In July 2003 the COT considered a draft of the third of these guidance documents, entitled "IGHRC report: guidelines for exposure assessment practice for human health effects of chemicals".

1.79 The document is aims to serve as an outline of exposure assessment for individuals without specialist knowledge of the area, who use the assessments either for risk assessment or risk management purposes. The document also provides an overview of differences in the ways exposure assessments are carried out by different departments and agencies and addresses different exposure scenarios (food, environment, etc.). The document does not aim to provide a comprehensive review of exposure assessment methodology or explicit details of how each stage in the process is carried out.

1.80 The COT considered the document provided a useful guide, and commended the stepwise approach and inclusion of case studies. Additional information needs were: the relative importance of different routes of exposure, perhaps illustrated by a case study on routes of exposure to a pesticide or a solvent in the domestic situation, information on literature searching and evaluation, and discussion of bias in sensitivity and uncertainty analysis.

1.81 The document is to be revised in the light of comments from the COT and other consultees and will be published in due course.

Physiologically-based pharmacokinetic modelling

1.82 Pharmacokinetics describes the relationship between exposure and the concentration-time profile of a chemical within the body. This relationship is usually expressed as an equation based on an abstract representation of the body as one or more boxes (compartments). The equation or model used is essentially empirical and may bear little relation to the physiological processes involved. Physiologically based pharmacokinetic modelling (PBPK) is a method based on physiological principles rather than observed data, which provides greater understanding of what actually occurs following exposure to a chemical. The concept of PBPK modelling was first described by Thorsten Teorell in 1937. However, at that time the lack of computing power to solve the resulting mathematical equations meant that the approach was impracticable.

1.83 Because PBPK modelling allows for the underlying physiological processes and the physico-chemical properties of the chemical administered it facilitates prediction of events in humans from animal data and helps to explain differences in the behaviour of different chemicals. PBPK modelling permits

prediction of chemical concentrations at specific target sites and can incorporate different exposure scenarios, disease states or changes with age and co-administration of other chemicals. Some PBPK models can simulate population response to exposure to a chemical by producing a distribution of outputs.

1.84 PBPK models are based on three main elements: physiological parameters, chemical specific parameters and design of the model. The physiological parameters define each tissue or organ by its structure, size, blood flow, and functionality. Overlaid onto these in the model are the chemical specific parameters: binding within blood (e.g. to proteins, red cells), tissue affinity (binding, partitioning), membrane permeability, and sensitivity to enzymic modification. The complexity of the model can be varied according to the information required. In a simplified model, tissues with similar physiological properties are considered as a single tissue.

1.85 The majority of work on development and validation of PBPK models has occurred in the development and selection of pharmaceutical candidates. However, there is increasing interest in using PBPK modelling as a tool in risk assessment in North America and the EU. The COT held a one-day meeting to discuss PBPK modelling and key issues regarding its use in risk assessment. COT recognised that PBPK modelling could be a useful approach in the risk assessment of chemicals where sufficient data existed but that there were difficulties with validation of PBPK models for non-pharmaceutical chemicals.

1.86 The COT statement is at the end of this report.

Uncertainty Factors: Their Use in Human Health Risk Assessment by UK Government

1.87 In December 2001, the COT considered a first draft of this document (2001 Annual Report, page 17), which is part of the IGHRC programme of work (see also paragraph 1.78). The document outlines the risk assessment process, highlighting areas of toxicological uncertainty, describing current approaches to dealing with uncertainties, approaches used in UK government regulatory decision-making and those used in other countries. It also includes a brief historical perspective and listed some of the recent advances in dealing with toxicological uncertainty.

1.88 The 2001 document had been revised in the light of comments from the COT and the four other expert advisory Committees consulted. The proposed final version was presented to COT in April 2003 to ensure no major points needed to be addressed prior to publication.

1.89 The COT noted that the document was a useful compilation of the *status quo* but raised a number of points that needed clarification in order to maintain a consistently high standard. The finalised report was published in October 2003 and is available at http://www.le.ac.uk/ieh/ighrc/ighrc.html

Ongoing work

Adverse trends in the development of the male reproductive system

1.90 In February 2003 the COT was invited to consider whether it was an appropriate time to review the available evidence for adverse trends in development of the male reproductive system and possible contribution of chemical exposure to these trends. The Committee noted that the subject had been reviewed extensively, including a comprehensive recent (2002) review by the International Programme on Chemical Safety (IPCS). In contrast to effects in wildlife, the Committee concluded that current evidence has not provided convincing evidence that exposure to endocrine disrupting chemicals has adversely affected the human male reproductive system.

1.91 However, the COT agreed there is a need for new approaches to consider possible causes of adverse trends in reproductive health. This includes the need to consider all chemicals, not just those reported to have endocrine disrupting activities, that may be involved in the reported decline in male reproductive health; and changes in lifestyle factors, which are not within the remit of the COT.

1.92 The Committee concluded that the evidence of adverse trends in human male reproductive health should be reviewed, before considering possible causes, including lifestyle factors and the role of chemicals in general. Since much of this would be outside of the remit of the COT, it was recommended that a scientific meeting be held to review the evidence, involving experts from the relevant medical and scientific disciplines.

1.93 In addition, the COT expected to issue a brief statement. However, the statement has not been finalised pending publication of a new and pertinent report.

Phosphorus, parathyroid hormone and bone metabolism

1.94 In December 2003, the COT was asked to consider the data on phosphorus, parathyroid hormone, calcium balance and bone health, in order to allow the FSA to formulate appropriate consumer advice in relation to food supplements containing phosphorus. Advice has been received from experts in bone health, and the COT discussion will continue in 2004.

Tryptophan and Eosinophilia Myalgia Syndrome

1.95 In 1990 the COT endorsed a ban on the addition of tryptophan to foods, including dietary supplements. This followed reports of a new epidemic illness in the US known as the Eosinophilia-Myalgia Syndrome (EMS), which was associated with the consumption of L-tryptophan supplements. EMS was a serious disorder which affected over 1500 people in the US and caused at least 37 deaths. Several cases of EMS also occurred in the UK.

1.96 In late 2002 the Institute for Optimum Nutrition submitted a document to the Food Standards Agency which claimed that the cause of EMS was now known to be a contaminant in the trytophan produced by one manufacturer and that there was no need for the continuing ban on the addition of tryptophan to foods. The COT was asked to consider the available data and advise on the risk to health of tryptophan, particularly in food supplements. Additional information needs were identified and the discussion will be continued in 2004.

Statements of the COT

Statement on arsenic in food: results of the 1999 Total Diet Study

Statement on brominated flame retardants in fish from the Skerne-Tees rivers system

Statement on fluorine in the 1997 Total Diet Study

Updated statement on a survey of mercury in fish and shellfish

Statement on a survey of metals in infant food

Statement on metals and other elements in the 2000 Total Diet Study

Statement on physiologically based pharmacokinetic modelling

Statement on arsenic in food: results of the 1999 Total Diet Study

Introduction

1. The Food Standards Agency (FSA) has recently completed a Total Diet Study (TDS) of total and inorganic arsenic levels in food, which was carried out between 1999 and 2002. The Committee was asked to comment on the survey and assess if the levels of arsenic in the diet posed a risk to human health.

Toxicology of arsenic

2. Arsenic is a metal with complex chemistry that can form a number of inorganic and organic compounds. It can exist in many oxidation states, the most common being the tri- and pentavalent forms. A variety of inorganic arsenic compounds such as arsenates (AsO_4^{3-}, pentavalent arsenic) and arsenites (AsO_3^{3-}, trivalent arsenic) are found in water and at low levels in food.

3. Inorganic arsenic compounds (arsenite and arsenate) are well absorbed by the oral route in humans with absorption values reported to be from 50% to >95%[1]. They are metabolised by methylation and then excreted in the urine with a half-life of 3 to 5 days[1]. Inorganic arsenic is clastogenic in *in vitro* and *in vivo* assays and some evidence suggests clastogenicity in humans[2,3,4]. Arsenic in drinking-water (primarily inorganic, as arsenate and to a lesser extent arsenite) was evaluated as "carcinogenic to humans" (Group 1) on the basis of "sufficient evidence" for an increased risk for cancer of the urinary bladder, lung and skin[4]. Increased risks of lung and bladder cancer and of arsenic-associated skin lesions and other skin changes (such as hyperkeratosis and pigmentation changes) have been reported to be associated with ingestion of drinking-water at concentrations from approximately 30 μg arsenic/litre[5]. Chronic exposure to arsenic in drinking water has also been associated with peripheral vascular diseases such as blackfoot disease, cardiovascular diseases and possibly with diabetes and reproductive effects[5].

4. Organic arsenic compounds such as arsenobetaine and arsenocholine are found in fish and shellfish. Most arsenic in fish (>90%) is in the form of arsenobetaine which is also the main form found in crustaceans and bi-valve molluscs[6], the remainder is arsenocholine and a small amount of inorganic arsenic (usually <1%). Fish is the main source of arsenic in the diet; arsenobetaine is therefore the main form of arsenic present in food.

5. The fate of organic arsenic has not been clearly defined in experimental animals or in humans. In general organoarsenicals are thought to be less extensively metabolised than inorganic arsenic and more rapidly excreted[5]. Yamauchi *et al.*[7] calculated biological half-lives after administration of organoarsenicals to hamsters, reporting a 6.1 hour half-life for arsenobetaine. In humans, exposure to arsenobetaine through consumption of plaice resulted in 69 to 85% of the arsenobetaine being excreted unchanged in the urine within 5 days[8]. In a study of women volunteers who consumed fish containing arsenobetaine, Lehmann *et al.*[9] observed rapid elimination of the arsenobetaine from blood with a half-life of approximately 7.1 hours during the first 2 to 10 hours following ingestion. Between 10 and 48 hours elimination from the blood was slower with a half-life of approximately 63 hours.

6. There are no data on tissue distribution of arsenic in humans following ingestion of organic arsenic present in fish and seafood. Following intravenous administration of arsenobetaine, the highest tissue concentrations were found in kidney, liver and pancreas of mice and rats[7], and in the liver, kidney, spleen, muscle, skin and brain of rabbits and hamsters[7, 10]. Limited data indicate that organic arsenic compounds such as arsenobetaine and arsenocholine are not converted to inorganic arsenic *in vivo*[5].

7. Despite the limited database, the organic forms of arsenic are generally assumed to be less toxic than the inorganic compounds[1, 11]. There are no adequate studies of toxicity in man or animals from the consumption of organoarsenicals in seafood. In the one toxicity study available, weanling rats were fed diets containing fish, which provided a dose of approximately 3 mg/kg bw/day organic arsenic for 42 days. No treatment-related toxic effects were reported in the limited range of endpoints studied[12]. Limited data indicate that arsenobetaine and arsenocholine are not genotoxic in mammalian cells *in vitro*[5].

Arsenic in fish

8. There does not appear to be any particular type of fish that contains higher levels of arsenic and bio-magnification in aquatic food chains has not been observed[5]. In the last multi-element survey of fish (1998), levels of total arsenic in the most commonly consumed fish (cod, haddock, salmon, tuna) in the UK were in the range of 1.9 mg/kg – 8.4 mg/kg fresh weight, with a mean of 4.6 mg/kg[13].

Previous Evaluations

JECFA

9. In 1983 the Joint FAO/WHO Expert Committee on Food Additives (JECFA) proposed a Provisional Maximum Tolerable Daily Intake (PMTDI) for inorganic arsenic of 2 μg/kg body-weight (bw) per day[14]. JECFA noted the epidemiological evidence of an association between overexposure of humans to inorganic arsenic from drinking-water and an increased cancer risk; 0.2 mg As/L was associated with a 5% increase in the lifetime risk of skin cancer. At that time JECFA also noted that skin cancer did not occur in the absence of other toxic effects of arsenic. The available epidemiological evidence allowed the tentative conclusion that arsenicism could be associated with water supplies containing an upper arsenic concentration of 1 mg/L or greater, and that a concentration of 0.1 mg/L may give rise to presumptive signs of toxicity. The chemical species of arsenic present in the drinking-water were not clearly determined but JECFA concluded it was reasonable to consider them to be inorganic arsenic. Assuming a daily water consumption of 1.5 litres, JECFA concluded that intakes of 1.5 mg/day of inorganic arsenic were likely to result in chronic arsenic toxicity and daily intakes of 0.15 mg may also be toxic in the long term to some individuals. However, the rationale for the PMTDI was unclear.

10. JECFA reviewed its evaluation in 1989, and established a Provisional Tolerable Weekly Intake (PTWI) for inorganic arsenic of 15 μg/kg bw/week based on the previous PMTDI of 2 μg/kg bw/day[11]. JECFA acknowledged that there was a narrow margin between the PTWI and intakes reported to have toxic effects in epidemiological studies, but again did not provide clear justification for the value of the PTWI.

11. In 1989 JECFA also considered organic arsenic present in seafood, and commented that further investigations of the type and levels of organic arsenic compounds naturally occurring in marine products and further animal studies on these specific compounds would be highly desirable[11]. The available data were not sufficient to set a PTWI for organic arsenic. JECFA noted reports of populations who consume large quantities of fish resulting in intakes of organic arsenic of about 50 μg/kg bw/day, with no subsequent reports of ill health effects[11]. However no information was provided on what possible effects were investigated in these fish eating populations, and there have been no specific epidemiological studies to determine if there are any health effects associated with this level of organic arsenic intake.

WHO drinking water guidelines

12. In 1993 the WHO established a provisional guideline value for arsenic in drinking water of 10 μg/L[15], which was described as the 'practical quantification limit'. This concentration was considered to be associated with an estimated excess lifetime skin cancer risk of 6×10^{-4} (or 6 additional cases per 10000 people). WHO noted that a similar value could be derived by assigning a 20% allocation of the JECFA PTWI to drinking water. The drinking water guideline value is currently under review. The draft text, which is open for consultation, proposes that the guideline value of 10 μg/L should be retained, whilst noting the uncertainty in the risk assessment and the practical difficulties in removing arsenic from drinking water[16].

COT

13. The COT last considered arsenic in food in 1995 when it reviewed the results of the 1991 TDS[17]. The estimated upper bound dietary intake of total arsenic from the 1991 TDS was 0.067 mg/day, approximately 1 μg/kg bw/day in a 70 kg adult. The Committee concluded that "since almost all of the estimated dietary intake of arsenic is expected to consist of organic compounds which are of low toxicity compared to inorganic arsenic compounds, it is unlikely to constitute a hazard to health. We would like, however, to see specific estimates of intakes of inorganic and organic compounds of arsenic, both for the general population and for particular groups with greater than average intakes of arsenic, such as adults consuming relatively large amounts of fish and shellfish."

Contaminated land guideline values

14. In 2001, the Committee endorsed a toxicological approach to setting guideline values for hazardous chemicals in contaminated soil. This approach defines the possibility of establishing an "Index Dose" for a genotoxic carcinogen, based on an accepted exposure standard, such as a drinking water standard. The Index Dose is applied to a single source of contaminant and is defined as a level at which the risk is considered minimal, but there is a requirement that exposure from each individual source should be as low as reasonably practicable. An Index Dose of 0.3 μg/kg bw/day was recommended for inorganic arsenic[1], based on the EU/WHO drinking water guideline of 10 μg/L, assuming consumption of 2L water per day.

The 1999 Total Diet Study (TDS)

15. In response to the previous request of the COT, analysis of samples from the 1999 TDS was carried out to investigate levels of both inorganic and total arsenic in foods. One hundred and nineteen different categories of food were collected from 24 towns throughout the UK and made into 20 composite food groups. The proportion of each food in a food group reflects its importance in the average UK diet (largely based on an average of three years previous consumption data from the National Food Survey).

16. Each of the 24 samples of the 20 food groups were analysed in duplicate for total and inorganic arsenic using both direct nebulisation inductively coupled plasma-mass spectrometry (ICP-MS) and hydride generation ICP-MS for total arsenic, and high resolution ICP-MS for inorganic arsenic. The limits of detection were 0.01mg/kg for inorganic arsenic in all food groups and ranged from 0.0005 to 0.004 mg/kg for total arsenic in different food groups. Specific organic arsenic compounds were not measured.

Results of the Total Diet Study

17. The full survey results are published in a Food Surveillance Information Sheet[18]. Total arsenic was detected in all samples of the carcass meat, offal, fish and "other vegetables" food groups and in some samples of each the other food groups. In approximately one quarter of all the samples analysed, the concentration of total arsenic was below the limit of detection. The highest levels of total arsenic were found in fish (mean 3214 μg/kg, range 1106-8423 μg/kg), poultry (mean 73.1 μg/kg, range <2.1-167 μg/kg) and the miscellaneous cereals food groups (mean 13 μg/kg, range <2.1-26 μg/kg). The mean total arsenic concentrations in all the other food groups were below 10 μg/kg. These data are similar to those from the 1994 and 1997 TDS[19,20].

18. Inorganic arsenic was detected in 20 of the 24 fish samples, 10 of the 24 miscellaneous cereals samples and 3 of the 24 poultry samples. The upper bound mean concentrations of inorganic arsenic in fish, poultry and miscellaneous cereals were 15.9, 12.5 and 11.6 μg/kg, respectively. The mean concentration of inorganic arsenic in fish was less than 0.5% of total arsenic. The concentrations of total arsenic in all other food groups were below the limit of detection for inorganic arsenic (i.e. < 10 μg/kg) and therefore inorganic arsenic was not measured because it was assumed that it would not be detectable.

19. Estimates of dietary exposure to arsenic (total and inorganic) for consumers of all age groups (toddlers to elderly) are summarised in Table 1, expressed as a range from lower bound to upper bound. For adult consumers the mean and high level estimates of dietary exposure to total arsenic were 1.3 and 4.4 μg/kg bw/day, respectively. The mean total arsenic level was lower than that of the previous TDS[19] (2.0 μg/kg bw/day), but the 97.5 percentile was the same (4.4 μg/kg bw/day). Intake estimates for children were higher than those for adults, as would be expected from their higher food consumption expressed relative to body weight. Intake data from previous surveys are not available for population groups other than the adults. The data indicate that fish was the major contributor to dietary exposure to total arsenic providing 4.6 μg/kg bw/day for the high level adult consumers of fish.

20. The upper bound estimate of intake of inorganic arsenic was calculated assuming that all the arsenic was inorganic in those food groups where the total arsenic content was below the limit of detection for inorganic arsenic. The upper bound mean estimates of inorganic arsenic intake ranged from 0.07 to 0.2 μg/kg bw/day for different consumer groups, upper bound high level estimates were 0.13 to 0.34 μg/kg bw/day. The miscellaneous cereals food group was the major contributor to inorganic arsenic, providing up to 0.064 μg/kg bw/day for the high level adult consumer.

21. Population mean exposures were calculated using the mean concentrations of arsenic in each food group and the average consumption of each food group based on data from the National Food Survey (NFS) of household food purchases. The upper bound population mean exposure to total arsenic was 0.83 μg/kg bw/day, which is slightly lower than for the 1991, 1994 and 1997 TDS (1.0 –1.1 μg/kg bw/day)[19,20,21]. The upper bound population mean exposure to inorganic arsenic was 0.09 μg/kg bw/day. No previous data are available for dietary exposure to inorganic arsenic.

Table 1: Estimated dietary exposure to arsenic (total and inorganic) for mean and high level consumers.

Survey Population Group	Estimated total dietary exposure to arsenic (μg/kg body-weight/day)			
	Mean		97.5th Percentile	
	Total arsenic[a]	Inorganic arsenic[b]	Total arsenic[a]	Inorganic arsenic[b]
Adults[c]	1.33	0.018 – 0.082	4.37	0.043 – 0.14
Toddlers (1.5 – 4.5 years)[d]	2.43 – 2.46	0.049 – 0.2	11.31 – 11.34	0.11 – 0.34
Young people aged 4-18[e]	1.60 – 1.61	0.033 – 0.13	6.65 – 6.66	0.076 – 0.25
Elderly (free living)[f]	1.60 – 1.61	0.017 – 0.073	5.33 – 5.34	0.041 – 0.13
Elderly (institutionalised)[f]	1.44 – 1.46	0.022 – 0.089	4.62 – 4.64	0.047 – 0.15
"Vegetarians"[g] (including fish eaters)	1.24 – 1.25	0.019 – 0.071	6.98 – 6.99	0.047 – 0.13

Notes:

a. Exposures to total arsenic have been estimated from the upper and lower bound mean concentrations, which assume non-detectable concentrations were the limit of detection and zero, respectively. Where the difference between the lower bound and upper bound mean concentrations is very small, rounding of the data leads to a single value.

b. The upper end of the range for inorganic arsenic was calculated assuming that all the arsenic was inorganic in food groups where the total arsenic was below the limit of detection for inorganic arsenic. The lower end of the range was calculated using the lower bound mean concentrations of inorganic arsenic in fish, poultry and miscellaneous cereals. For those food groups where the total arsenic level was lower than the limit of detection for inorganic arsenic, it was assumed that none of the arsenic was inorganic.

c. Dietary and Nutritional Surveys of British Adults. (1990)[22]

d. National Diet and Nutrition Surveys Children Aged 1½ -4½ years. (1995)[23]

e. National Diet and Nutrition Survey: young people aged 4-18 years. (2000)[24]

f. National Diet and Nutrition Survey: People aged 65 years and over. (1998)[25]

g. Vegetarians Dietary Survey: Technical Report on Weighed Intake Diary Data. (1990) (individuals describing themselves as vegetarians, some of whom ate fish):[26]

Arsenic in drinking water

22. A significant proportion of inorganic arsenic intake comes from drinking water. The current statutory limit for arsenic in drinking water is 50 μg/L, although this will be reduced to 10 μg/L in December 2003. Information provided by the Drinking Water Inspectorate for England and Wales (DWI), Department for Environment Northern Ireland (DOENI) and the Drinking Water Quality Regulator for Scotland (DWQRfS) suggests that the level of arsenic in drinking water for the majority of the population in the UK does not exceed the incoming standard of 10 μg/L. A consumption level of 2 L/day is commonly assumed for drinking water, this would contribute up to 20 μg/day or (0.28 μg/kg bw/day for a 70kg adult) to total arsenic exposure. Data available from a 1995 national survey of tap water consumption indicate that children aged 0-5 years consume an average of about 0.5 L/day, which would contribute 0.34 μg/kg bw/day for a 14.5 kg toddler aged 1.5-4.5 years[27]. However, for a significant proportion of the population, arsenic levels in water are considerably lower than the incoming standard of 10 μg/L, therefore exposure from drinking water would be far less.

COT evaluation

23. Having reviewed the previous evaluations of arsenic, the Committee concluded that there are no relevant tolerable intakes or reference doses by which to assess the safety of either inorganic or organic arsenic in the diet. The JECFA PTWI for inorganic arsenic was established in 1989 using an approach that would not now be considered appropriate in view of the evidence of genotoxicity and carcinogenicity. The index dose was proposed as a risk management tool in support of guideline values for hazardous chemicals in contaminated land, and is also not appropriate for evaluation of dietary exposure. The Committee therefore concluded that exposure to inorganic arsenic from all sources should be as low as reasonably practicable (ALARP).

24. Very few data are available on clearance and toxicity in animals and humans of the forms of organic arsenic found in fish. The general assumption that organic arsenic is less toxic than inorganic arsenic is therefore based on an extremely limited database, which is not adequate to establish tolerable intakes.

25. Interpretation of the data is restricted by the limited sensitivity of the analyses, particularly for inorganic arsenic. Nevertheless, the data confirm that fish is the major contributor to arsenic in the diet, and the predominant form of arsenic in fish is organic, most of which is likely to be arsenobetaine. Overall, inorganic arsenic contributed less that 10% of the total dietary exposure to arsenic. Whilst the low analytical sensitivity results in considerable uncertainty in the estimates of dietary exposure to inorganic arsenic, the large number of food samples with inorganic arsenic concentration below the limit of detection appears to be consistent with dietary exposure being ALARP.

26. It has previously been noted that some fish eating populations are exposed to organic arsenic at levels up to 50 μg/kg bw/day and there is no evidence to suggest that these populations suffer ill-effects as a result. In the absence of information on the toxicological properties of organic arsenic in fish, it is not possible to define the nature of potential ill-effects that should be investigated in such populations.

27. The adult consumer and population mean exposures to total arsenic appeared slightly lower than for previous surveys. Although this decrease may be due to refinements in the methodology used to measure total arsenic over the years, it offers reassurance that the level of arsenic in food is not increasing.

Conclusions

28. We *consider* that there are no relevant tolerable intakes or reference doses by which to assess safety of either inorganic or organic arsenic in the diet. Inorganic arsenic is genotoxic and a known human carcinogen. We therefore *conclude* that exposure to inorganic arsenic should be as low as reasonably practicable (ALARP).

29. We *note* the low sensitivity of the method used to measure inorganic arsenic. The large number of food samples with inorganic arsenic concentration below the limit of detection appears to be consistent with dietary exposure being ALARP. However we would welcome any refinements to the methodology that would increase the sensitivity of the analysis.

30. We *note* that fish is the major contributor to dietary exposure to arsenic, and the predominant form of arsenic in fish is organic.

31. We *note* that the general assumption that organic arsenic is less toxic than inorganic arsenic is based on an extremely limited database. However there is no evidence that exposure to organic arsenic through high levels of fish consumption has resulted in harmful effects, which indicates that the dietary exposure to organic arsenic identified in this survey is unlikely to constitute a hazard to health.

32. We *note* that the average population dietary exposure to total arsenic is lower than that estimated for previous years providing reassurance that exposure to total arsenic through food is not increasing. No data are available on trends in dietary exposure to inorganic arsenic.

May 2003

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COT statement on brominated flame retardants in fish from the Skerne-Tees rivers system

Introduction

1. The Food Standards Agency (FSA) has recently completed a survey to determine the concentrations of brominated flame-retardants (BFRs) in brown trout and eels from the Skerne-Tees river system. The Committee was asked to assess the toxicological properties of selected BFRs in order to advise on any health implications of the estimates of dietary exposure.

Background

2. Brominated flame-retardants (BFRs) are structurally diverse chemicals used in plastics, textiles and other materials to enhance their flame-retardant properties. Some BFRs, including polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD) are mixed into polymers rather than being chemically bound to them and can leach out of the products/materials in which they are used and into the environment.

3. PBDEs are produced by direct bromination of diphenyl ether. There are 209 individual PBDE congeners, each of which is identifiable by a unique congener number. Three commercial PBDE flame-retardants, pentabromodiphenyl ether (pentaBDE), octabromodiphenyl ether (octaBDE) and decabromodiphenyl ether (decaBDE) have been available in the UK. The commercial PBDEs are not pure products but a mixture of various diphenyl ethers with varying degrees of bromination.

4. The actual composition of the commercial products varies with supplier and is considered to be commercially sensitive information. However, example compositions of PBDEs have been published (see Table 1). These figures are broadly representative of the commercial products currently supplied. The commercial products are usually named on the basis of the principal PBDE congener e.g. pentaBDE. Trade-name nomenclature may also incorporate a number, which is related to the performance characteristics (e.g. flame retardant properties) of the commercial mixture rather than the constituent congeners[1].

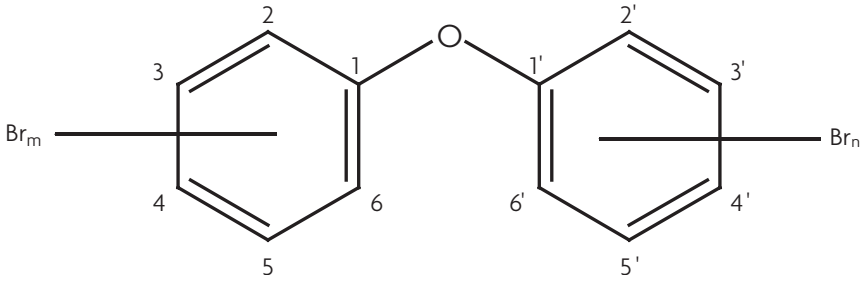
Table 1. Relative congener distribution for penta- and octaBDE

Commercial product	% congeners in commercial product						
	tetra	penta	hexa	hepta	octa	nona	deca
PentaBDE[1]	24 – 38	50 – 62	4 – 12	–	–	–	–
OctaBDE[2]	–	–	⩽12	⩽45	⩽33	⩽10	–
DecaBDE[3]	–	–	–	–	–	⩽3	⩽97

5. The commercial PBDEs have recently been evaluated under the EU Existing Substances Regulations. As a result of their potential to bioaccumulate in the environment, the EU has agreed to ban the marketing and use of penta- and octaBDE from 1 July 2004. However, for some time after this date there will still be existing PBDE-containing products in use.

6. There are limited data available on the potential of decaBDE to bioaccumulate in the environment and it is not currently included in the EU prohibition. In addition, it was not measured in the Skerne Tees survey. However, information on decaBDE has been included in this statement for completeness and as a basis for future evaluations because decaBDE will be the only PBDE product commercially available when the ban on penta- and octaBDE comes into force. The chemical structure of PBDEs is given in Figure 1.

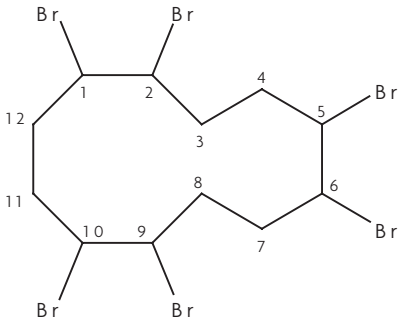
Figure 1. Chemical structure of PBDEs



Where (m) plus (n) equal between 1 and 10 bromine atoms.

7. HBCD is synthesised through bromination of cyclododecatriene. It is commercially available in the UK as a mixture of three stereoisomers α, β and γ. There is currently no proposal to ban HBCD in the EU[4]. The chemical structure of HBCD is given in Figure 2.

Figure 2. Chemical structure of HBCD



Toxicology of PBDEs and HBCD

8. Completed EU risk assessments are available for pentaBDE[1] and octaBDE[2], and draft risk assessments are available for decaBDE[3] and HBCD[4]. Unless otherwise indicated, the following summary is based on the information provided in these risk assessments. The COT also considered new studies published subsequent to the final literature searches for the EU risk assessments. A more detailed summary of the toxicological data is available at http://www.food.gov.uk/multimedia/pdfs/tox14.pdf. Throughout this statement the terms pentaBDE, octaBDE, decaBDE and HBCD refer to the commercial mixtures of brominated flame-retardants whereas individual congeners are denoted by inclusion of the specific congener number e.g. PBDE-99.

PBDEs

9. There is limited information on the toxicokinetics of penta-, octa- and decaBDE. Studies in laboratory animals have indicated that penta- and octaBDE are absorbed following oral administration however, the extent of absorption is unknown[1,2]. DecaBDE is not well absorbed after oral administration (<10%)[3].

10. The primary route of excretion for all PBDEs is considered to be the faeces, although it is unclear how much of the PBDE present in the faeces represents unabsorbed material. In rats, following oral administration, the majority of pentaBDE was detected unchanged in the faeces[1]. Limited information indicates that decaBDE is metabolised to lesser brominated phenolic products[3]. There is no information on the metabolism of octaBDE. Elimination of pentaBDE from rat adipose tissue is slow ($t_{1/2}$ = 25-47 days) indicating that it has the potential for bioaccumulation[1]. There is no information on the elimination of octa- or decaBDE in animals, or on the bioaccumulation or the route of elimination of PBDEs in humans.

11. There is no information on PBDE levels in adipose tissue from the UK. However, PBDE-47 (2,2',4,4'-tetraBDE), PBDE-99 (2,2',4,4',5-pentaBDE), PBDE-100 (2,2',4,4',6-pentaBDE), PBDE-153 (2,2',4,4',5,5'-hexaBDE) and PBDE-154 (2,2',4,4',5,6'-hexaBDE) have been detected in human breast adipose tissue in the US. The sum of total PBDEs detected was 86 ng/g fat[5]. PBDE-47 has also been detected in adipose tissue in Sweden (1.0-98.2 ng/g lipid)[6].

12. In Sweden, there has been an increase in total PBDE levels in samples of human milk over a 25 year period from 1972-1997. The predominant congener was PDBE-47 (2,2',4,4'-tetraBDE) which accounted for 62% of the total (2.28 ng/g lipid). PBDE-99 (2,2',4,4',5-pentaBDE) accounted for 13% (0.48 ng/g lipid) and PBDE-153 (2,2',4,4',5,5'-hexaBDE) accounted for a further 8% of the total (0.46 ng/g lipid). The remaining 17% was accounted for by other tri-, tetra-, penta- and hexa congeners[7]. Data from North America also indicate an increase in total PBDE levels in breast milk. In 1992, samples of breast milk from the Canadian milk bank contained less than 50 ng PBDE/g fat. In 1997, concentrations of approximately 150 ng PBDE/g fat were detected in samples from women in New York State and 200 ng PBDE/g fat was detected in samples from Austin and Denver in 2000[8]. A recent abstract reported a mean concentration of total PBDE of 6.6 ng/g lipid in breast milk sampled from women in the UK in 2001-3[9].

13. Repeat dose studies of commercial pentaBBDE in rodents have identified the liver as a key target organ, with effects seen at doses of 2 mg/kg bw/day and greater. Based on a study in which a commercial pentaBDE product was administered to rats in the diet for 30-days (0-1 mg/kg bw/day) with no treatment related changes, the EU risk assessment concluded, the no observable adverse effect level (NOAEL) for pentaBDE was 0.45 mg/kg bw/day[1]. This value was derived based on the content of 50-62% pentaBDE in the commercial product and assuming a maximum oral absorption of 90%, by analogy with other polyhalogenated diaromatic compounds. Applying similar correction factors to the doses at which liver toxicity has been observed indicates a LOAEL of 0.9 mg/kg bw/day.

14. For octaBDE, a LOAEL of 7.2 mg/kg bw/day was identified for histopathological liver changes in the rat[2]. A NOAEL for liver changes following administration of octaBDE has not been established. The repeat dose toxicity of decaBDE is low. The EU risk assessment reported a NOAEL of 1,120 mg/kg bw/day for liver changes seen in the carcinogenicity study in rats (paragraph 19)[3].

15. In short term gavage studies in rats commercial mixtures of pentaBDE (10-300 mg/kg bw/day), PBDE-47 (2,2',4,4'-tetraBDE; 18 mg/kg bw/day) and a commercial mixture of octaBDE (10-100 mg/kg bw/day) have been shown to increase the metabolism of model substrates for drug metabolising enzymes, in a manner consistent with induction of cytochrome P450 isozymes of the CYP1A and CYP2B subfamilies and UDP-glucuronosyl transferase. This induction was associated with perturbation of thyroid hormones, liver enlargement and histopathological changes in the thyroid[1,10,11,12]. DecaBDE was not found to induce a similar spectrum of changes in CYP subfamilies and thyroid hormones[10,13]. In this study the effect of decaBDE was investigated in rats at doses up 100 mg/kg/day for 4 consecutive days. This dose is an order of magnitude below the LOAEL for lesions in the liver and thyroid in the carcinogenicity studies and as such, may have been insufficient to produce an effect in short-term studies.

16. Penta-BDE has not been shown to be mutagenic in four studies in *S. typhimurium* and one study in *S. cerevisiae*. A cytogenetic study in human peripheral blood lymphocytes also gave negative results. In a single study in *S. typhimurium*, a commercial pentaBDE referred to as Tardex 50 (10-10000 μg/plate) was shown to increase point mutations by 3-fold at the highest concentration in the absence, but not in the presence, of metabolic activation. This single positive result was considered in the EU risk assessment to be a chance finding[1]. PentaBDE has not been tested for genotoxicity *in vivo*.

17. Commercial octaBDE preparations were not mutagenic in four studies in *S. typhimurium* and one in *S. cerevisiae* in the presence and absence of metabolic activation. One preparation referred to as Muster 82 showed weak mutagenic activity in *S. typhimurium* without activation. No information is available on the composition of this preparation. Commercial octaBDE did not induce unscheduled DNA synthesis in human fibroblasts, sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells or chromosomal aberrations in human peripheral blood lymphocytes. OctaBDE has not been tested for genotoxicity *in vivo*[2].

18. Commercial decaBDE preparations of known purity (97-98%) were not mutagenic in *S. typhimurium* or *E. coli* in the presence and absence of rat metabolic activation. Two preparations referred to as Muster 83 and Muster 88 had positive effects in strains TA 98, 100 and 1535 with and without activation, but not in strains TA 1537 or 1538. No information is available on the composition of these preparations. In studies reported by the NTP, decaBDE was not mutagenic in the mouse lymphoma assay and did not induce SCE or chromosomal aberrations in CHO cells. In a reproductive study with dietary administration of decaBDE (3-100 mg/kg/day), there was no increase in chromosomal aberrations in the bone marrow cells of parent rats or of the offspring at weaning[3].

19. There are no carcinogenicity data for pentaBDE and octaBDE. The EU risk assessment noted that the evidence for carcinogenicity of decaBDE was considered to be equivocal. In a 103-week feeding study in mice there was an increase in hepatocellular adenomas or carcinomas at the lowest dose (3200 mg/kg bw/day), but not at the higher dose (6650 mg/kg bw/day). Thyroid gland follicular cell adenomas were reported in male mice at both doses. There was no evidence of carcinogenicity in female mice. In a 103-week feeding study in rats there was a dose dependant increase in neoplastic liver nodules, which was significantly greater than control in low dose males (1120 mg/kg bw/day) and in both sexes at the high dose (2240 mg/kg bw/day)[3].

20. In a developmental study in rats, oral administration of commercial pentaBDE on days 6-15 of gestation resulted in no adverse fetal effects at the doses up to 200 mg/kg bw/day[1]. Commercial preparations of octaBDE have been shown to cause fetal toxicity and malformations at doses below those causing maternal toxicity in rats and rabbits. The EU risk assessment identified 2 mg/kg bw/day as the lowest NOAEL for octaBDE, from a study in rabbits in which slight fetotoxicity was observed at 5 mg/kg bw/day[2]. A commercial preparation of decaBDE did not show developmental effects following dietary administration in the diet to rats at doses up to 100 mg/kg bw/day for 60 days prior to mating until weaning[3].

21. The PBDE congeners PBDE-47 (2,2',4,4'-tetraBDE) and PBDE-99 (2,2',4,4',5-pentaBDE) have been reported to cause neurobehavioural changes in NMRI mice following a single oral dose administered on post natal day (PND) 3, 10 or 19. Neurobehavioural effects were detected at 60 and 120 days of age[14,15,16]. In addition, perinatal exposure of CD1 mice to PBDE-99 resulted in neurobehavioural effects detected at 60 days[17]. The main neurobehavioural effect of PBDE-99 was delayed habituation behaviour, which was found to occur at the lowest doses tested (0.6 mg/kg[17]; and 0.8 mg/kg[15,16]).

22. Limited data on the interaction of a range of PBDE congeners with the arylhydrocarbon (Ah) receptor suggest that those measured have much lower potency than the dioxins and co-planar PCBs[18,19]. *In vitro* studies have suggested that a range of PBDEs have endocrine disrupting activity mediated via the oestrogen receptor[19,20].

HBCD

23. All toxicological studies with HBCD were conducted using the commercial mixture. Studies in laboratory animals have shown that, following oral administration, HBCD can be detected in the adipose tissue, liver and muscle. Longer-term exposure shows HBCD has the potential to bioaccumulate. The α-isomer has been found to accumulate more than the β- and γ-isomers. The extent of metabolism of the commercial HBCD is unknown. Following oral administration, the majority of HBCD was detected unchanged in the faeces, although it is unclear how much of this was unabsorbed material. There is no information on the toxicokinetics of HBCD in humans[4].

24. Repeat dose studies of HBCD have identified the liver as a key target organ. Increased liver weights and disturbances in thyroid hormones were observed at 100 mg/kg bw/day which was the lowest dose tested[4].

25. HBCD was not mutagenic in one study using *S. typhimurium* and did not induce chromosomal aberrations in human peripheral blood lymphocytes in the presence and absence of metabolic activation. HBCD caused a slight but significant increase in somatic recombinations in a non-standard assay using two Chinese hamster cell lines containing duplication mutations in the *hprt* gene. The relevance of this is unclear. *In vivo*, there were no significant increases in the frequency of micronuclei in mouse bone marrow cells. In an 18-month lifetime study of dietary administration to mice (available to the EU rapporteur in summary form only) there were no treatment related increases in tumour incidence at HBCD doses of 13-1300 mg/kg bw/day)[4].

26. Administration of HBCD to pregnant rats at dietary doses up to 750 mg/kg bw/day, or gavage doses up to 1000 mg/kg bw/day did not result in fetal toxicity or teratogenicity[4]. HBCD has also been investigated for neurodevelopmental effects[21]. A single dose of HBCD resulted in changes in spontaneous behaviour. However, this information was only available as an abstract, the doses resulting in these effects were unclear and therefore the data could not be used in the risk assessment.

COT evaluation of the toxicological properties of PBDEs and HBCDs

27. There are deficiencies in the toxicological database of the PBDEs and HBCD and these uncertainties need to be reflected in the evaluation. The majority of studies reviewed were relatively old and, although conducted to the standards of the time would not meet current requirements for study design and reporting. In addition, the duration of the longest studies undertaken with pentaBDE were similar to the reported half-life and the resulting tissue concentrations would only reach half of their maximal value by the end of the study.

28. The limited data on the toxicokinetics of the PBDEs suggest differences in absorption and excretion of individual compounds. Data on the genotoxicity, carcinogenicity and reproductive toxicity of PBDEs and HBCD are also limited. As the EU is introducing prohibitions on the use of some PBDEs, it is unlikely that new studies will be undertaken to address the deficiencies in the toxicological databases.

29. The toxicity studies have generally been conducted using commercial mixtures of PBDEs and HBCD. The composition of the material used in many of the studies was unclear and likely to differ from the mixture of congeners measured in food and the environment. Although a similar pattern of biological effects was reported for different mixtures, extrapolation of findings between mixtures should be treated with caution.

30. Whilst some Ah receptor mediated activity could be measured with PBDEs, the potency was low and the most sensitive end-points of toxicity were unlikely to be mediated by this mechanism. It has also been suggested that PBDEs have endocrine disrupting activity mediated via the oestrogen receptor, although the current data are limited.

31. The liver is a target organ for the PBDEs, with pentaBDE being the most toxic, and decaBDE the least. OctaBDE has been found to exhibit reproductive toxicity, whereas pentaBDE and decaBDE did not produce adverse effects in routine developmental studies.

32. Non-routine studies suggest that the most sensitive endpoints are neurodevelopmental. Two of the congeners that are present in commercial pentaBDE, have been shown to cause neurobehavioural effects in adult mice following administration of a single postnatal oral dose. Octa- and decaBDE, and the congeners commonly found in them, have not been investigated using this protocol.

33. HBCD is also hepatotoxic. It has not shown evidence of developmental toxicity in routine studies. One study, available in abstract form only, indicates that it might produce neurodevelopmental effects but there is insufficient detail to use the data in risk assessment.

34. Table 2 shows the NOAELs and LOAELs for the key effects of the PBDEs and HBCD. Based on the available data, pentaBDE appears to be the most toxic of the PBDEs, with a NOAEL of 0.45 mg/kg bw/day for liver effects following repeat dosing and a LOAEL of 0.6 mg/kg bw/day for neurodevelopmental effects following a single post-natal dose. For HBCD, the LOAELs are 100 mg/kg bw/day for liver effects following repeat dosing and 0.9 mg/kg bw/day for neurodevelopmental effects following a single post-natal dose.

35. It is anticipated that the human perinatal blood-brain barrier would be as permeable to PBDE as that of the mouse neonatal blood-brain barrier. There is no single neurodevelopmental stage of the human brain that is directly comparable with the mouse, as different brain parts develop at different rates in the two species. These studies involved administration at postnatal days 3 and 10, at which age the mouse brain probably models the human brain from 1 month pre-natal to 1 month post-natal. There is a lack of data on levels in breast milk, which might be a major source at the critical time for neurodevelopmental toxicity.

Table 2. NOAELs and LOAELs for PBDEs or HBCD

BFR	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Target	Comments
Commercial pentaBDE[1]	0.45	0.9	Liver	No chronic studies available
PBDE-99 (2,2',4,4',5-pentaBDE)[15]	ND	0.6	Neurodevelopment	
Commercial octaBDE[2]	2 ND	5 7.2	Reproduction	No neurodevelopmental data
Commercial decaBDE[3]	ND	1,120	Liver	No neurodevelopmental data
Commercial HBCD[4]	ND	100	Liver	Chronic data seen in summary form only

ND: NOAEL was not determined in the study identifying the LOAEL

36. In view of the inadequacies in the toxicological database and the absence of identifiable no-effect levels, it was not possible to determine a tolerable daily intake (TDI). The Committee therefore decided to take a Margin of Exposure (MoE) approach in which the estimated human exposures are compared with the relevant NOAEL or LOAEL identified from the animal studies. Had it been possible to establish a TDI from a NOAEL, uncertainty factors (UFs) would be required to allow for inter-and intraspecies differences in toxicokinetics and toxicodynamics (100) and limitations in the database such as study duration and gaps in the data (up to 10). Combining these uncertainty factors suggests a target MoE of 1000 for liver toxicity of penta-BDE, above which risks to health would not be expected. A NOAEL has not been identified for the neurodevelopmental effects of penta-BDE and therefore an additional UF of 3-10 would be required for extrapolation from a LOAEL to a NOAEL. This suggests a target MoE of 3,000-10,000. Similarly, a NOAEL has not been identified for the hepatic effects of HBCD, indicating a target MoE of 3,000-10,000. The exposure is not expected to represent a risk to health if the calculated MoE exceeds the target MoE.

PBDEs and HBCDs in fish from the Skerne Tees survey and in the 2001 Total Diet Study (TDS)

37. In 1999, a study sponsored by the Department of the Environment, Transport and Regions measured the concentration of PBDEs in rivers and estuaries downsteam of potential sources. The maximum concentrations of PBDEs were detected in the livers of fish (1294 μg/kg wet wt) and sediment (239 μg/kg dry wt) from the Skerne-Tees river system and the Tees estuary at Newton Aycliffe, which is downstream from the Great Lakes Chemical Company[22]. The Great Lakes Chemical Company is known to have manufactured both penta- and octaBDE at this site until the late 1990's, and still produces HBCD. DecaBDE was never manufactured at the site but may have been distributed via this site. The concentrations detected in the fish livers and sediment were only measured at one time-point and it is important to note that the trout in this river are restocked annually indicating these figures may not accurately represent the actual levels of contamination in the river.

38. Following these reports, the Food Standards Agency conducted a survey to determine the concentrations of congeners known to be components of commercial penta- and octaBDE in brown trout and eels from the Skerne-Tees river system. The Great Lakes Chemical Company is also known to have manufactured HBCD and thus, it was included in the survey. The chemical formula of the each congener and the BFR to which each congener corresponds is given in Table 3. A preliminary assessment of dietary exposure based on analysis of food samples from the 2001 Total Diet Study (TDS) was also conducted.

39. A survey was commenced in late 2001 to determine the concentrations of PBDE and HBCD in brown trout and eels from the Skerne-Tees river system. The samples examined included control samples of trout and eels from the Skerne and eels from the Tees. Samples were obtained from the river Skerne and river Tees at eight easily accessible locations that were upstream and downstream of the Great Lakes Chemical Company and at the confluence of the two rivers (see Figure 3). The PBDE congeners analysed in the survey were selected as a representative sample of those produced and used in the Skerne-Tees area. The chemical formula of each congener and the commercial PBDE to which each congener corresponds is given in Table 3.

40. At the time of this survey no data were available on other sources of dietary exposure to PBDEs and HBCDs in the UK. Therefore, a survey of the concentrations of PBDE congeners in food samples from the 2001 Total Diet Study (TDS) was commissioned in 2002. Single composite food group samples were formed by homogenising individual foods groups (excluding beverages) from 24 locations. These composite samples were analysed for the same range of PBDE congeners as the fish survey. It had been planned to additionally analyse these samples for decaBDE, however since none of the congeners measured were detectable this analysis was not undertaken.

Table 3. PBDE and HBCD congeners measured in the FSA survey

Congener	Chemical formula	Component
PBDE 28	2, 4, 4'-TriBDE	Possible component of commercial pentaBDE
PBDE 47	2, 2', 4, 4'-TetraBDE	Known substantial component of commercial pentaBDE
PBDE 99	2, 2', 4, 4', 5-PentaBDE	Known substantial component of commercial pentaBDE
PBDE 100	2, 2', 4, 4', 6-PentaBDE	Known substantial component of commercial pentaBDE
PBDE 153	2, 2', 4, 4', 5, 5'-HexaBDE	Possible component of commercial pentaBDE and known component of commercial octaBDE
PBDE 154	2, 2', 4, 4', 5, 6'-HexaBDE	Possible component of commercial pentaBDE and commercial octaBDE
α-HBCD	1R, 2S, 5R, 6R, 9S, 10S-HBCD	Known component of commercial HBCD
β-HBCD	1R, 2R, 5R, 6S, 9R, 10S-HBCD	Known component of commercial HBCD
γ-HBCD	1S, 2S, 5S, 6S, 9S, 10S-HBCD	Known component of commercial HBCD

R & S indicate the stereo position of the bromine on the HBCD molecule

Analytical methodology

41. The analytical method involved solvent extraction of the fat component of composite samples from the TDS or a portion of flesh removed from fish or eels. The extracts contained BFRs and other compounds that were separated from the dissolved fat component by adsorption chromatography. The PBDEs were measured using gas chromatography coupled to a mass spectrometric detector (GC-MS).

42. For HBCD, a simplified clean-up stage was performed which consisted of shaking another aliquot of the crude extract with concentrated sulphuric acid. The acid destroys the fats but leaves HBCD compounds intact. The temperatures used to separate PBDEs during GC analysis can affect the structures of the isomers and result in conversion between the three HBCD isomers. Therefore HBCD was determined using a liquid chromatography mass spectrometry (LC-MS) method.

43. The production of composite samples from the individual foods that compr Due to their lipophilicity BFRs are most likely to be detected in fatty foods ise a particular food group in the TDS may result in dilution of the overall fat content and thus may reduce the ability to detect these substances.

Dietary exposure to PBDEs and HBCD from Skerne Tees trout and eels

44. Table 4 shows the concerntration ranges of total PBDEs and HCDB in trout and eels taken from those test sites where the highest concentrations were found and from the control sites. The most contaminated trout were caught at the Haughton Road site, which was the closest river Skerne location downstream of the Great Lakes Chemical Company. No eels are caught at this site, and the most contaminated eels were caught from the next river Skerne downstream location at Oxenfield Bridge.The sum of the concentrations of individual PBDE congeners detected in the edible portion varied from 12 to 14 μg/kg freshweight in trout and was 53 μg/kg freshweight in the eel at control sites. At test sites, the sum of the concentrations varied from 59 to 197 μg/kg freshweight in trout and 164 to 288 μg/kg freshweight in eels.

Table 4. Estimated average dietary intake of PBDE and HBCD following consumption of trout or eels from the Skerne-Tees river system

BFR and sampling	Species	No. of samples	Concentration range (μg/kg freshweight	Maximum intake (μg/portion)[c]	Maximum intake (mg/kg bw/day)[d]
PBDE (Ricknall Grange) [a]	Trout	5	12-14	1.6	0.003
PDBE (Haughton Rd) [b]	Trout	7	59-197	24	0.056
PBDE (Ricknall Grange) [a]	Eels	1	53	3.7	0.0088
PBDE (Oxenfield Bridge) [b]	Eels	5	164-288	20.2	0.048
HBCD (Ricknall Grange) [a]	Trout	5	21-119	14	0.034
HBCD (Haughton Road) [b]	Trout	7	159-6758	810	1.9
HBCD (Ricknall Grange) [a]	Eels	1	159	11.1	0.027
HBCD (Oxenfield Bridge) [b]	Eels	3	570-9432	660	1.57

a Control site for Skerne River

b Test site showing the highest concentration of PBDEs or HCBD in trout or eels

c Portion sizes were assumed to be 120g trout or 70g eels, as cited in MAFF Food Portion Sizes[23]

d Average daily intake was calculated assuming consumption of one portion of trout or eels per week and an adult bodyweight of 60kg

45. For HBCD the concentration in the edible portion of trout varied from 21-119μg/kg freshweight and was 159 μg/kg freshweight in the eel at control sites. At test sites, the sum of the concentrations was 159 to 6758 μg/kg freshweight in trout and 570 to 9432 μg/kg freshweight in eels. The trout population of the Skerne Tees River system is restocked annually and no information was available to ascertain the ages of the fish sampled and whether concentrations increased in older fish. Detailed results will be published in a Food Surveillance Information Sheet.

46. The estimated average intake from consumption of one weekly portion (120g) of trout at the maximum levels detected were 0.056 μg/kg bw/day of PBDEs and 1.9 μg/kg bw/day of HBCD. The estimated average intake from consumption of one weekly portion (70g) of eels, were 0.048 μg/kg bw/day of PBDEs and 1.57 μg/kg bw/day of HBCD.

47. There are no commercial fisheries in the river and consumption would be limited to fish caught by anglers.

Total dietary exposure to PBDEs and HBCD

48 None of the congeners measured was present at concentrations exceeding the limit of detection (LOD) in any of the composite TDS samples analysed. Estimated intakes were therefore calculated from the upper bound concentrations (assuming that PBDE and HBCD were present at the LOD in all foods) together with consumption data from the 2000 National Diet and Nutrition Survey[24]. Dietary exposure for mean adult consumers was estimated to be $\leq$0.047 μg/kg bw/day for the sum of the PBDE congeners measured and ≤0.010 μg/kg bw/day for the sum of HBCD isomers. The actual intakes might be very much lower.

COT evaluation of dietary exposure to PBDEs and HBCD

49. The concentrations of PBDEs and HBCD detected varied widely in the fish sampled from the test sites and also from those sites considered to be control sites. In the absence of information to the contrary, it is assumed that the fish will move freely around the Skerne-Tees river system and therefore concentrations in the fish taken from one site are not representative. It is therefore not possible to identify an average concentration of PBDEs or HBCD which could be used to estimate intake for an individual regularly consuming fish caught from an individual site. Therefore worst-case intake estimations have been calculated from the highest measured concentration at any site. It is unlikely that this worst case intake would be achieved on a regular basis.

50. The PBDE congeners measured in the survey were selected as major representative components of penta- and octaBDE. Toxicity data are not available for the individual congeners. Concentrations of the individual congeners have therefore been summed for comparison with the toxicity data on the commercial PBDE mixtures. Studies on the commercial PBDEs indicate that pentaBDE is the most toxic. Comparison of the estimated intakes of the sum of the measured PBDE congeners with the reported effect levels for pentaBDE provides a precautionary approach because some of the congeners are expected to be less toxic.

51. The most sensitive effect of pentaBDE and HBCD was considered to be neurodevelopmental. The LOAEL for pentaBDE (600μg/kg bw/day) for this effect was obtained from studies in which the test material was administered by a single oral dose to mice on postnatal days 3 or 10. Limited evidence suggests that HBCD also has this effect. Human infants of comparable developmental stage (up to 1 month) would not eat fish and so would not be directly exposed to PBDE or HBCD from fish. Although pentaBDE is known to pass into breast-milk, the available data are not sufficient to estimate the potential exposure to the breast-fed infant resulting from consumption of contaminated fish by the mother. There is a need for data on levels of PBDEs and HBCD in breast-milk in the UK, in order to determine whether the breast-fed infant is at risk of neurodevelopmental effects arising from consumption of contaminated fish. The available studies on reproductive toxicity have not included investigation of neurobehavioural effects, and therefore there are no data of relevance to exposure by

pregnant women. Overall, it was considered not possible to calculate a relevant MoE with respect to neurodevelopmental effects.

52. For older children and adults eating trout or eels contaminated with PBDEs and HBCD, the liver toxicity is the most relevant and sensitive effect on which to base a risk assessment.

53. The worst-case estimated intake of total PBDEs from consuming one portion of trout per week from the Skerne-Tees river system was 0.056 μg/kg bw/day indicating a MoE of approximately 10,000 compared with the NOAEL of 450 μg/kg bw/day for liver effects of pentaBDE in rats. The MoE for intake of PBDEs from consuming one portion of eels per week would also be about 10,000. Since these MoEs are larger than the target MoE of 1000 for pentaBDE, these intakes are unlikely to pose a health risk.

54. The worst case estimated intake of total HBCD from consuming one portion of trout per week was 1.9 μg/kg bw/day indicating a MoE of approximately 50,000 compared with the LOAEL of 100,000 μg/kg bw/day for liver effects of HBCD in rats. The MoE for intake of HBCD from consuming one portion of eels per week would be about 60,000. Since these MoEs are larger than the target MoE of 3,000-10,000 for HBCD, these intakes are unlikely to pose a health risk.

Conclusions

55. We *conclude* that the uncertainties and deficiencies in the toxicological databases for PBDEs and HBCD prevent establishment of tolerable daily intakes. A Margin of Exposure (MoE) approach has therefore been used in this risk assessment.

56. We *consider* that the most sensitive endpoint for the PBDEs appears to be neurodevelopmental effects resulting from a single oral administration to neonatal mice at a developmental stage comparable to infants up to one month of age, and limited data indicate that HBCD could also have this effect. It is reassuring that infants of this age do not eat fish and therefore are not directly exposed to PBDEs from this source.

57. We *note* the uncertainty in the relevance of the neurodevelopmental effects for exposure to the fetus or breast-fed infant following maternal consumption of fish containing high levels of PBDEs or HBCD. This results from the lack of neurodevelopmental studies with exposure during pregnancy and the lack of information on concentrations in breast milk that could result from consumption of fish by the mother.

58. We *note* that consumption of fish from the Skerne Tees is unlikely to be widespread since there are no commercial fisheries in the area. However given the variability in BFR levels observed in this limited survey, it is not possible to exclude higher intakes in a small number of anglers or others eating their fish.

59. We *consider* that comparison of the worst case estimated intakes from consumption of a single portion of eels or trout per week from the Skerne Tees with the available toxicological data indicates that these intakes are unlikely to represent a risk to health. However, in view of the uncertainties surrounding the toxicological database and exposure assessments, this conclusion should be considered tentative.

60. PentaBDE and octaBDE are being phased out in 2004, which offers some reassurance that exposure to these compounds is unlikely to increase significantly. Concentrations of deca-BDE and HBCD should continue to be monitored, particularly in fatty foods.

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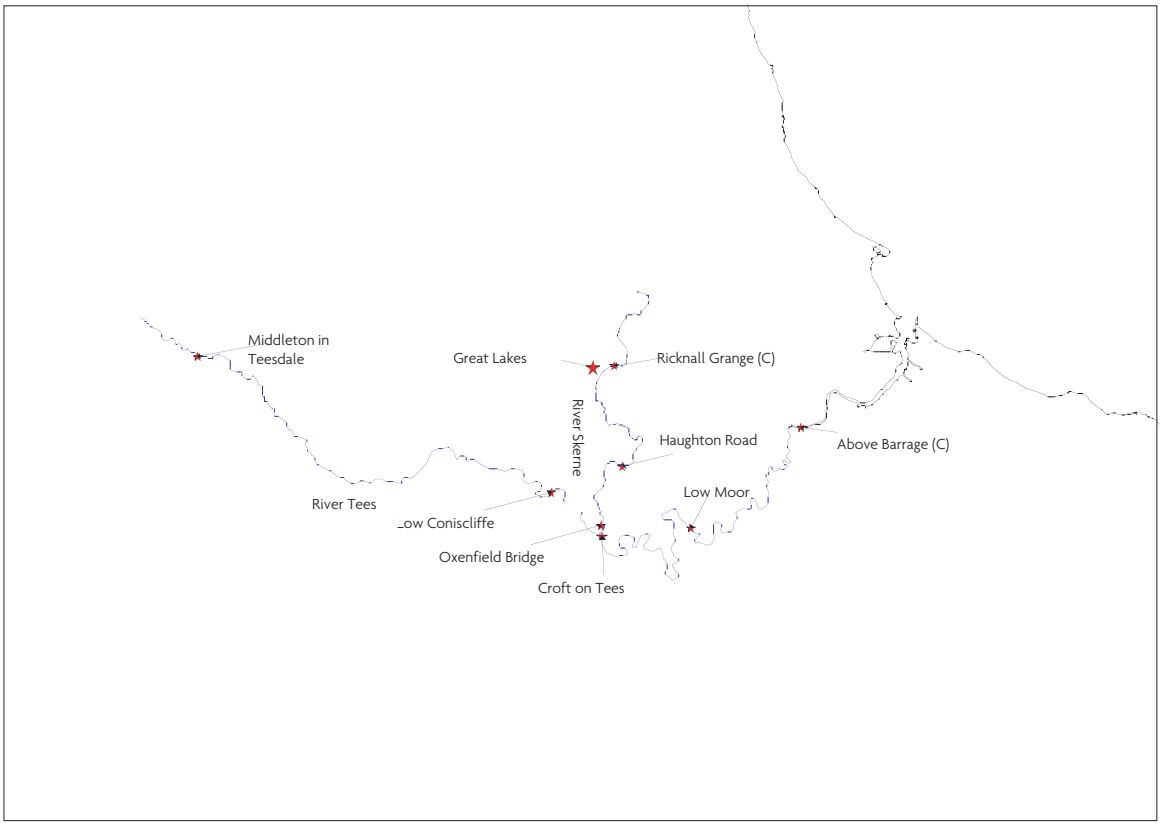
Figure 3. Sampling locations for the survey for brominated flame-retardants in fish from the Skerne-Tees River system



The sites shown on the map are the sites where samples of fish and eels were taken from. The sampling sites were upstream and downstream of the Great Lakes Chemical Company and at the confluence of the two rivers. Control samples (c) were obtained from the River Skerne at Ricknall Grange and from the River Tees at above the Tees Barrage. It was only possible to sample both trout and eels at the Oxenfield Bridge and Croft-on-Tees sampling sites.

Statement on fluorine in the 1997 Total Diet Study

Introduction

1. In 2000 the COT considered the results of a study conducted by the Food Standards Agency in which samples collected in the 1997 Total Diet Study (TDS) were analysed for the presence of fluorine, bromine and iodine. The Committee concluded that the total dietary intakes of bromine and iodine estimated from the survey were unlikely to pose a risk to health[1]. However, consideration of fluorine was deferred as the toxicity of this trace element was due to be considered by the *ad hoc* Expert Group on Vitamins and Minerals (EVM). The final report of the EVM was published in May 2003. The EVM concluded that fluoride was not within its remit as food fortification with fluoride is carried out as a public health measure. Determination of maximum levels of supplementation therefore has to take place within the context of local exposure and involves a consideration of risks and benefits, which was not in the terms of reference of the EVM. The EVM report is available at http://www.food.gov.uk/science/ouradvisors/vitandmin/.

Background

2. Fluorine is a trace element which is ubiquitous in the environment and is present at low levels in all plants and animals. The analytical method used in this survey did not distinguish between different forms of fluorine. Elemental fluorine is a highly reactive gas, and the ionic form fluoride is present in food. Therefore this statement considers the toxicity of fluoride, and uses the term fluoride throughout for ease of clarity.

3. Based on studies in animals, fluoride was considered by a WHO expert committee to be necessary for animal life[2]. However, although low intakes of fluoride in humans are associated with increased incidences of dental caries and general weaknesses of bones and teeth, a true fluoride deficiency state has not been documented. Human requirements have therefore not been determined.

4. Fluoride has a well-documented beneficial effect in protecting against dental caries[3]. Systemic exposure to fluoride during the pre-eruptive development of teeth results in its incorporation into the enamel matrix of the tooth, forming an enamel which is more resistant to acid decay. Post-eruption, fluoride has a beneficial topical effect, apparently by reducing enamel demineralisation and promoting remineralisation, and by inhibiting plaque acid-producing bacteria. For these reasons many dental products and some public water supplies are artificially fluoridated.

Toxicity of fluoride

Dental fluorosis

5. The most sensitive effect of excessive fluoride exposure in humans is considered to be dental fluorosis, a developmental defect of the tooth enamel. Dental fluorosis is caused by the over-incorporation of fluoride into the dental enamel to the effect that the composition and structure of the enamel are altered.

6. Dental fluorosis may be classified, using Dean's classification, as very mild, mild, moderate or severe. Pictures of the various forms of dental fluorosis can be viewed on pages 32-34 of the book 'Health Effects of Ingested Fluoride', by the US National Research Council[4], which is available to view electronically at http://books.nap.edu/books/030904975X/html. In its mildest forms, dental fluorosis presents as a barely visible white mottling of the teeth, which may not be apparent to the affected individual and is not considered to be aesthetically significant. The dental integrity of mild to moderately fluorosed teeth is not affected, and they may be more resistant to acid decay than non fluorosed teeth[5]. Moderate and severe effects of dental fluorosis include more noticeable white mottling, yellow/brown staining and pitting of the enamel[6].

7. Data from epidemiological studies suggest that the enamel tissue is most susceptible to fluoride-induced changes during the third or fourth years of life for the permanent anterior teeth and at 22-26 months for the maxillary central incisors, which is when the enamel is in the transitional or early maturation stages[7]. The maxillary central incisors are the two teeth most visible when smiling and therefore fluoride-induced changes in these teeth would be of most concern. The pre-eruptive maturation of the permanent teeth is completed by the age of 8 years, and children over the age of 8 years and adults are not susceptible to dental fluorosis.

8. Epidemiological studies by Dean (1942)[8] showed that in populations with drinking water containing about 2 mg/L fluoride, less than 5% of the population had moderate dental fluorosis. According to the US Food and Nutrition Board, total fluoride intakes from food and water in these populations were estimated as 0.08-0.12 mg/kg bw/day[5]. Fluoride-containing dental products and supplements were not available at the time. In populations with water containing close to 1 mg/L fluoride, a low prevalence of very mild to mild dental fluorosis (10-12%) and no cases of moderate dental fluorosis were observed[8] (estimated average total fluoride intake, 0.05 mg/kg bw/day[5]). An intake of 0.05 mg/kg bw/day is therefore assumed to be a no observed adverse effect level (NOAEL) for moderate dental fluorosis.

9. The prevalence of aesthetically significant fluorosis (moderate or severe) is estimated to be 3-4% in areas of the UK where the drinking water is artificially fluoridated and 0.5-1% where it is not artificially fluoridated[3].

Skeletal fluorosis

10. Symptomatic or clinical skeletal fluorosis is a condition characterised by skeletal abnormalities and joint pain. It is caused by pathological bone formation due to the mitogenic action of fluoride on osteoblasts. In its more severe forms, skeletal fluorosis causes kyphosis, crippling and invalidism. Secondary neurological complications in the form of myelopathy, with or without radiculopathy, may also occur.

11. Clinical skeletal fluorosis is endemic in regions of the world which have high fluoride levels in the water (up to 18 mg/L in 15 states of India) and hot, dry climates. In such climates clinical skeletal fluorosis has been associated with consumption of water containing fluoride levels as low as 1.5 mg/L[9]. However, studies conducted in the US in the 1950s indicate that in more temperate climates, no cases of clinical skeletal fluorosis were associated with fluoride levels up to 4 mg/L in drinking water[10]. The reason for the difference is uncertain, but it is likely to be largely due to the increased consumption of water in hot, dry climates. Dietary differences and fluoride exposures from other sources may also have contributed to the difference. There is no evidence of clinical skeletal fluorosis arising from exposures in the UK.

Other skeletal effects

12. A number of studies have investigated possible links of fluoride exposure, primarily through fluoridation of water, with fracture risk. Some studies reported a protective effect of increased fluoride exposure and others an increase in fracture incidence. In a recent meta-analysis of studies on bone fracture frequency and water fluoridation, no significant associations were found, except for studies of 10 years or longer, which showed a protective effect of water fluoridation on fracture risk[11].

13. A number of studies in humans and animals have investigated a possible relationship between fluoride intake and incidence of osteosarcoma because fluoride accumulates in bone and has a mitogenic action on osteoblasts.

14. The Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) reviewed the mutagenicity of fluoride in 1990. The COM concluded that although *in-vitro* mutagenic effects were seen at relatively high concentrations, the activity was considered to be indirect and unlikely to occur at low concentrations. All well-conducted *in-vivo* mutagenicity tests were negative. The COM therefore concluded that the consumption of fluoridated water would not constitute a mutagenic hazard to man. This view was endorsed in 1995 when some additional studies were considered[12].

15. The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) considered the available epidemiology and animal bioassay data in 1990, including the US National Toxicology Program (NTP) 2 year carcinogenicity study in F344/N rats and B6C3F1 mice, with drinking water concentrations up to 175 mg/L sodium fluoride (79 mg/L fluoride ion)[13]. The COC concluded that there was no evidence to indicate any carcinogenic risk to humans from exposure to fluoride[14]. There have been no data published since then to warrant seeking a further view from the COC.

Renal toxicity

16. Fluoride nephrotoxicity has been investigated in a number of animal species but the observed effects have generally been subtle, e.g. dilatation of the renal tubules and increased diuresis. No renal effects were observed in the 2-year NTP studies in rats and mice given drinking water containing 79 mg/L fluoride, providing intakes of approximately 7.9 and 15.8 mg/kg bw/day, respectively[13].

17. No renal disorders have been identified in humans in areas of endemic dental and skeletal fluorosis. One report exists of a single case of renal failure occurring in an individual who consumed, over a long period of time, large amounts of a mineral water containing 8.5 mg/L fluoride. Osteosclerosis was also diagnosed and the effects were attributed to the fluoride. However, it was not possible to calculate the fluoride intake of this individual[15].

Cardiac effects

18. Research conducted in China has shown that the percentage of patients with abnormal electrocardiograms (ECG) increased with increasing severity of skeletal fluorosis symptoms[16]. The relevance of this to fluoride exposure in the UK is unclear.

Reproductive effects

19. Fluoride has been shown to be toxic to the male reproductive system following administration to rats at 9 mg/kg bw/day for 29 days (as sodium fluoride, given by oral gavage). Effects on testis, prostate and seminal vesicle weights, reduced plasma testosterone levels, reduced epididymal sperm counts and reduced testicular Δ5,3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase activities have been reported. Histological findings included dilatation of seminiferous tubules and reduced numbers of mature luminal spermatozoa[17]. However, other studies in rats and rabbits have shown no adverse effects at higher doses (8.1-9.5 and 27 mg/kg bw/day in rats and 18 mg/kg bw/day in rabbits) given in the drinking water[18,19].

20. In humans, high fluoride intakes and symptoms of skeletal fluorosis have been associated with decreased serum testosterone levels[20]. The relevance of this observation to fluoride exposure in the UK is also unclear.

Neurotoxicity and neurobehavioural effects

21. Nine adult male Long-Evans rats were exposed for up to 52 weeks to drinking-water reported to contain 2.1 mg/L sodium fluoride (0.95 mg/L fluoride, or about 0.06 mg fluoride/kg bw/day)[21]. Although the administered fluoride is likely to have been insignificant in comparison to the fluoride content of the normal rat diet (which was not assessed), the authors reported statistically significant differences from a control group for brain aluminium, neuronal cell injury, and cerebral IgM and immunoreactivity for beta-amyloid. This study was seriously flawed by a high incidence of intercurrent infections[22] and mortality, which may have contributed to the findings.

22. The behavioural effects of pre-natal exposure to sodium fluoride have been studied in two experiments in Sprague-Dawley rats[23]. Pregnant dams were administered sodium fluoride by 9 subcutaneous injections of 0.13 mg/kg bw (0.06 mg fluoride per kg bw) in order to produce high peak plasma fluoride levels. In the first experiment, 1 or 2 injections per day were given to 7 dams on gestation days 14-18 inclusive. In the second experiment, 3 injections per day were given to 9 dams on gestation days 17-19 inclusive. Plasma fluoride levels were measured in pups at 3 and 9 weeks of age, and did not differ from levels in controls. Behavioural testing on the pups was undertaken at 9 weeks of age, leading to three measures of spontaneous behaviour (initiations, total time, and time structure). The only statistically significant difference from matched controls was for behavioural time structure, in males, in the GD 17-19 study.

23. These authors applied the same behavioural tests in a study of Sprague-Dawley rats provided with drinking-water containing fluoride at 0, 75, 100 or 125 mg/L from weaning at age 3 weeks, for 6-20 weeks[23]. At 75 mg/L (corresponding to a daily fluoride intake of about 3.8 mg/kg body weight), there was no statistically significant difference from controls. At 100 mg/L (corresponding to a daily fluoride intake of about 5 mg/kg body weight), differences in behaviour were found in females; no data on males at this dose were presented. The concentration of 125 mg/L (corresponding to a daily fluoride intake of about 6.3 mg/kg bw) was associated with reduced weight gain (8-17% reduction) and differences in behaviour, in both males and females. In a further study[23], adult male and female Sprague-Dawley rats were given drinking-water containing 100 mg/L fluoride for 6 weeks, from age 12 weeks; differences in behaviour were found in females but not in males.

24. Dose-related reductions in cell size and number of neurons in the hippocampus and dentate gyrus were noted in a study of adult female Swiss albino mice given drinking-water containing sodium fluoride at 0, 30, 60 and 120 mg/L for 30 days (5 animals per dose)[24]. It is not clear whether the concentrations were stated as fluoride or sodium fluoride; if the latter, they correspond to fluoride concentrations of 0, 13.6, 27 and 54.3 mg/L, and estimated fluoride intakes of approximately 0, 2.7, 5.4 and 10.9 mg/kg bw per day). Adverse effects on motor co-ordination, swim endurance and maze skill were noted at the top dose but not at the lower doses.

25. No abnormalities were seen in the brain (frontal cortex and basal ganglia, parietal cortex and thalamus, cerebellum and pons) pituitary gland, and spinal cord, in F344N rats given up to 300 mg/L sodium fluoride or in B6C3F1 mice given up to 600 mg/l sodium fluoride in drinking-water for 6 months[13]. No abnormalities were seen in these tissues, or in sciatic nerve, in these strains of rat and mouse given up to 175 mg/L sodium fluoride in drinking-water for 2 years[13]. These studies did not include routine examination of the hippocampus, or specific neurobehavioural tests.

The 1997 Total Diet Study

26. The Total Diet Study (TDS) forms part of the Food Standards Agency's surveillance programme for chemicals in food. Analyses for metals and other elements are generally carried out every three years. However, 1997 was the first year since 1980 in which fluoride had been considered.

27. A total of 400 samples were collected from retail outlets in 20 locations throughout the UK. Each of the samples was prepared or cooked according to normal domestic practice at a central location. The samples were combined into 20 composite food groups, the proportion of each food in a food group reflecting its importance in the average UK diet (largely based on an average of three years previous consumption data from the National Food Survey). The fluoride present in each sample was diffused as hydrogen fluoride at room temperature in the presence of perchloric acid saturated with hexamethyldisiloxane. The released fluoride was absorbed into a trapping layer of sodium hydroxide, which was then dried, dissolved in water and the fluoride content determined by ion exchange chromatography[25].

Results of the Total Diet Study

28. The full results of the survey were published in a Food Surveillance Information Sheet[25]. The highest mean fluoride concentrations were found in fish (1.9 mg/kg) and beverages (1.1 mg/kg). The fluoride content of beverages largely reflects the fluoride content of the water used in their preparation. However, tea contains higher amounts as fluoride is selectively taken up from the soil by the tea plant. The high fluoride levels in fish are thought to originate mainly from the skeleton, as fluoride accumulates in the bones of fish and some canned fish contains small bones.

Dietary exposure to fluoride

29. The TDS data were used to estimate dietary exposure to fluoride. Using food consumption data from the National Food Survey, which is updated every year based on household food purchases and so reflects changes in consumption patterns, the mean population intake of fluoride was estimated to be 1.2 mg/person/day (0.02 mg/kg bw/day for an average 60 kg person). Dietary exposure to fluoride was last estimated in 1984, when the mean population intake, calculated from concentrations of fluoride determined in selected food samples from the 1978, 1979 and 1980 Total Diet Studies, was estimated to be 1.8 mg/person/day. However, due to changes in the TDS design since 1981 and the limited number of samples that were used to estimate the intake in 1984, a direct comparison between the 1997 TDS and this earlier estimate cannot be made.

30. Mean and high level consumer intakes of fluoride for adults and children were estimated using consumption data from the National Diet and Nutrition Survey (NDNS) and are shown in Table 1. The highest intakes were for the 4 to 6 years age group, for whom high level dietary exposure was 0.06 mg/kg bw/day.

Table 1: Estimated dietary exposure to fluoride by children and adult consumers

Population group	Dietary exposure (mg/kg bw/day)	
	Mean	97.5th percentile
1½ to 4½ years[a]	0.023	0.053
4 to 6 years[b]	0.031	0.060
7 to 10 years[b]	0.024	0.047
11 to 14 years[b]	0.017	0.037
15 to 18 years[b]	0.015	0.034
Adults (19+ years)[c]	0.016	0.033

Notes:

a. Food consumption data from the NDNS: children aged 1½ to 4½ years[26]

b. Food consumption data from the NDNS: young people aged 4 to 18 years[27]

c. Food consumption data from the 1986/87 Dietary and Nutritional Survey of British Adults[28]

Other sources of exposure

31. Drinking water is a notable source of fluoride. The regulatory limit for fluoride in the UK public water supply, defined by The Water Supply (Water Quality) Regulations 1989, is 1.5 mg/L. Most public water supplies contain less than 0.7 mg/L fluoride. However, 10% of the UK water supply is artificially fluoridated to a level of 1.0 mg/L as a public health measure to protect against dental decay.

32. The regulatory limit for fluoride in spring water and bottled drinking water, defined by the Natural Mineral Water, Spring Water and Bottled Drinking Water Regulations 1999, is 1.5 mg/L, the same as for tap water. There is currently no regulatory limit on the amount of fluoride that natural mineral water may contain; however, an EC directive specifying a limit of 5 mg/L has been proposed, to apply from 1 July 2004 onwards. In a recent survey of 25 brands of bottled waters purchased in the UK, the maximum fluoride concentration identified was 0.37 mg/L[29].

33. Estimated fluoride intakes from water are 0.062, 0.033, 0.023 and 0.021 mg/kg bw/day for children aged 7 months to 4 years, 5 to 11 years, above the age of 12 years and adults, respectively. This assumes consumption of 0.8, 0.9, 1.3 and 1.5 L/day[30, 31] of water containing 1 mg/L fluoride and average body weights of 13, 27, 57 and 70 kg[30, 31], respectively for these age groups. Table 2 indicates total possible intakes from the diet and drinking water combined.

Table 2: Total possible fluoride intakes (mg/kg bw/day) from the diet and drinking water combined assuming water fluoride concentrations of 0.7 and 1.0 mg/L and mean or 97.5th percentile dietary intake

Population group	Fluoride concentration of drinking water 0.7 mg/L Mean intake (mg/kg bw/day)	97.5th %ile intake (mg/kg bw/day)	1 mg/L Mean intake (mg/kg bw/day)	97.5th %ile intake (mg/kg bw/day)
1½ to 4½ years	0.066	0.096	0.085	0.115
4 to 6 years	0.054	0.083	0.064	0.093
7 to 10 years	0.047	0.070	0.057	0.080
11 to 14 years	0.033	0.053	0.040	0.060
15 to 18 years	0.031	0.050	0.038	0.057
Adults	0.031	0.048	0.037	0.054

34. Few data are available on dietary exposure of infants to fluoride. This is likely to vary greatly between breast-fed and formula-fed infants, particularly where the formula is reconstituted using water with high fluoride content. Breast milk contains only trace amounts of fluoride and has been reported to provide less than 0.01 mg/day. In a survey conducted in Australia, fluoride contents of infant formulae reconstituted using deionised water ranged from 0.031 mg/L to 0.532 mg/L[32]. Assuming an average infant weight of 7 kg and consumption of formula reconstituted with 750 mL of water containing 1 mg/L fluoride, the intake of fluoride would range from 0.11 to 0.16 mg/kg bw/day. It is not known how relevant these data are to infant formulae on the UK market, but the water would provide the major contribution.

35. Dental products such as toothpaste and mouthwash generally contain added fluoride. Most toothpaste brands contain approximately 1000 mg/kg fluoride. Low-fluoride toothpastes for children contain 400-526 mg/kg fluoride. Fluoridated mouthwashes typically contain 230 mg/kg fluoride; they are not recommended for use by children under the age of 6 years. Some of the toothpaste and mouthwash used will be ingested, especially by young children. The amount of toothpaste used varies considerably, as does the amount swallowed, but it has been suggested that children under the age of 4 use 0.2 – 0.5 g/day of toothpaste and swallow 50% on average[33]. If toothpaste containing 1000 mg/kg fluoride is used, fluoride intakes would be 0.1 to 0.25 mg/day (equivalent to 0.008 to 0.019 mg/kg bw/day, assuming an average body weight of 13 kg).

36. The use of fluoride supplements is recommended by the British Dental Association for infants and young children in areas where the water supply contains less than 0.7 mg/L water. The dosage recommended varies depending on age and the level of fluoride in the public water supply.

COT evaluation

37. The Committee considered that a study of pre-natal exposure to injected sodium fluoride in rats did not provide persuasive evidence of an effect on postnatal behaviour. Exposure of weanling and adult rats to fluoride in drinking-water at concentrations equivalent to doses of about 5 mg/kg bw/day was associated, in females only, with abnormalities in behaviour (not found at the lower dose of about 3.8 mg/kg bw/day); this dose was close to that which caused evident systemic toxicity (reduced weight gain) at about 6.3 mg/kg bw/day.

38. A study which found structural abnormalities in the brain of rats exposed to fluoride in drinking-water at concentrations equivalent to doses of about 0.06 mg/kg bw/day was seriously flawed by a high incidence of intercurrent infections and mortality. A brief account of a small short-term study in mice reported dose-related abnormalities in the hippocampus, at fluoride concentrations in drinking-water presumed to be equivalent to daily fluoride doses of about 2.7, 5.4 and 10.9 mg/kg bw, but behavioural abnormalities were found at the top dose only.

39. Neurotoxicity was not detected in rats and mice in well-conducted long-term studies which included fluoride concentrations in drinking-water higher than those used in the behavioural and neurotoxicity studies described above, but which did not include routine examination of the hippocampus, or specific neurobehavioural tests.

40. The Committee noted that the most sensitive effect in humans is dental fluorosis, which occurs in children under the age of 8 years. Mild and very mild forms of dental fluorosis are generally not considered to be aesthetically significant. Moderate and severe forms of dental fluorosis are characterised by more noticeable white mottling, yellow/brown staining and pitting of the enamel. The integrity of teeth with mild to moderate dental fluorosis is not affected, and the teeth may be more resistant to dental decay than non-fluorosed teeth. Research is needed to determine the impact of the cosmetic effect of dental fluorosis on the affected individual, in order to determine whether the effects should be considered to be adverse.

41. An intake of 0.05 mg/kg bw/day has been reported to be a NOAEL for moderate dental fluorosis. This intake level was associated with a low incidence (10-12%) of very mild to mild dental fluorosis, which is not usually considered to be aesthetically significant. The threshold dose at which fluoride causes moderate or aesthetically significant dental fluorosis is 0.1 mg/kg bw/day, based on studies in which less than 5% of populations exposed to intakes of fluoride in the range 0.08-0.12 mg/kg bw/day had moderate dental fluorosis.

42. Information on total fluoride intakes is limited. The data in Table 1 derived from the 1997 TDS show that dietary exposure of high level consumers aged 11/2 to 6 years exceeds the NOAEL of 0.05 mg/kg bw/day by up to 20%. Taking into account other sources of exposure such as water and dental products, it is likely that a significant proportion of children under the age of 8 years have a total fluoride exposure above the NOAEL. Some of these children may be at risk of mild to moderate dental fluorosis, particularly during the third and fourth years during formation of the permanent anterior teeth. Because of the imprecise information on total exposure, it is not possible to predict the proportion that would exceed the threshold of 0.1 mg/kg bw/day, at which 5% of the exposed population would be expected to develop moderate (aesthetically significant) dental fluorosis. However, data on the prevalence of dental fluorosis in the UK indicate it to be low.

43. Breast milk contains only trace amounts of fluoride and has been reported to provide less than 0.01 mg/day. Based on the results of an Australian survey of fluoride concentrations in infant formula, intake in formula-fed infants could exceed the threshold for aesthetically significant dental fluorosis. However, although dental fluorosis may occur in the primary teeth, this may not lead to dental fluorosis of the permanent teeth if fluoride intakes have decreased by the time of the development and maturation of the dental enamel of the permanent teeth. Therefore infants may be at lesser risk than children aged 3 to 4 years.

44. There is a lack of studies to follow up long-term health outcomes of children with dental fluorosis. However, on the basis of the available information, the most sensitive effect of fluoride in children above the age of 8 years and in adults is clinical skeletal fluorosis. In regions with temperate climates, clinical skeletal fluorosis is not seen in populations with water fluoride concentrations below 4 mg/L. Other possible adverse effects of fluoride are seen at doses higher than those required to cause clinical skeletal fluorosis. It therefore appears unlikely that clinical skeletal fluorosis or any other adverse effects would occur in the general population from typical total fluoride intakes in the UK.

Conclusions

45. We *note* that a small number of studies of sodium fluoride in rodents have variously suggested abnormalities in behaviour, and structural abnormalities in the brain. These findings cannot be fully assessed without confirmatory studies. We note that neurotoxicity was not observed in well-conducted long-term studies in rodents at higher doses (more than 50 times the NOAEL in humans).

46. We *note* that the most sensitive effect of fluoride in humans appears to be dental fluorosis, which occurs in children under the age of 8 years. A total fluoride intake of 0.05 mg/kg bw/day represents a NOAEL for moderate (aesthetically significant) dental fluorosis.

47. We *consider* the results of this survey indicate that during formation of the permanent teeth, a small proportion of children may be at risk of moderate dental fluorosis due to dietary exposure to fluoride. However, we *note* that the prevalence of moderate dental fluorosis in the UK appears to be low.

48. We *note* that fluoride intakes of formula-fed infants may exceed the NOAEL for dental fluorosis, but *consider* that infants are at lesser risk because the critical time for development of aesthetically significant dental fluorosis is during formation of the permanent teeth.

49. We *note* that the integrity of teeth with mild to moderate dental fluorosis is not affected, and that the teeth may be more resistant to dental decay than non-fluorosed teeth. However, we *recommend* that more research is needed to determine the impact of the cosmetic effect of dental fluorosis on the affected individual and on any possible long-term health outcomes in people affected by dental fluorosis.

50. We *note* that more information is needed on total fluoride exposure, including intakes from toothpastes and mouthwashes.

51. We *conclude* that, based on the current information available and the dietary intakes estimated from the 1997 TDS, no adverse effects other than mild to moderate dental fluorosis would be expected to be associated with fluoride intake from food, either in adults or in children, at the intake levels in the UK.

COT Statement 2003/03

September 2003

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Updated statement on a survey of mercury in fish and shellfish

Introduction

1. In 2002, the Committee reviewed the results of a Food Standards Agency (FSA) survey of the mercury levels in imported fish and shellfish and UK farmed fish and their products[1] and the provisional results of blood mercury levels in UK adults[2].

2. The Committee concluded that the Provisional Tolerable Weekly Intake (PTWI) of 3.3 μg/kg bw/week could be used in assessing methylmercury intakes by the general population. This PTWI was initially established by the Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) in 1972 and confirmed on a number of occasions up to the year 2000, However, the 2000 JECFA PTWI was not considered adequate to protect against neurodevelopmental effects. The EPA reference dose of 0.1 μg/kg bw/day (0.7 μg/kg bw/week) was therefore applied for women who are pregnant, or who may become pregnant within the following year, or for breast-feeding mothers. The COT also noted that its conclusions should be reviewed following the JECFA evaluation of methylmercury in 2003[3].

3. In June 2003, JECFA recommended that the PTWI for methylmercury should be reduced from 3.3 μg/kg bw/week to 1.6 μg/kg bw/week. The Committee has therefore reviewed its previous evaluation in the light of the new JECFA PTWI, also taking into account more recent data on fish consumption by adults. This statement on mercury in fish and shellfish supersedes COT statement 2002-04.

4. The FSA has asked a subgroup of members of the COT and the Scientific Advisory Committee on Nutrition (SACN) to provide combined advice on the risks and benefits associated with fish consumption. The advice expressed in this COT statement therefore aims to protect the populations who are most susceptible to the risks of methylmercury, without being over-protective of individuals at lesser risk.

Background

5. The toxicity of mercury is dependent on whether it is inorganic, elemental or organic (e.g. methylmercury). Methylmercury affects the kidneys and also the central nervous system, particularly during development, as it crosses both the blood-brain barrier and the placenta[4]. Both neuro- and nephrotoxicity have been associated with acute methylmercury poisoning incidents in humans, and neurotoxicity, particularly in the developing fetus, has been associated with lower level chronic exposures.

6. Exposure of the general population to mercury can occur via inhalation of mercury vapour from dental amalgam fillings (elemental), or through the diet (methylmercury and inorganic mercury)[5]. Methylmercury in fish makes the most significant contribution to dietary exposure to mercury, although smaller amounts of inorganic mercury are present in other food sources. All forms of mercury entering the aquatic environment, as a result of man's activities or from geological sources, are converted into methylmercury by microorganisms and subsequently concentrated in fish and other aquatic species. Fish may concentrate the methylmercury either directly from the water or through consuming other components of the food chain. Methylmercury has a half-life of approximately 2 years in fish; thus, large older fish, particularly predatory species, will have accumulated considerably more methylmercury than small younger fish.

Previous COT evaluation

7. The COT previously considered the results of a survey of metals and other elements in marine fish and shellfish[6] published by the Ministry of Agriculture, Fisheries and Food (MAFF) in 1998. The survey examined a number of fish and shellfish species landed in the UK or imported from overseas ports including cod, haddock, herring, mackerel, lobster, mussels, crab and shrimps and samples of cod fish fingers. The survey also produced estimates of the mean and 97.5th percentile dietary intakes of the elements surveyed.

8. The 1998 survey demonstrated that the levels of mercury in the fish and shellfish tested were low and that average and high level fish and shellfish consumers in the UK would not exceed the then current JECFA PTWI for methylmercury of 3.3 μg/kg bw/week, even assuming all the mercury in fish was in this form. The estimated mercury intake for the highest level consumer was 1.1 μg/kg bw/week including mercury intake from the rest of the diet. The main conclusion drawn from the survey was that "dietary intakes of the elements surveyed were below safe limits, where defined, and did not represent any known health risk even to consumers who eat large amounts of marine fish or shellfish".

International Safety Guidelines

Previous Joint FAO/WHO Expert Committee on Food Additives (JECFA) Evaluations

9. In 1972, JECFA established a PTWI of 5 μg/kg bw/week for total mercury, of which no more than two thirds (3.3 μg/kg bw/week) should be from methylmercury[7] The PTWI of 3.3 μg/kg bw/week for methylmercury was subsequently confirmed in 1989 and 2000[8,9]. The PTWI was derived from toxicity data resulting from poisoning incidents at Minamata and Niigata in Japan. In these incidents the lowest mercury levels associated with the onset of clinical disease in adults were reported to be 50 μg/g in hair and 200 μg/L in whole blood. Individuals displaying clinical effects, such as peripheral neuropathy, at these mercury levels were considered to be more sensitive than the general population, because there were a number of persons in Japan and other countries with higher mercury levels in hair or blood who did not experience such effects. However, the methods employed in determining the intake associated with toxicity, and the subsequent establishment of the PTWI are unclear.

10. In 1989, JECFA had noted that pregnant women and nursing mothers may be at greater risk than the general population of adverse effects from methylmercury. Therefore in its 2000 re-evaluation of methylmercury, JECFA paid particular attention to possible effects of prenatal and postnatal exposure, looking at large long-term prospective epidemiological studies conducted in the Seychelles Islands and the Faroe Islands. These studies attempted to identify the lowest dietary mercury exposure associated with subtle effects on the developing nervous system[10-13]. They followed the neurological development of the children by testing their learning and spatial abilities at a number of time-points during their childhood. A number of smaller studies were also considered.

11. JECFA compared the two main studies;

- The Faroe Islands cohort was tested up to the age of 7 years, whereas at the time of the JECFA evaluation, the Seychelles cohort had only been tested up to the age of 5.5 years.

- Exposure in the Seychelles was through consumption of a range of fish species with average mercury concentrations between 0.05 and 0.25 mg/kg. In the Faroe Islands, most of the population consumed fish at least three times a week and occasionally (approximately once per month) consumed pilot whale, which contains up to 3 mg/kg mercury. Pilot whale also contains high concentrations of polychlorinated biphenyls (PCBs), but a reanalysis of the data indicated that any effects seen in the Faroes cohort could not be attributed to confounding by the PCBs[14].

- The two studies used different methodology in assessing methylmercury exposure. The Seychelles study used maternal hair samples (approx. 9cm long), one taken shortly after birth to estimate methylmercury exposure during pregnancy and one taken 6 months later. The Faroe Islands study used cord blood and maternal hair (various lengths) taken at birth.

- The studies used different batches of tests to assess the effects of methylmercury on neurological development. The tests used in the Faroe Islands study examined specific domains in the brain (visual, auditory, etc.). The Seychelles study used tests of a more global nature, with each test examining a number of domains.

12. JECFA found that although the mean mercury exposures during pregnancy (assessed by maternal hair mercury) were similar*, the results of these two studies were conflicting. In the Faroes study, regression analysis showed an association between methylmercury exposure and impaired performance in neuropsychological tests, an association that remained even after excluding the results of children with exposures associated with greater than 10 μg/g maternal hair mercury. However in the Seychelles study regression analysis identified no adverse trends, but increased maternal hair mercury was associated with a small statistically significant improvement in test scores on several of the developmental outcomes. The investigators noted that this could be due to beneficial nutritional effects of fish. A secondary analysis was performed where the results were split into sub-groups based on the maternal hair mercury level. Test scores in children with the highest mercury exposures (12 – 27 μg/g maternal hair) were not significantly different from the test scores in children with lowest exposure (< 3 μg/g maternal hair).

* Seychelles: arithmetic mean 6.8 μg/g, range 0.5-26.7 μg/g; Faroes: geometric mean, 4.27 μg/g, the upper mercury level in maternal hair is not clear from the reported data but may be as high as 70 μg/g.

13. A smaller study carried out in New Zealand on 6 year-old children[15] used a similar batch of tests to the Seychelles study and had similar exposure to methylmercury, yet found methylmercury related detrimental effects on behavioural test scores. However there were possible confounding factors that may have influenced the results of the New Zealand study, such as the ethnic group and social class of the children studied.

14. Having considered all of the epidemiological evidence, JECFA concluded that it did not provide consistent evidence of neurodevelopmental effects in children whose mothers had hair mercury levels of 20 μg/g or less. Since there was no clear indication of a consistent risk, JECFA did not revise its PTWI, but recommended that methylmercury should be re-evaluated when the latest evaluation of the Seychelles study and other relevant data become available[9].

Environmental Protection Agency (EPA)

15. In 1997 the US EPA established a reference dose of 0.1 μg/kg bw/day for methylmercury[16]. This was based on a peak maternal hair mercury level during pregnancy of 11 μg/g, which was associated with developmental effects (e.g. late walking, late talking, mental symptoms, seizures) in children exposed *in utero* during a poisoning incident in Iraq in 1971.

16. In 2000, the US National Research Council (NRC) published a review of this EPA reference dose[17]. Following analysis of the data resulting from the available epidemiological studies, the NRC identified a benchmark dose lower confidence limit of 12 μg/g in maternal hair (corresponding to 58 μg/L in cord blood, assuming a ratio of hair:cord blood of 200:1). This was the lower 5% confidence limit of the lowest dose considered to produce a sufficiently reliable neurological endpoint (a 5% increase in abnormal scores on the Boston Naming Test†) in the Faroe Islands study. The NRC made a number of assumptions in deriving an estimate of methylmercury intake and included a composite uncertainty factor of 10, to account for interindividual variability and database insufficiencies, concluding that the reference dose of 0.1 μg/kg bw/day, as had previously been used by the EPA, was scientifically justifiable.

2003 JECFA Evaluation

17. At its 61st meeting in June 2003[18], JECFA reviewed the new data from the Seychelles Child Development Study[19], re-analyses of the Faroes and New Zealand studies, epidemiological data from a number of small scale cross-sectional studies, and additional epidemiological data on reproductive toxicity, immunotoxicity, cardiotoxicity and general medical status.

18. The 9-year neurodevelopmental evaluations from the Seychelles study were performed using neurodevelopmental tests which, in contrast to the earlier assessments, allowed a direct comparison with the results of the Faroes Islands Study. The new data from the Seychelles study were consistent with results obtained at younger ages and provided no evidence for an inverse relationship between

† The Boston Naming Test is a neuropsychological test that assesses an individual's ability to retrieve a word that appropriately expresses a particular concern, for example naming an object portrayed by a simple line drawing.

maternal methylmercury exposure and neurodevelopmental performance in infants. Additional analyses carried out on the Seychelles data from younger ages did not alter the conclusion that in the Seychelles population of frequent fish-consumers, no adverse effects of prenatal methylmercury exposure have been detected.

19. No new data were available from the Faroes Islands study. New analyses of the existing data did not support a role of occasional exposure to higher levels of methylmercury or polychlorinated biphenyls (PCBs) from consumption of whale-meat, in accounting for the positive associations in this study[14,20-22]. The additional epidemiological data from smaller cross-sectional studies on neurodevelopmental effects of methylmercury were reviewed. Because of the cross-sectional design and because adult hair mercury levels do not accurately reflect previous exposure during the critical period for neurodevelopmental effects, JECFA did not consider that the results from these studies could be used to form the basis of a dose response assessment.

20. JECFA noted that despite additional evidence of immunotoxicity, cardiotoxicity, and reproductive toxicity, neurotoxicity was still considered to be the most sensitive endpoint, and concluded that the PTWI should be based on studies of this endpoint. It was uncertainty about the possibility that significant immunotoxicity or cardiovascular effects could occur at levels below the neurodevelopmental benchmark dose that had led to the inclusion of an additional safety factor for database insufficiencies in the composite factor of 10 recommended by the NRC.

21. JECFA based its evaluation on the Seychelles and Faroe Islands studies. In the absence of a dose response analysis of the latest Seychelles data, the analysis of the data from younger ages was used since it was consistent with the latest data. Exposure associated with a maternal hair concentration of 15.3 μg/g mercury was identified as the no observed adverse effect level (NOAEL) for the Seychelles study[23]. A benchmark dose lower confidence limit (BMDL) of 12 μg/g mercury in maternal hair was determined from the Faroes data[24-27]. This was viewed as a surrogate for the NOAEL.

22. Averaging the NOAEL and the BMDL resulted in a composite maternal hair concentration of 14 μg/g mercury reflecting exposure that was without effects in these study populations. Dividing by the average hair:blood ratio of 250 allowed conversion of the 14 μg/g in hair to a maternal blood mercury level of 56 μg/L. A pharmacokinetic model appropriate to pregnancy was then used to convert the blood mercury level to a steady-state daily ingestion of methylmercury of 1.5 g/kg bw/day, which would be without appreciable adverse effects in the offspring of the Seychelles and Faroe Islands study populations. The model assumed a maternal blood volume of 7 L (9% of body weight) whereas the EPA used a value of 5 L and the NRC 3.6 L.

23. JECFA then applied a data-specific adjustment factor of 2 to allow for inter-individual variability in the hair:blood ratio, and a default uncertainty factor of 3.2 to account for inter-individual variability in the association between blood mercury concentration and intake. This resulted in a PTWI of 1.6 g/kg bw/week, which JECFA considered to be sufficiently protective of the developing fetus. A factor for inter-individual variability in toxicodynamics was not required because the PTWI was based on studies in the most sensitive subgroup.

24. In its review, JECFA found no additional information that would suggest that the general population is at risk of methylmercury toxicity at intakes up to the previous PTWI of 3.3 g/kg bw/week.

Survey of the mercury levels in fish

25. The 2002 FSA survey complemented the previous MAFF survey since it examined a wider range of fish, including imported exotic species of fish that have become more widely available on the UK market. These included shark, swordfish, marlin, orange roughy, red snapper and monkfish, as well as UK farmed fish such as salmon and trout[1].

26. Of the fish species covered by the survey, all but 3 species had mean mercury levels falling within the range 0.01–0.6 mg/kg of fish. This range is in line with the levels defined by European Commission Regulation 466/2001 as amended by European Commission Regulation 221/2002 (0.5 mg of mercury/kg for fish in general and 1.0 mg mercury/kg for certain larger predatory species of fish including shark, swordfish, marlin, tuna and orange roughy).

27. The 3 species with the highest mercury content were shark, swordfish and marlin. These fish had mean mercury levels of 1.52, 1.36, and 1.09 mg/kg respectively and were therefore above the levels defined in European Commission Regulation 221/2002. Fresh tuna contained mercury levels ranging from 0.141 to 1.50 mg/kg with a mean of 0.40 mg/kg (only one sample out of 20 exceeded 1 mg/kg, the maximum mercury concentration in the other 19 samples was 0.62 mg/kg), whereas canned tuna had a lower mean mercury level of 0.19 mg/kg.

Blood mercury levels in British adults

28. A report produced by the Medical Research Council Human Nutrition Research in March 2002 detailed the provisional blood total mercury data obtained from 1320 adults (aged 19-64 years) participating in the National Diet and Nutritional Survey (NDNS)[2].

29. The mean and 97.5th percentile blood mercury levels in the survey were 1.6 and 5.88 g mercury/L respectively. The highest blood mercury level found in the study was approximately 26 μg/L in an individual with a high fish intake. If the blood mercury level was at steady state, and assuming a body weight of 70 kg and a blood volume of 9% of the body weight, then using the same pharmacokinetic model employed by JECFA in its 2003 evaluation, this would correspond to a mercury intake of approximately 5.39 μg/kg bw/week (0.77 μg/kg bw/day).

30. Of the population covered by the survey, 97.5% had blood mercury levels indicating that their mercury intakes were within the 2003 JECFA PTWI of 1.6 μg/kg bw/week.

COT evaluation

31. The Committee discussed the possible risks associated with dietary exposure to methylmercury, in the light of the new JECFA PTWI and the information on intakes from fish and on blood mercury levels in the UK population.

Toxicokinetic considerations

32. Following ingestion, approximately 95% of methylmercury is absorbed through the gastrointestinal tract, and it is subsequently distributed to all tissues in about 30 hours with approximately 5% found in blood and 10% in the brain. The methylmercury concentration in red blood cells is approximately 20 times higher than that in the plasma. Methylmercury readily crosses the placental barrier. Fetal brain mercury levels are approximately 5-7 times higher than in maternal blood. Methylmercury readily accumulates in hair and the ratio of hair mercury level μg/g) to maternal blood mercury level g/L) is approximately 250:1. Based on comparisons to hair concentrations, cord blood concentrations are reported to be 25% higher than the concentrations in maternal blood[10].

33. The excretion process for methylmercury involves transfer of the glutathione-mercury complex into the bile, demethylation by gut microflora to the inorganic form, then elimination from the body in the faeces. The half-life of mercury in the body is approximately 70 days in adults, with steady state being reached in about one year. Significant amounts of methylmercury also pass into the breast milk of lactating women, resulting in a decreased mercury half-life of approximately 45 days[28].

34. Doherty and Gates[29] reported that the excretion rate of mercury in the suckling rodent is less than 1% of the adult excretion rate. Sundberg *et al.*[30] reported a low elimination of mercury in suckling mice until lactational day 17. This is probably because biliary secretion and demethylation by microflora (which lead to faecal excretion) do not occur in suckling animals. The role of these processes in suckling human infants is unknown [4].

35. The concentration of mercury in breast-milk is approximately 5% of the blood mercury concentration of the mother[29]. Amin-Zaki *et al.*[31] reported that in women exposed to high levels of methylmercury during the Iraqi poisoning incident, 60% of the mercury in breast-milk was in the form of methylmercury. Therefore it may be estimated that the concentration of methylmercury in the breast-milk is approximately 3% of the total mercury concentration in the blood. For an infant to be exposed to methylmercury at the new JECFA PTWI of 1.6 μg/kg bw/week, the mother would have to be exposed to the following methylmercury level:

    Methylmercury intake of infant: = 0.23 μg/kg bw/day

    Assuming a daily milk intake of 150 mL/kg bw
    Concentration of methylmercury in milk = 1.53 μg/L

    Assuming 3% methylmercury transfer from maternal blood to milk
    Maternal blood mercury level = 51.1 μg/L

    Using the pharmacokinetic model employed by JECFA in its 2003 evaluation, and assuming a maternal body weight of 65kg

    Maternal methylmercury intake = 1.36 μg/kg bw/day (9.5 μg/kg bw/week)

Susceptible populations

36. In its 2003 evaluation of methylmercury, JECFA established a PTWI of 1.6 μg/kg bw/week in order to protect against neurodevelopmental effects but found no information to indicate that the previous PTWI of 3.3 μg/kg bw/week was not sufficiently protective for groups not susceptible to neurodevelopmental effects. The COT has been asked to advise on safety guidelines for methylmercury that could be used in assessing risks associated with fish consumption. The Committee concluded that the previous JECFA PTWI of 3.3 μg/kg bw/week could be used for the general population.

37. In its 2002 statement, the Committee had used the EPA reference dose of 0.1 μg/kg bw/day (0.7 μg/kg bw/week) in considering dietary exposure of the subpopulations at risk of neurodevelopmental effects. Members therefore discussed the differences between the 2003 JECFA PTWI and the EPA reference dose. The major differences related to the use of default uncertainty factors in derivation of the EPA reference dose, whereas chemical-specific data had been incorporated into the JECFA PTWI. The 2003 JECFA evaluation also took into account data published since the EPA review. The Committee had previously noted that the EPA reference dose was precautionary and agreed that the 2003 JECFA PTWI of 1.6 μg/kg bw/week should be used to protect against neurodevelopmental effects in susceptible populations. This PTWI is only necessary for the neurodevelopmental endpoint and therefore does not apply to the general population.

38. Due to this approach of applying different guidelines for different population groups, the Committee has given particular consideration to determining which groups are at higher risk and can be considered to be susceptible populations.

39. The critical effect of methylmercury is on the developing central nervous system and therefore pregnant women are considered to be the most susceptible population because of the risk to the fetus. There have been no studies of the effects of exposure prior to becoming pregnant. However, because the half-life of methylmercury in the human body is approximately 70 days, steady state concentration is attained in approximately one year and a woman's blood mercury level at the time of becoming pregnant is dependent on the exposure to methylmercury during the preceding year. The Committee therefore agreed that women who may become pregnant within the next year should also be considered as a susceptible population.

40. The evidence regarding consideration of other susceptible populations is not conclusive. Animal experiments indicate that exposure via breast-milk has less serious consequences to the central nervous system than prenatal exposure. Spyker and Spyker[32] reported that the effects of prenatal exposure to methylmercury dicyandiamide on the survival and weight gain of the offspring were more severe than those seen with postnatal exposure, and were greatest when the methylmercury was administered late in the period of organogenesis. However, these results are not necessarily relevant to the health effects of concern in human exposure.

41. Data from a 5-year longitudinal study following the Iraq poisoning incident have suggested that some children exposed to methylmercury via breast-milk demonstrated delayed motor development[31]. The maternal blood mercury levels immediately following the incident were estimated by extrapolation to

be in the range of approximately 100 to 5000 μg/L. Mothers who showed signs and symptoms of poisoning (ataxia, dysarthria, visual disturbance etc.) tended to have the higher blood levels (3000 to 5000 μg/L) although some women with levels in this range were asymptomatic.

42. The affected infants all had blood mercury levels above those associated with the 2000 JECFA PTWI of 3.3 μg/kg bw/week, and most of them had blood mercury levels higher than the minimum toxic level for adults of 200 μg/L, defined by JECFA. There was no paralysis, ataxia, blindness or apparent sensory change and there were no cases of the severe mental destruction and cerebral palsy that had been seen in the prenatally exposed infants of Minamata. However, language and motor development of the children were delayed. The authors of the study concluded that breast-fed infants are at less risk than the fetus, since most of the brain development has already occurred and the effects seen in the breast-feeding infant are different from those seen in infants exposed prenatally and not as severe.

43. There is no evidence that chronic exposure to methylmercury via breast milk at levels below those observed in the Iraqi incident has any adverse effect on the neurophysiological/psychological development of the child. Data from the Faroe Islands study suggests that the beneficial effects of nursing on early motor development are sufficient to compensate for any adverse impact that prenatal exposure to low concentrations of methylmercury might have on these endpoints[33,34]. Grandjean *et al.*[33] looked at the relationship between seafood consumption and concentrations of contaminants in breast-milk in the Faroes Island population. Of 88 samples of breast-milk, three had a mercury level that would cause the infant to exceed the old PTWI for mercury.

44. There have been few studies of the effects of methylmercury on young children. Most information has come from the poisoning incidents in Minamata, Niigata and Iraq. In all of these cases the exposures were very high, and in Iraq, the exposure was acute. Methylmercury is excreted by children as efficiently as by adults[4]. In the incidents where children were exposed to methylmercury directly rather than prenatally, the damage seen in the brain was similar to that seen in adults: focal lesions of necrosis. The damage seen when the fetus is exposed is much more widespread[4].

45. The longitudinal study in the Seychelles has attempted to examine the effects of postnatal exposure to methylmercury[12]. This is complicated by the facts that in the Seychelles, the children exposed to methylmercury postnatally are also exposed prenatally, and the study has been unable to demonstrate any mercury-related deficits in the neurological development of children. However higher postnatal methylmercury exposure had a positive association with test scores. It was suggested that this may be because a higher mercury level indicates a high fish intake and therefore a diet rich in n-3-polyunsaturated fatty acids and vitamin E, which have beneficial effects and may mask any subtle neurological deficits due to chronic low level exposure to methylmercury.

46. The risk is greater for women who are pregnant or likely to become pregnant within the following year because of the effects of methylmercury on the developing central nervous system of the fetus. There is uncertainty with respect to whether infants and young children are at greater risk of methylmercury toxicity whilst the central nervous system is still developing. The limited data available indicate that this is not the case for children but the possibility of increased sensitivity of infants cannot be discounted. Correlation of intakes by the breast-fed infant and the mother (paragraph 35) indicates that the methylmercury intake of the breast-fed infant is within the 2003 PTWI of 1.6 g/kg bw/week if the mother's intake is within the 2000 PTWI of 3.3 μg/kg bw/week.

Assessment of dietary exposure estimates

47. Dietary exposure to mercury was estimated for those fish species for which reliable consumption data were available[35-38] (salmon, prawns and canned tuna) together with exposure from the rest of the diet. Dietary exposures to these fish were also calculated for adult women as this population group contains the most susceptible populations (Table 1). This table is a revised version of that which appears in the FSIS[1] as it incorporates the most up-to-date consumption and occurrence data available for the rest of the diet from the TDS. Of these fish, canned tuna provided the largest contribution to dietary mercury exposure for high level consumers. Total fish consumption by the high level consumer was equivalent to approximately five portions per week (688g).

48. The estimates of average and high level total dietary exposure for almost all age groups, from fish for which consumption data are available, are within the 2003 JECFA PTWI for methylmercury of 1.6 μg/kg bw/week, and not expected to be harmful. The mercury exposure from the whole diet in toddlers and young people aged 4-6 years who are high level consumers exceeds the 2003 PTWI of 1.6 μg/kg bw/week by between 13 and 26% but are well within the 2000 PTWI. The estimated intakes of toddlers who are high level consumers of canned tuna exceeds the 2003 PTWI by 50%, but again are within the 2000 PTWI. Children of this age (1.5-4.5 years) are likely to be less susceptible to neurodevelopmental effects. Therefore this exceedance of the 2003 PTWI is not likely to result in harmful effects.

49. Estimates were also made of the methylmercury intake resulting from consumption of one portion of shark, marlin, swordfish or fresh tuna, for which consumption data are not available (Table 2), using portion sizes as recorded in the NDNS for fish consumption[36-38]. For comparative purposes similar estimates were made for canned tuna.

50. For adults, consumption of one weekly portion of shark, swordfish or marlin could result in a mercury intake in the range of 2.2 to 3.0 μg/kg bw/week, before considering intake from the rest of the diet (upper bound mean 0.28 μg mercury/kg bw/week, not all as methylmercury). Regular intake at this level during pregnancy, or in the year leading up to pregnancy could be associated with a risk of neurodevelopmental effects in the fetus. The methylmercury intake resulting from consumption of either two 140g portions of fresh tuna or four 140g portions of canned tuna would not be expected to result in neurodevelopmental effects.

51. Regular consumption of more than one portion of shark, swordfish or marlin per week could be associated with a risk of neurotoxicity in adults.

52. Dietary exposure of children is higher because their food intake is greater on a body weight basis. Regular consumption of one weekly portion of shark, swordfish or marlin per week by children under the age of 14 could result in a methylmercury intake in the range of 3.0 to 5.2 μg/kg bw/week, before considering intake from the rest of the diet. Consumption of two portions per week of fresh tuna, or 6 portions of canned tuna would not be expected to result in adverse effects in any of the age groups.

Conclusions

53. We *note* that there has been no new information published to indicate that the 2000 PTWI of 3.3 g/kg bw/week is not sufficiently protective of the general population. We therefore *consider* that a methylmercury intake of 3.3 μg/kg bw/week may be used as a guideline to protect against non-developmental adverse effects.

54. We *conclude* that the 2003 JECFA PTWI of 1.6 μg/kg bw/week is sufficient to protect against neurodevelopmental effects in the fetus. This PTWI should be used in assessing the dietary exposure to methylmercury of women who are pregnant, and who may become pregnant within the following year.

55. We *consider* that a guideline of 3.3 μg/kg bw/week is appropriate in considering intakes by breastfeeding mothers as the intake of the breast-fed infant would be within the new PTWI of 1.6 μg/kg bw/week.

56. We *consider* the NDNS blood level data are reassuring with respect to average and high level consumption of fish. The adults surveyed had blood mercury levels indicating that 97.5% of the population had dietary intakes below 1.6 g/kg bw/week.

57. We *conclude* that average and high-level dietary exposure to methylmercury, resulting from the wide range of fish for which consumption data are available, is not likely to be associated with adverse effects in the developing fetus or at other life stages.

58. We *note* that consuming one weekly 140 g portion of either shark, swordfish or marlin would result in a dietary methylmercury exposure close to or above 3.3 μg/kg bw/week in all age groups. We *consider* that this consumption could be harmful to the fetus of women who are pregnant or become pregnant within a year, but would not be expected to result in adverse effects in other adults.

59. We *note* that the mercury content of tuna is lower than that of shark, swordfish or marlin, but higher than that of other commonly consumed fish. We *consider* that consumption of two 140g portions of fresh tuna, or four 140g portions of canned tuna, per week, before or during pregnancy would not be expected to result in adverse effects on the developing fetus.

60. We *recommend* that further research should include development of analytical methodology to allow direct measurement of methylmercury, mechanistic studies to help elucidate population groups more at risk and research integrating the risks with nutritional benefits of fish consumption.

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Table 1: Estimated mean and high level dietary intakes of mercury from salmon, prawns, canned tuna and the whole diet.

Consumer group	Mercury Intake – µg/kg bw/week[a]							
	Salmon[b]		Prawns[b]		Canned Tuna[b]		Whole Diet[c,d]	
	Mean	97.5%	Mean	97.5%	Mean	97.5%	Mean	97.5%
Infants	0.01	0.01	–[e]	–[e]	0.04	0.13	0.04	0.13
Toddlers	0.18	0.53[f]	0.13	0.45[f]	0.84	2.45	0.56	2.17
Young People aged 4 – 6	0.18	0.39[g]	0.09	0.34[f]	0.53	1.61	0.55	1.82
Young People aged 7 – 10	0.11	0.36[f]	0.06	0.15[f]	0.39	1.26	0.41	1.40
Young People aged 11 – 14	0.09	0.23[g]	0.04	0.13[f]	0.32	0.98	0.29	1.05
Young People aged 15 – 18	0.08	0.15[g]	0.04	0.11	0.27	0.68	0.25	0.84
Adults	0.10	0.32	0.04	0.14	0.30	1.05	0.31	1.19
Adults – Women only	0.11	0.32	0.05	0.16	0.34	1.19	0.34	1.19

a. Consumption data for salmon, prawns and tuna are taken from the following sources:
   - 2002 National Diet and Nutritional Survey: adults aged 19 to 64 years[38].
   - Food and Nutrient Intakes of British Infants Aged 6-12 Months[35].
   - National Diet and Nutrition Surveys Children Aged 1.5 – 4.5 years[37].
   - National Diet and Nutrition Survey: young people aged 4-18 years. Volume 1 report of the diet and nutrition survey[36].

b. Mercury intake from eating the named fish only, for the mean and 97.5th percentile consumers.

c. Mercury exposure from the whole diet for individuals of the whole study population, including those that eat the named fish (taken from the 2000 Total Diet Study[39]). The whole diet mercury exposure does not equal the sum of the mercury exposures from the named fish and other foods in the typical UK diet.

d. The measurement of mercury does not distinguish between inorganic and organic mercury. Therefore although methylmercury is the major contributor to mercury intake from fish, the estimate of intake from the whole diet also includes inorganic mercury.

e. No infant consumption data were recorded for prawns in the Infant Survey.

f. Based on consumption data for fewer than 60 recorded consumers, therefore exposures to be regarded with caution.

g. Based on consumption data for fewer than 20 recorded consumers, therefore exposures to be regarded with extreme caution.

These estimates have been revised to incorporate most up-to-date consumption and occurrence data for the rest of the diet from the TDS.

Table 2: Mercury intake from one weekly portion of shark, swordfish, marlin, fresh tuna or canned tuna.

Age group (years)	Body Weight (kg)	Av. Portion Size[a] (g)	Weekly mercury intake assuming one portion of fish per week[b] (μg/kg bw/week)				
			Shark	Swordfish	Marlin	Fresh Tuna	Canned Tuna
1.5 – 4.5	14.5	50	5.24	4.62	3.79	1.38	0.66
4 – 6	20.5	60	4.44	3.90	3.22	1.17	0.56
7 –10	30.9	85	4.17	3.69	3.04	1.10	0.52
11 – 14	48.0	140	4.44	3.92	3.21	1.17	0.55
15 – 18	63.8	105	2.51	2.21	1.82	0.66	0.31
Adults	70.1	140	3.04	2.68	2.20	0.80	0.38

a. The average portion size that each age group of the population would consume at a single meal event for fish consumption, as recorded in the following National Diet and Nutrition Surveys (NDNS):
   - 1995 National Diet and Nutrition Survey: Children aged 1½ to 4½ years[37].
   - 2000 National Diet and Nutrition Survey: young people aged 4 to 18 years[36].
   - 1990 The Dietary and Nutritional Survey of British Adults[38].

b. This intake estimate does not include the intake from the rest of the diet, which is estimated to be 0.04 mg/kg bw/day (0.28 μg/kg bw/week)[39].

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Statement on a survey of metals in infant food

Introduction

1. The Food Standards Agency (FSA) has recently completed a survey of metals in infant food. This survey was carried out to establish the concentrations of 12 metals in a representative range of commercial infant foods and formulae. The Committee was asked to comment on the survey and assess if the levels of each element in the diet posed a risk to human health.

2. This survey follows on from a previous survey of metals in infant foods, which the Committee considered in 1999[1], concluding:

   - "We *note* that the estimates of intake by infants rely on assumptions about feeding patterns (infants aged 0-6 months) or on survey data that may now be outdated (infants aged 6-12 months). We would welcome new studies to determine the patterns of consumption of foodstuffs in infants.

   - However, we *consider* that the consumption of the infant foods sampled in the survey will not result in the intake of such quantities of any of the analysed elements such as would give concern for the health of infants."

Current Survey of Metals in Infant Foods

3. This survey was carried out between March 2001 and July 2002 to establish the concentrations of 12 metals in a representative range of commercial infant foods and formulae. It was designed to provide a picture of the elemental concentrations of the main types and brands of infant foods on sale in the UK and to allow an assessment of infants' exposures from these elements in these foods.

4. To assess the levels of each element in infant foods, 189 samples of commercial baby foods (infant formulae, manufactured baby foods, desserts, rusks and infant drinks) were analysed using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS), which does not determine the individual species of each metal.

5. In the absence of a more recent NDNS survey for 6-12 month olds three different approaches were used to provide consumption data for estimation of the dietary exposure of infants to each metal. Details of these methods, and descriptions of their limitations are available in COT paper TOX 2003-05 at: http://www.food.gov.uk/science/ouradvisors/toxicity/cotmeets/cot_2003/115049/.

6. The first approach used the same source of consumption data as the previous survey of infant foods[1], i.e. the 1986 survey of British Infants[2] for age 6-12 months, thereby allowing direct comparison of the data. Dietary exposures were calculated using the mean concentration of metal in each food category allowing a dilution factor for dried/concentrated foods. This method provides mean and high level dietary exposure of infants consuming a combination of one or more of any of the foods studied (formulae, manufactured baby foods, drinks and rusks), which is not possible from feeding instructions alone.

7. The second approach used a food consumption figure of 48 g/kg body weight/day for a high level infant consumer which was identified by the Scientific Committee on Food (SCF) when deriving maximum residue levels for pesticides in infant foods[3]. The basis for this consumption value is not clear. Estimates for formulae consumption were based on a volume of 500-600 ml which is recommended by the Committee on the Medical Aspects of food and nutrition policy (COMA) for infants up to 12 months old[4]. The average weight of powder in 600 ml of made-up formula was calculated for use in exposure estimates. This approach did not allow for a contribution to dietary exposure from juices or other drinks.

8. The third approach used manufacturers' feeding guidelines, as detailed on each product label, as the source of consumption data for formula. An average consumption level of food and drinks for each age range from weaning at 4 months of age was calculated from three different manufacturers' feeding guidelines[5,6,7]. The mean concentration of each element was calculated from the concentration of that element in every eligible food for a particular age group (using a dilution factor for samples of dried food). Average weights of 5.9, 7.7, 8.9 and 9.9 kg were assumed for infants of 0-3, 4-6, 7-9 and 10-12 months respectively[4]. Because the selection of infant foods surveyed was based on market share, the resulting mean concentration is assumed to reflect greater weight to more frequently consumed foods (such as ready-to-feed jar meals). Drinks, including juices, were taken into account in this approach. Due to the higher levels of some elements in soya based formula, separate exposure estimates were calculated, one based on soya formulae and infant foods (excluding dairy) and the other based on cows' milk-based formulae (from birth and follow on formulae) and foods. However only three samples of soya based formula were taken, so these data may not be representative.

9. The exposure estimates do not include the metal content of water used to reconstitute formula or dried food, or offered as a drink. They also do not include any contribution from foods not manufactured specifically for infants (e.g. normal 'adult' foods or home-prepared baby meals) or from breast milk. Nor do they consider wastage of food.

10. The Committee considered that the first approach using the 1986 NDNS consumption data was probably an under-estimation, but was useful in providing a comparison with the results of the previous survey. The third approach based on manufacturers' feeding guidelines generated the highest intakes, and could be considered a worst case scenario. Using the data derived from these two approaches provided a range in which the actual exposures are likely to be found. The Committee considered that there were a number of uncertainties and assumptions made in approach 2 and noted that the intakes calculated using this approach always fell within the range created by approaches 1 and 3. Therefore approach 2 was considered superfluous.

11. The survey results are reported in a food surveillance information sheet [8] and are summarised below.

Concentrations of elements in the products surveyed.

12. The levels of arsenic, cadmium, lead, mercury and tin were below the relevant regulatory levels for all foods surveyed[9, 10, 11]. Regulatory levels have not been set for the other metals surveyed. Copper and zinc are added to infant formula to ensure that infants receive adequate intakes of these essential elements. The levels of copper and zinc in all formulae surveyed fell within the acceptable range of fortification set by The Infant Formulae and Follow-on Formulae Regulations 1995[12].

13. With the exception of mercury, the mean concentrations of all elements in the products surveyed were in the region of, or lower than in the previous survey. Antimony, arsenic, cadmium and lead concentrations were above the limit of detection (LOD) in most samples. Zinc was detected in all samples and copper in all but one.

14. Mercury was detected at concentrations at or above the LOD in approximately one quarter of the samples, but the majority of those samples exceeding the LOD were very close to it. The mean concentration and the upper end of the range of mercury in infant foods appeared to be twice those seen in the previous survey (3 μg/kg, range <0.5 – 20, compared to 1.4 μg/kg, range <0.3 – 10). About 50% of this increase is likely to be due to the higher LOD for mercury in this survey (due to a decrease in the sensitivity of the equipment used in the analysis). In the current survey there were more foods containing fish than in the previous survey (7 out of 189 compared to 2 out of 97), however the fish containing meals only provided a minor contribution to the overall mean mercury concentration. Overall, it is apparent that the average mercury concentrations in infant foods have increased since the last survey.

15. With the exception of mercury, the average metal concentrations were higher in soya formula than in cows' milk formula, the most notable differences being seen with nickel and aluminium where concentrations were 2 to 3 times higher in soya formula. The concentrations in soya formula were similar to those reported in the previous survey.

Dietary exposure

16. The estimated dietary exposures for each metal are shown in Table 1, together with the comparable results from the previous survey. These were compared with available tolerable intakes, such as Provisional Tolerable Weekly intakes (PTWIs) set by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), taking into account previous COT evaluations. The COT evaluation was also informed by a summary of the toxicological data on these metals, which is available at: http://www.food.gov.uk/multimedia/pdfs/TOX-2003-05.PDF.

17. The term Provisional Tolerable Weekly Intake (PTWI) is used by JECFA in identifying tolerable intakes of food contaminants with cumulative properties. Within this statement, the PTWI has been by divided by 7 to provide a tolerable daily intake for comparison with the estimated daily dietary exposures. Like the Acceptable Daily Intake (ADI) set for food additives, the PTWI is considered to be applicable to all age groups above 12 weeks of age. Evaluation of dietary exposure of younger infants requires case-by-case consideration of the toxicological database.

COT evaluation

18. Water used to reconstitute infant formula and dried foods could make an important contribution to the metal concentration in the food as consumed. This is particularly important in the case of arsenic, where water is a significant source of dietary exposure to inorganic arsenic. The Committee recommended that future surveys of this type should allow for water used in reconstituting foods and formula.

19. The methods used to analyse the concentration of each metal have not determined which metal species are present, only the total concentration. Therefore risk assessment must allow for the possibility that where one form of a metal is more toxic (for example organic or inorganic) and where there is no information on the speciation of that metal in food, it is the more toxic form that is present predominantly in the food. However, this is a worst case scenario. Information on the speciation of each metal would allow for a more robust risk assessment.

Aluminium

20. The maximum estimated intake was lower than for the previous survey and approximately 18% of the JECFA PTWI[13] which is equivalent to 1000 μg/kg bw/day. Aluminium intakes resulting from a soya based diet were higher than those from a normal diet, probably due to the higher levels of aluminium in soya formulae with a maximum intake of 24% of the PTWI. There is no information available on whether infants are more susceptible to the effects of aluminium. However taking into account the additional margin of safety compared with the PTWI and that this is likely to be an over estimate of exposure due to the use of upper bound concentrations and worst case scenario consumption data, the intake of aluminium from infant foods and formulae is unlikely to be of concern.

Antimony

21. The maximum estimated intake was lower than for the previous survey and approximately 29% of the WHO TDI[14, 15] of 0.86 μg/kg bw/day. There is no information available on whether infants are more susceptible to the effects of antimony. However taking into account the additional margin of safety compared with the PTWI and that this is likely to be an over estimate of exposure due to the use of upper bound concentrations and worst case scenario consumption data, the intake of antimony from infant foods and formulae is unlikely to be of concern.

Arsenic

22. All dietary exposures were within the JECFA PTWI for inorganic arsenic[16]. However, in its latest consideration of arsenic in the diet, the COT concluded that there are no appropriate safety guidelines for inorganic or organic arsenic and that exposure to inorganic arsenic should be As Low As Reasonably Practicable (ALARP)[17]. Where comparable data are available, the estimated mean dietary exposure resulting from this survey is similar to that derived from the 1999 survey. The highest arsenic levels were found in fish-containing dishes, which are likely to contain predominantly organic arsenic[18]. Overall, these data suggest that dietary exposure of infants to inorganic arsenic have not increased.

23. Based on the current permitted level of inorganic arsenic in drinking water (50 μg/L), the contribution to the daily inorganic arsenic intake from water used to reconstitute formula could potentially be 3 to 5 μg/kg bw/day§. This is approximately twice the contribution from infant foods. The maximum permitted level of inorganic arsenic in water is due to be reduced from 50 to 10 μg/L in December 2003. However the vast majority of water companies are already complying with the lower level at which the potential inorganic arsenic intake from water used to reconstitute infant formulae could be 0.6 to 1 μg /kg bw/day.

Cadmium

24. The maximum estimated intake was lower than for the previous survey and approximately 72% of the JECFA PTWI for cadmium[19] which is equivalent to 1 μg/kg bw/day. There is no information available on whether infants are more susceptible to the effects of cadmium. However taking into account that this is likely to be an over estimate of exposure due to the use of upper bound concentrations and worst case scenario consumption data, the intake of cadmium from infant foods and formulae is unlikely to be of concern.

Chromium*

25. The maximum estimated intake was lower than for the previous survey and approximately 3% of the guidance level for trivalent chromium of 150 μg/kg bw/day recommended by the Expert Group on Vitamins and Minerals (EVM)[20]. Trivalent chromium is considered to be an essential trace element, whereas hexavalent chromium has been classified as carcinogenic[21]. The vast majority of chromium found in food is in the trivalent form[22] and so comparison of the total chromium levels in food with guidance levels for trivalent chromium is appropriate. There is no information available on whether infants are more susceptible to the effects of chromium. However taking into account the additional margin of safety compared with the PTWI and that this is likely to be an over estimate of exposure due to the use of upper bound concentrations and worst case scenario consumption data, the intake of chromium from infant foods and formulae is unlikely to be of concern.

§ Based on a water consumption of 600ml used to reconstitute formulae and a body weight of between 5.9 to 9.8 kg.

* Essential element.

Copper*

26. The maximum estimated intake was lower than for the previous survey and approximately 20% of the JECFA Provisional Maximal Tolerable Daily Intake (PMTDI)[23] of 500 μg/kg bw/day and 61% of the Safe Upper Level (SUL) of 160 μg/kg bw/day recommended by the EVM[20]. Infants may be less able to absorb copper, but may also be less efficient at excreting copper than adults and so it is uncertain if infants would be more susceptible to copper toxicity than adults. However taking into account the additional margin of safety compared with the PMTDI/SUL and the fact that this is likely to be an over estimate of exposure, the intake of copper from infant foods and formulae is unlikely to be of concern.

Lead

27. The maximum estimated intake was lower than for the previous survey and approximately 17% of the PTWI for lead[24] which is equivalent to 3.6 μg/kg bw/day. The COT has previously concluded that it is not possible to establish a threshold for lead[25]. Infants absorb a higher percentage of lead than adults following oral ingestion and are more susceptible to the neurotoxic effects of lead, particularly those leading to deficits in Intelligence Quotient (IQ). However the JECFA PTWI is a level of exposure that is not expected to increase the blood lead concentration of children. The decrease in exposure compared with the previous survey is consistent with the COT view that efforts should continue to reduce lead exposure from all sources.

Mercury

28. In 2002 when the COT considered methylmercury in fish[26] it concluded that the then current JECFA PTWI[27] may not be sufficiently protective for breast-feeding women because of the potential risk to the neonate. The EPA reference dose[28], which was derived from subtle neurobehavioural effects seen in children exposed prenatally, was used in assessing fish consumption by breastfeeding women in order to protect the young infant. However the COT noted inconsistencies in the evidence and agreed to review this conclusion following the JECFA evaluation of methylmercury in June 2003. JECFA has now revised its PTWI to 1.6 μg/kg bw/week[29]. The new lower JECFA PTWI is intended to be protective of both the general population and the high-risk groups, and therefore it can be used in assessing the dietary exposure of infants to mercury.

* Essential element.

29. The estimated intakes of mercury were higher than those from the previous survey. The maximum estimated intake (0.2 μg/kg bw/day for infants of 9-12 months) was approximately 87% of the JECFA PTWI for methylmercury which is equivalent to 0.23 μg/kg bw/day. Estimated intakes for infants aged 0-3 months, who are at greatest risk from methylmercury, was 30% of the PTWI. It is probable that mercury absorption would be lower in older infants due to concomitant intake of food and formula. In addition, these are likely to be overestimates of exposure estimates due to the use of upper bound concentrations and worst case scenario consumption data, and it is likely that not all of the mercury in infant foods is in the organic form. Overall, the Committee concluded that the estimated mercury intakes did not give cause for concern, but concentrations of mercury in infant foods should continue to be monitored.

Nickel

30. The estimated intakes were lower than for the previous survey. The worst case intakes (based on manufacturers' feeding guidelines) for 7-12 month old infants (normal diet) and for 4-12 month old infants (soya diet) exceeded the WHO TDI[14] of 5 μg/kg bw/day by up to 68%. Taking into account that this is likely to be an over estimate of exposure due to the use of upper bound concentrations and worst case scenario consumption, this exceedance of the TDI was considered unlikely to be of significance. Ingestion of nickel may exacerbate contact dermatitis/eczema in pre-sensitised individuals. Infants are less likely than adults to be sensitised to nickel and are therefore not to be considered a susceptible sub group. Overall, the dietary exposures were not considered to be of concern.

Selenium*

31. The maximum estimate intake was similar to the previous survey. The estimated intakes for all ages were within the upper limit of the safe range recommended for adults by the WHO[30] (400 μg/day) and the SUL of 450 μg/day recommended for adults by the EVM[20]. This comparison assumes that it is appropriate to use bodyweight in scaling from the adult safe upper levels to levels applicable to infants since it is not clear whether this would produce an apparent safe upper level below an infant's nutritional requirement for selenium.

Tin

32. The maximum estimated intake was lower than for the previous survey and approximately 1% of the JECFA PTWI[31] which is equivalent to 2000 μg/kg bw/day and 9% of the EVM[20] guidance level of 220 μg/kg bw/day. There is no information available on whether infants are more susceptible to the effects of tin. However taking into account the additional margin of safety compared with the PTWI and that this is likely to be an over estimate of exposure due to the use of upper bound concentrations and worst case scenario consumption data, the intake of tin from infant foods and formulae is unlikely to be of concern.[7]

* Essential element.

Zinc*

33. The maximum estimated intake was similar to the previous survey. Most of the estimated intakes of zinc exceeded the SUL recommended by the EVM[20], and some exceed the JECFA PMTDI[32]. However the SUL and PMTDI may not be applicable to infants due to their high nutritional requirements for zinc; 4 mg/day 0-6 months (690 μg/kg bw/day), and 5 mg/day 7-12 months (510 μg/kg bw/day). For this reason infant foods are often fortified with zinc (0.5-1.5mg/100 kcal for formulae and 2 mg/100 kcal for infant foods).

34. The intakes calculated using the 1986 NDNS data suggest that the average infant diet does not provide enough zinc, despite fortification (an infant of 7-12 months, with an average weight of 9.8 kg would require approximately 510 μg/kg bw day to achieve 5 mg/day). However, this approach may not reflect current intakes due to the age of the consumption data. Whilst the estimated intakes of zinc were higher for those infants consuming a soya based diet, soya is known to inhibit absorption of zinc in the gut[20] and so it is possible that the actual amount absorbed could be lower than those infants on a normal diet.

Essential elements

35. For most of the metals, estimated intakes have decreased since the previous survey. Whilst this is desirable for contaminants such as lead, cadmium, antimony, nickel and tin, decreasing intakes of essential elements (chromium, copper, selenium and zinc) may have the potential to lead to nutritional deficiency. However, consideration of nutritional deficiency is not within the remit of the COT.

Conclusions

36. We *note* that, with the exception of mercury, the concentrations of each metal in infant foods do not appear to have increased since the previous survey in 1999. Whilst some of the apparent increase in the concentration of mercury in infant foods may be attributable to methodological differences between the surveys we *consider* that the levels of mercury should continue to be monitored. Information on the forms of mercury in infant foods would help to demonstrate an adequate margin of safety for methylmercury.

37. We *note* that the estimates of intake by infants rely on survey data that may now be outdated or on assumptions about feeding patterns that may represent an overestimate of food consumption. Whilst these approaches permit an assessment of the results of this survey we would *welcome* new studies to determine the patterns of consumption of foodstuffs in infants.

* Essential element.

38. We *consider* that there are no relevant tolerable intakes or reference doses by which to assess dietary exposure to either inorganic or organic arsenic. Inorganic arsenic is genotoxic and a known human carcinogen. We therefore *conclude* that exposure to inorganic arsenic should be as low as reasonably practicable (ALARP). However we are *reassured* that since the previous survey arsenic intakes do not appear to have increased.

39. We *welcome* the apparent decline in lead exposure since the previous survey. However since it is not possible to identify a threshold for the association between lead exposure and decrements in intelligence quotient, efforts should continue to reduce lead exposure from all sources.

40. We *consider* that the consumption of the infant foods sampled in the survey will not result in the intake of such quantities of any of the analysed elements such as would give concern for the health of infants.

41. We *consider* that future assessments of metals in infant foods would be more robust if information was made available on the actual species of metal present in the food and on the contribution of the metal concentrations in water used to reconstitute formula and dried foods.

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July 2003

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Table 1: Estimated dietary exposure of infants to metals from infant foods (excluding water)

		Mean intakes calculated using manufacturers' consumption guidelines – µg/kg bw/day				Mean (and 97.5 percentile) intakes calculated using 1986 NDNS – µg/kg bw/day		Safety guideline
		2002 survey				2002 survey	1999 survey	
		0-3[a]	4-6[a]	7-9[a]	10-12[a]	7-12[a,b]	7-12[a,b]	
Aluminium[c]	Normal Diet	14	142	175	177	22 (76)	39 (98)	JECFA PTWI equivalent to 1000 µg/kg bw/day[13]
	Soya Diet	82	242	222	218	–	–	
Antimony[c]	Normal Diet	0.02	0.08	0.15	0.15	0.03 (0.10)	0.092 (0.29)	WHO TDI of 0.86 µg/kg bw/day (New TDI of 6 µg/kg bw/day proposed)[14,15]
	Soya Diet	0.18	0.25	0.21	0.20	–	–	
Arsenic[c]	Normal Diet	0.09	1.3	1.8	1.8	0.25 (0.87)	0.24 (0.61)	JECFA PTWI for inorganic arsenic equivalent to 2.14 µg/kg bw/day[16] COT has concluded there are no appropriate safety guidelines[17]
	Soya Diet	0.18	1.6	2.0	1.9	–	–	
Cadmium[c]	Normal Diet	0.04	0.35	0.61	0.64	0.09 (0.31)	0.16 (0.41)	JECFA PTWI equivalent to 1 µg/kg bw/day[19]
	Soya Diet	0.22	0.57	0.68	0.72	–	–	
Chromium[c]	Normal Diet	1.2	2.9	3.6	3.6	0.65 (1.91)	1.8 (4.2)	EVM Guidance Level = 150 µg/kg bw/day for total dietary intake of trivalent chromium[20]
	Soya Diet	1.5	3.3	3.7	3.7	–	–	
Copper[c]	Normal Diet	41	72	78	76	13 (40)	21 (52)	JECFA PMTDI = 500 µg/kg bw/day[23] EVM Safe Upper Level = 160 µg/kg bw/day for total dietary intake[20]
	Soya Diet	62	98	82	81	–	–	
Lead[c]	Normal Diet	0.08	0.37	0.51	0.52	0.08 (0.22)	0.21 (0.52)	JECFA PTWI equivalent to 3.6 µg/kg bw/day.[24] COT considered it is not possible to establish a threshold for lead[25]
	Soya Diet	0.22	0.56	0.59	0.61	–	–	
Mercury[c]	Normal Diet	0.07	0.18	0.18	0.19	0.04 (0.11)	0.023 (0.046)	JECFA PTWI for methylmercury equivalent to 0.23 µg/kg bw/day[29]
	Soya Diet	0.07	0.19	0.19	0.20	–	–	
Nickel[c]	Normal Diet	0.7	4.2	5.8	5.9	0.96 (3.0)	2.0 (5.1)	WHO TDI = 5 µg/kg bw/day[14]
	Soya Diet	4.2	8.4	7.6	7.9	–	–	

Continued

		Mean intakes calculated using manufacturers' consumption guidelines – µg/kg bw/day				Mean (and 97.5 percentile) intakes calculated using 1986 NDNS – µg/kg bw/day		Safety guideline
		2002 survey				2002 survey	1999 survey	
		0-3[a]	4-6[a]	7-9[a]	10-12[a]	7-12[a,b]	7-12[a,b]	
Selenium[c]	Normal Diet	1.3	2.2	2.2	2.1	0.43 (1.42)	0.54 (1.4)	The upper limit of the safe range proposed by the WHO was 400 mg/day determined for adults only based on epidemiological data[30]
	Soya Diet	2.5	3.5	2.6	2.6	-	-	EVM Safe Upper Level = 450 µg/day for total dietary intake, equivalent to 7.5 mg/kg bw/day for a 60 kg adult[20]
Tin[c]	Normal Diet	0.57	4.6	18.6	18.5	2.6 (8.9)	8.1 (32)	JECFA PTWI is equivalent to 2000 µg/kg bw/day[31]
	Soya Diet	0.62	4.7	19.7	20.1	-	-	EVM Guidance Level = 220 µg/kg bw/day for total dietary intake[20]
Zinc	Normal Diet	756	1262	1089	1062	198 (687)	220 (690)	JECFA PMTDI = 1000 µg/kg bw/day[32]
	Soya Diet	946	1503	1148	1128	-	-	EVM Safe Upper Level = 42 mg/day (equivalent to 700 mg/kg bw/day in a 60 kg adult) for total dietary intake[20]

Notes:

[a] Age range in months

[b] Dietary exposure in brackets are for the 97.5th percentile consumers

[c] For all metals except zinc, data are upper bound means calculated using the limit of detection (LOD) when an element is not detected in a sample. The LOD was defined as 3 times the standard deviation of measured values for reagent blanks after correction for typical sample weight and dilution.

Statement on twelve metals and other elements in the 2000 Total Diet Study

Introduction

1. The Food Standards Agency has completed a survey of aluminium, arsenic, cadmium, chromium, copper, lead, manganese, mercury, nickel, selenium, tin and zinc in the 2000 UK Total Diet Study (TDS). The results provide up to date information on the concentrations of these elements in foods and were used to estimate dietary exposures for UK consumers. The Committee was asked to comment on the survey results and assess if the levels of each element in the diet posed a risk to human health. The COT last evaluated population and consumer exposures to the twelve elements in the TDS in 1995.

The Survey

2. The TDS is an important part of the UK Government's surveillance programme for chemicals in food and has been carried out on a continuous annual basis since 1966. Results from the TDS are used to estimate dietary exposures of the general UK population to chemicals in food, such as nutrients and contaminants, to identify trends in exposure and make assessments on the safety and quality of the food supply. Analysis for metals and other elements in the TDS is carried out every 3 years.

3. The design of the UK TDS has been described in detail elsewhere[1] and involves 119 categories of foods combined into 20 groups of similar foods for analysis. The relative proportion of each food category within a group reflects its importance in the average UK household diet and is largely based on an average of three previous years of consumption data from the National Food Survey. Foods are grouped so that commodities known to be susceptible to contamination (e.g. offal, fish) are kept separate, as are foods which are consumed in large quantities (e.g. bread, potatoes, milk)[1,2].

4. The foods making up the 20 groups of the TDS were obtained from retail outlets in 24 towns throughout the UK. Each food group obtained from each town was analysed for the twelve elements of interest. The mean element concentrations for each food group were used together with data on the consumption of these food groups[3-10] to estimate dietary exposure for the average UK population and mean and high level (97.5th percentile) consumers.

Concentrations of the elements in the foods surveyed

5. The full results of this TDS will be published in a Food Surveillance Information Sheet[11]. The concentrations of each of the elements in the food groups were lower than or similar to those reported in the previous TDS, conducted in 1997[12], with the exception of aluminium and mercury.

6. The aluminium concentrations in the miscellaneous cereals, sugars and preserves and nuts groups were higher than those reported for the 1997 TDS. The largest increase (approximately 3 fold) seen in the miscellaneous cereals group may be due to increases in the use of aluminium containing preservatives in these foods, or the different proportions of products sampled in this group compared to previous total diet studies.

7. Mercury concentrations were similar to or lower than those reported in the 1997 TDS except for the fish group, in which the mean concentration was 0.071 mg/kg compared to 0.043 mg/kg in 1997.

Dietary exposures

8. Estimates of dietary exposure were compared with available tolerable intakes, such as Provisional Tolerable Weekly intakes (PTWIs) set by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), taking into account previous COT evaluations. The COT evaluation was also informed by a summary of the toxicological data on these metals[13]. The PTWI is used by JECFA in identifying tolerable intakes of food contaminants with cumulative properties. Within this statement, the PTWI has been divided by 7 to provide a tolerable daily intake for comparison with the estimated daily dietary exposures (Table 1).

9. Population dietary exposures have also been estimated, using the amounts of food consumed (based on consumption data from the National Food Survey from 1996 to 1998)[8-10]. These are shown in Table 2 with the population dietary exposures for each element from the UK TDS from 1976 to 2000.

COT evaluation

10. The estimated mean and high-level dietary exposures to aluminium, cadmium, chromium, copper and selenium for each consumer group were within the relevant safety guidelines and therefore are unlikely to be of any toxicological concern. Population exposures to these elements have generally declined over the course of the TDS programme, with exposures to most of these elements now at the lowest level.

Arsenic

11. The Committee has concluded previously, when considering 1999 TDS of Total and Inorganic Arsenic, that there are no relevant tolerable intakes or reference doses by which to assess safety of either inorganic or organic arsenic in the diet. Inorganic arsenic is genotoxic and a known human carcinogen and therefore exposure should be as low as reasonably practicable (ALARP)[14].

12. The estimates of consumer dietary exposures to total arsenic in the 2000 TDS were similar to those reported in the 1999 TDS of Total and Inorganic Arsenic[14]. The current population exposure to total arsenic was also similar to that reported in the 1999 TDS (0.055 mg/day and 0.05 mg/day, respectively) and lower than previous estimates (0.065 mg/day in 1997). In discussing the 1999 TDS, the Committee noted that fish was the major contributor to dietary exposure to arsenic and the predominant form of arsenic in fish is organic. Inorganic arsenic contributed less than 10% of the total dietary exposure to arsenic. The Committee noted that the data on inorganic arsenic appeared to be consistent with dietary exposure being ALARP, that the dietary exposure to organic arsenic identified in the survey was unlikely to constitute a hazard to health, and that the downward trend for total arsenic was reassuring. Although different forms of arsenic were not measured in the 2000 TDS, it is likely that there was a similar distribution of inorganic to organic arsenic to that reported for the 1999 TDS, and that the previous COT conclusions are still valid.

13. The Committee recommended that future surveys should measure both total and inorganic arsenic and include consideration of other sources of exposure such as water.

Lead

14. The highest estimate of dietary exposure to lead was 0.47 μg/kg bw/day (for toddlers at the 97.5 percentile of consumption). This is approximately 13% of the JECFA PTWI for lead[15] (equivalent to 3.6 μg/kg bw/day) which is a level of exposure from all sources that is not expected to cause an increase in blood lead concentration in young children. Young children are vulnerable to the effects of lead, because they absorb a higher percentage of ingested lead and are more susceptible to the neurotoxicity, which may result in deficits in Intelligence Quotient. A UK study of lead intake in children of 2 years of age showed that dietary exposure to lead contributed approximately 30% of total lead exposure with the remainder coming mainly from sources such as house dust, water and the air[16]. Thus dietary exposure to toddlers that is within 30% of the JECFA PTWI (i.e. less than 1.2 μg/kg bw/day) is not expected to result in an increase in the blood lead concentration above background levels. Therefore the dietary exposures to lead identified from the 2000 TDS are unlikely to represent a toxicological concern. However, the COT confirmed its previous opinion, from when they considered a survey of metals in infant foods, that because it has not been possible to identify a threshold for the effects of lead, efforts should continue to reduce exposure from all sources[17].

15. Table 2 illustrates that population dietary exposures have declined considerably since 1976, with the current population exposure at its lowest level (7.4 μg/day compared to 26 μg/day in 1997), which is in accordance with the COT opinion on reducing lead exposure.

Manganese

16. Manganese is an essential trace element but is neurotoxic at high occupational levels of inhalation exposure and there is limited evidence of neurological effects at lower doses. The dose response relationship in experimental animals has not been adequately clarified and the effects observed in animals may not reflect the subtle neurological effects reported in humans[18]. There is insufficient information to determine whether there are toxicological risks associated with dietary exposure to manganese and no available safety guideline. The population exposures to manganese have remained fairly constant since manganese was first included in a TDS in 1983 (4.6 mg/day) and there is no basis for assuming that the current dietary exposure to manganese (4.9 mg/day) is a concern for health to consumers.

Mercury

17. With the exception of high-level consumption by children aged 1.5-4.5 years, the estimates of dietary exposure to mercury (mean and high-level) for all consumer groups were within the PTWI for methylmercury set by JECFA in 2003 to protect against neurodevelopmental effects[19] (equivalent to 0.23 μg/kg bw/day). The estimate for high-level consumption by children aged 1.5-4.5 years exceeded the JECFA PTWI for methylmercury by 17%. It is unlikely that all the mercury in the diet is in the form of methylmercury. Inorganic mercury is less well-absorbed than methylmercury by the oral route, and therefore comparing dietary exposure to total mercury to the PTWI for methylmercury is a worst case scenario. Furthermore, the COT has previously noted that toddlers are likely to be less sensitive to the neurodevelopmental effects of methylmercury than the fetus or infant[20]. Therefore the dietary exposures to mercury do not give rise to toxicological concerns for consumers. The Committee also noted that the population exposures to mercury have decreased since 1976 (0.005 mg/day), with the current dietary exposure at its lowest level (0.0015 mg/day).

Nickel

18. The estimates of dietary exposures to nickel for high-level consumers aged 1.5-4.5 years and 4-18 years exceeded the WHO TDI (5 μg/kg bw/day)[21] for nickel by 44% and 6%, respectively. The TDI was set as a basis for establishing a WHO guideline for drinking water quality. It was derived from an animal study showing general toxicity in a 2 year dietary study and incorporated an uncertainty factor of 1000 to allow for inadequacies in the data and a higher absorption of nickel from drinking water than from food. The EVM noted that ingested nickel may exacerbate contact dermatitis/eczema in pre-sensitised individuals[18], however toddlers are less likely than adults to be sensitised and would not therefore be considered to be a sensitive group. Population exposures to nickel have decreased since 1976 (0.33 mg/day), with the current dietary exposure at its lowest level (0.13 mg/day). Overall the Committee concluded that the estimated nickel intakes were unlikely to result in any adverse health effects.

Tin

19. The estimates of dietary exposures to tin for high-level consumers aged 1.5 – 4.5 years were lower than the PTWI of 2000 μg/kg bw/day[22], but exceeded the EVM guidance level of 220 μg/kg bw/day by approximately 29%. The PTWI is not directly applicable to long term dietary exposures since it is based on intakes associated with acute toxicity (the threshold concentration for manifestation of gastric irritation). The EVM guidance level was based on a no observed adverse effect level (NOAEL) of 22-33 mg tin/kg bw/day from a sub-chronic study in rats, in which anaemia and changes to liver cells were observed at higher doses[23]. The EVM used the lower NOAEL (22 mg/kg bw) and an uncertainty factor of 100 to derived the guidance level of 0.22 mg/kg bw/day. The small exceedance of this guidance level is therefore within an area of uncertainty, but is not expected to result in adverse effects.

Zinc

20. The estimated dietary exposure for the high level consumers aged 1.5-4.5 years exceeded the EVM safe upper level (700 μg/kg bw/day)[18] by approximately 8%, but did not exceed the JECFA Provisional Maximum Tolerable Daily Intake (PMTDI) of 1000 μg/kg bw/day[24]. Estimated intakes for other consumer groups were within the EVM safe upper level. The EVM safe upper level was derived from studies of zinc supplementation in adults, taking into account adult dietary intake of zinc, and cannot be directly extrapolated for assessing safety of dietary intake by children. Overall, the Committee concluded that the estimated zinc intakes were unlikely to result in any adverse health effects.

Conclusions

21. We *conclude* that current dietary exposures to aluminium, cadmium, chromium, copper, mercury, nickel, selenium, tin and zinc are unlikely to be of any toxicological concern for consumers.

22. We *note* that the current survey measured total arsenic only, but that the data appear consistent with a survey of total and inorganic arsenic in food, which we reviewed recently. We *reaffirm* our previous conclusions that current dietary exposure to organic arsenic is unlikely to constitute a hazard to health, and exposure to inorganic arsenic should be as low as reasonably practicable (ALARP).

23. We *note* that estimates of total exposure to lead, including that from the diet, do not exceed the PTWI. We *conclude* that current dietary intakes are unlikely to result in adverse effects, but that efforts should continue to reduce exposure to lead from all sources.

24. We *note* there is insufficient information to determine whether there are risks associated with dietary exposure to manganese. However dietary exposures to manganese have remained fairly constant since monitoring began in 1983, and there is no basis for assuming any concern for health.

25. We *recommend* that in future surveys of elements in food, priority should be given to those of greatest toxicological concern, such as arsenic, mercury and lead. Speciation of metals such as mercury, arsenic and chromium would be helpful for the risk assessment.

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Table 1: Comparison of the estimated dietary intakes of each element for each population group with the relevant safety guidelines

Elements	Estimated Dietary exposure (µgkg bw/day) a, b, c												Safety Guidelines
	Adults		Toddlers (1.5-4.5 years)		Young People (4-18 years)		Elderly (free living)		Elderly (institutional)		"Vegetarians"[d]		
	Mean	High level	Mean	High level	Mean	High level	Mean	High level	Mean	High level	Mean	High level	
Aluminium	67-68	134-135	165	327	120-121	244-245	59	126-127	81-82	162-163	71-72	133-134	JECFA PTWI equivalent to 1000 µg/kg bw/day[25]
Arsenic	1.5-1.6	5.8	2.7	12	1.7	7.0	1.7	5.6	1.6	4.9	1.4	7.4	JECFA PTWI for inorganic arsenic equivalent to 2.14 mg/kg bw/day[26] COT has concluded there are no appropriate safety guidelines[14]
Cadmium	0.12	0.21	0.31-0.32	0.56	0.22	0.42	0.12	0.21	0.14	0.24	0.13	0.23	JECFA PTWI equivalent to 1 µg/kg bw/day[27]
Chromium	0.66-0.67	1.0-1.11	1.7	2.7-2.8	1.14-1.15	2.1	0.60-	0.98-0.99	0.72	1.1	0.55	0.92-0.93	EVM Guidance Level = 150 µg/kg bw/day for total dietary intake of trivalent chromium[18]
Copper	18	33	46	81	30	56	18	40	20	41	16	29	JECFA PMTDI = 500 mg/kg bw/day[28] EVM Safe Upper Level = 160 µg/kg bw/day for total dietary intake[18]
Lead	0.1	0.18	0.25	0.47	0.17	0.32	0.094-0.095	0.17	0.12	0.19	0.1	0.18-0.19	JECFA PTWI equivalent to 3.6 µg/kg bw/day[15] COT considered it is not possible to establish a threshold for lead[17]
Manganese	67	118	132	235	101	195	57	100	67	113	65	123	None available
Mercury	0.03-0.04	0.12-0.13	0.06-0.07	0.26-0.27	0.04-0.05	0.15-0.16	0.04	0.12	0.03-0.04	0.11-0.12	0.03	0.16	2003 JECFA PTWI for methylmercury equivalent to 0.23 µg/kg bw/day to protect against developmental effects[19]

Table 1: Comparison of the estimated dietary intakes of each element for each population group with the relevant safety guidelines *continued*

Elements	Estimated Dietary exposure (µgkg bw/day) a, b, c												Safety Guidelines
	Adults		Toddlers (1.5-4.5 years)		Young People (4-18 years)		Elderly (free living)		Elderly (institutional)		"Vegetarians"[d]		
	Mean	High level	Mean	High level	Mean	High level	Mean	High level	Mean	High level	Mean	High level	
Nickel	1.5	2.9	3.9	7.2	2.6	5.3	1.3	2.5	1.6	2.8	1.5	3.0	WHO TDI = 5 µg/kg bw/day[21]
Selenium	0.63-0.67	1.2-1.3	1.3-1.4	2.6-2.7	0.86-0.92	1.9-2.0	0.57-0.60	1.1	0.57-0.62	1.0-1.1	0.36-0.4	0.94-0.98	WHO upper limit of the safe range for adults only = 400 µg/day [29] EVM Safe Upper Level for total dietary intake equivalent to 7.5 µg/kg bw/day[18]
Tin	20	70	70	283	38	150	17	76	17	61	26	101	JECFA PTWI is equivalent to 2000 µg/kg bw/day[22] EVM Guidance Level = 220 µg/kg bw/day for total dietary intake[18]
Zinc	141	252	386	759	226	453	133	250	156	250	84	149	JECFA PMTDI = 1000 µg/kg bw/day[24] EVM Safe Upper Level for total dietary intake equivalent to 700 µg/kg bw/day (for 60 kg adult)[18]

Notes

a. Exposures have been estimated from the upper and lower bound mean concentrations, which assume non-detectable concentrations were the limit of detection and zero, respectively. Where the difference between the lower bound and upper bound mean concentrations is very small, rounding of the data leads to a single value.

b. The dietary exposure (mean and high level) for all foods combined is not equal to the sum of the exposure from the individual food. It refers to the dietary exposure by a consumer consuming one or any combination of the foods containing the metals. These values are derived from a distribution of the individual consumer's consumption patterns with regards to the individual foods.

c. Consumption data taken from the relevant National Diet and Nutritional Surveys.[3-7]

d. Some of the respondents of the dietary survey of vegetarians were consumers of fish.

Table 2: Comparison of population dietary exposures to aluminium (Al), arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), lead (Pb), manganese (Mn), mercury (Hg), nickel (Ni), selenium (Se), tin (Sn) and zinc (Zn) from UK Total Diet Studies 1976 to 2000

	Population dietary exposure (mg/day) [a,b]											
Year	Al	As	Cd	Cr	Cu	Pb	Mn	Hg	Ni	Se	Sn	Zn
1976	–	0.075	0.02	0.13	1.8	0.11	–	0.005	0.33	–	4.4	10
1977	–	0.1	0.018	0.17	1.8	0.1	–	0.005	0.26	–	4.2	10
1978	–	0.081	0.02	0.1	1.6	0.11	–	0.005	0.27	–	3.6	10
1979	–	–	0.017	–	–	0.09	–	0.004	–	–	3.2	–
1980	–	–	0.026	–	–	0.12	–	0.005	0.27	–	–	–
1981	–	–	0.019	–	–	0.08	–	–	0.23	–	2.4	–
1982	–	0.09	0.018	–	1.3	0.069	–	0.003	0.15	–	3.1	10
1983	–	0.07	0.018	–	1.2	0.067	4.6	–	0.15	–	2.3	10
1984	–	–	0.019	0.073	1.4	0.065	5.3	–	0.16	–	2.7	10
1985	–	–	0.018	–	1.3	0.066	5.0	–	0.14	0.063	1.7	10
1986	–	–	0.017	–	–	0.06	–	–	0.13	–	2.2	–
1987	–	–	0.018	–	–	0.06	–	–	0.15	–	2.0	–
1988	3.9	–	0.019	–	–	0.06	–	–	–	–	–	–
1991	10	0.07	0.018	0.25	1.4	0.028	6.2	0.002	0.17	0.060	5.3	10
1994	11	0.063	0.014	0.34	1.2	0.024	4.9	0.004	0.13	0.043	2.4	8.4
1995	–	–	–	–	–	–	–	–	–	0.039 c	–	–
1997	3.4	0.065	0.012	0.1	1.2	0.026	–	0.003	0.13	0.039	1.8	8.4
2000	4.7	0.055	0.009	0.046	1.3	0.0074	4.9	0.0015	0.13	0.034	1.4	8.4

Notes

" – " = not included in that TDS for metals and other elements.

a. The above population dietary exposures have been estimated using upper bound mean concentrations for each food group and consumption data taken from the National Food Survey 1997, Ministry of Agriculture, Fisheries and Food (1998). The Stationery Office, London.

b. Changes in the organisation of the TDS from 1981 onwards mean that exposures from TDSs before 1981 and from 1981 onwards are not directly comparable[1].

c. Dietary exposure estimates for selenium from the 1995 TDS are not directly comparable with those from other years as they are based on analyses of composite samples of each food from all the towns in the TDS rather than the upper bound mean concentrations of analyses of each food group from each town.

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Statement on physiologically based pharmacokinetic modelling

Introduction

1. In February 2003 the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) hosted a workshop on physiologically based pharmacokinetic (PBPK) modelling. The workshop comprised several presentations; these considered the use of PBPK models in risk assessment, requirements for PBPK models and parameters for incorporation of PBPK methods into risk assessment. The presentations were followed by a general discussion which focussed on the strengths and weaknesses of PBPK modelling, whether PBPK models could be integrated into COT risk assessments and how this could be achieved.

Background

2. Pharmacokinetics describes the relationship between exposure and the concentration-time profile of a chemical within the body. This relationship is usually expressed as an equation based on a representation of the body as one or more compartments. These approaches are limited, since the equation or model used is essentially empirical, and may bear little relation to the physiological processes involved. A more meaningful approach based on physiological principles rather than observed data would provide greater understanding of what actually occurs following exposure to a chemical. This is the concept of PBPK modelling as first described by Thorsten Teorell in 1937. However, at that time the lack of computing power to solve the resulting mathematical equations meant that the approach was impracticable.

3. Because PBPK modelling accounts for the underlying physiological processes and the physico-chemical properties of the chemical administered it facilitates prediction of events in humans from animal data and explains differences across chemicals. PBPK modelling permits prediction of chemical concentrations at specific target sites and can incorporate different exposure scenarios, disease states or changes with age and co-administration of other chemicals.

4. PBPK models are based on three main elements; physiological parameters, chemical specific parameters and design of the model. The physiological parameters are independent of the chemical and define each tissue or organ by its structure, size, blood flow, and functionality. Overlaid onto physiological parameters in the model are the chemical specific parameters: binding within blood (e.g. to proteins, red cells), tissue affinity (binding, partitioning), membrane permeability, and sensitivity to enzymic modification. The complexity of the model can be varied according to the information required. In a simplified model, tissues with similar physiological properties are considered as a single tissue. Variation of the biological parameters of a model (e.g. body weight) allows some PBPK models to simulate population response to exposure to a chemical by producing a distribution of outputs.

5. PBPK models, although complex and initially demanding of data and resources;

   - are highly informative
   - allow ready integration and scaling of in vitro and structural information
   - allow ready exploration of a wide variety of conditions and
   - improve successful modelling and prediction of pharmacokinetic events.

6. The use of PBPK modelling has become increasingly common in the development and selection of pharmaceutical candidates. The majority of work on development and validation of PBPK models has occurred in this context, although there have been some detailed studies of specific environmental chemicals.

7. Interest in PBPK modelling as a tool in risk assessment is increasing in North America and the EU. Regulators will need to be in a position to respond intelligently to use of PBPK by industry. The information generated will be useful in risk assessment and might provide insights when developing positions on generic risk assessment issues.

Validation of PBPK Models

8. A PBPK model requires validation to establish that the model accurately predicts what happens following exposure to a chemical. Validation contrasts the predictions generated by a model to data observed experimentally. However, little consensus exists on the nature and extent of experimental data required for validation of a model.

9. Where there are considerable data on the concentration of a chemical in human and animal systems, validation is relatively straightforward. When a model appears to predict the empirical fate of a chemical in the body with accuracy over a range of inputs there can be a high level of confidence in the model. This is relatively easy for a pharmaceutical compound where there are generally human data available to compare with the model output. There might occasionally be sufficient data available to validate a model in occupational settings.

10. In the case of contaminants and other non-pharmaceutical chemicals of toxicological concern human data is often scarce. The validation process may be limited to contrasting model predictions with observed data in animals. However, in contrast to the situation in humans, in animal studies it is also possible to undertake mechanistic validation, e.g. by manipulating the activity of a specific process. Nevertheless, generally there will be greater uncertainty about the accuracy of models generated for non-pharmaceutical chemicals and their ability to predict the behaviour of the chemical in humans.

Utility of PBPK modelling in the risk assessment/management process

11. Validated models can be very useful for informing the risk assessment and risk management of chemicals. An example is the use of PBPK to determine tissue levels following different exposure scenarios based on occupational exposure limits for carbon monoxide in order to examine options for setting new limits. However, generation and validation of a PBPK model is resource and time intensive, and it would be neither possible nor practicable to generate PBPK models for all chemicals. The emphasis should be that where models are available they have the potential to decrease the reliance on default assumptions about interspecies extrapolation and animal experiments.

The applicability of PBPK to risk assessments as carried out by the Committee

12. The majority of the risk assessments undertaken by the Committee are reactive. The effort and time required to produce and validate a model mean that it would not be feasible to generate a model in the usual time-scale for preparing papers for the Committee. However, where PBPK models already exist for a chemical these should be included in the information considered by the Committee in undertaking the risk assessment. The Committee noted that for many chemicals there were limited toxicological databases and little or no pharmacokinetic data. In addition, for most contaminants it was unlikely to be ethically possible to generate human pharmacokinetic data to fully validate the model. The adequacy and predictability of the model would then be a greater source of uncertainty.

13. There may, however, be the possibility to generate models that inform the risk assessment process for a chemical in more proactive risk assessments. This would require identifying and defining specific questions that the model would need to answer but could be valuable in an integrated risk assessment examining the relative contributions of different routes when exposure occurs via several routes. Considerable resource investment would be necessary in order to generate the model and, if necessary, data for validation.

14. The development of a small range of generic models with consensus biological parameters might be of value in comparing chemicals with different but limited data.

Conclusions

15. We *conclude* that PBPK modelling is an established technique, capable of predicting the behaviour of chemicals in the body, which is widely used in the development and assessment of pharmaceuticals. We *consider* that PBPK models can be used as part of the risk assessment process. We *note* that PBPK modelling may also be helpful in evaluating risk management options. PBPK models can also be valuable in identifying those parameters exerting most influence on the behaviour of the compound (sensitivity analysis) and as a means of exploring inter-individual variability.

16. We *conclude* that the generation and development of PBPK models is an iterative process and that each model requires validation. We *note* that the concept of validation is often based on empirical verification but currently there appears to be little consensus amongst practitioners on criteria for the adequacy of validation.

17. We *recognise* that full validation usually requires verification of the model predictions with human data. We *recognise* that for many chemicals it may not be possible to generate human data. We *note* that animal data can go a long way towards validation if it can be assumed, or there is evidence, that the chemical behaves similarly in animals and humans. We *conclude* that there would be limited confidence in the predictions of such models; this would need to be expressed as a source of greater uncertainty in the risk assessment.

18. Whilst validation requires data on the pharmacokinetics of a chemical in human and/or animal systems, we *note* that for many chemicals evaluated by this Committee there are very limited data on pharmacokinetics. We *conclude* that for many of these chemicals full validation of a specific PBPK model would not yet be possible. Validation could be enhanced by mechanistic studies in experimental animals

19. We *note* that the generation and validation of a PBPK model is resource and time intensive. We *conclude* that it would not be feasible to undertake PBPK modelling routinely for our risk assessments but that we should incorporate existing published PBPK models into our assessment when available.

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Urgent opinions requested of the COT

Fumonisins in maize meal: risk assessment

Possible health risks from consumption of contaminated maize meal

Issue

1. As part of a wider FSA survey of maize products analysis of two maize meal products (the only maize meal samples taken), 'Fresh and Wild' and 'Infinity Foods' organic maize-meal were found to contain high levels of fumonisins. The original laboratory found levels of 3605 and 8358 mg total fumonisins/kg, respectively. These samples were reanalysed and found to contain significantly higher levels 4712 and 20435 mg total fumonisins/kg, respectively. A further 30 samples have now been taken and are currently being analysed. Levels of fumonisins were low in other maize products analysed, such as maize flour.

Background

2. Fumonisins are mycotoxins, which are considered to be possibly carcinogenic in humans although evidence for their genotoxicity and carcinogenicity was considered inadequate by the Scientific Committee on Food (SCF). Information on the mechanism of action justified a threshold approach. Therefore, in 2003 the SCF set a tolerable daily intake (TDI) of 2 μg/kg bw/day for fumonisin B1, B2, and B3, alone or in combination (the committee considered a group TDI was appropriate). This was based on kidney and liver damage in sub-chronic and long-term studies in rodents (immunotoxicity was also observed at higher dose levels) and incorporates a 100-uncertainty factor. The TDI also took account of neurotoxicity in a short-term study in horses, as this was a severe effect that did not need long-term exposure. The committee considered that this effect, if induced in humans, would also be observed after short-term exposure. Fumonisin B1 has a low acute toxicity in several animal species and there are no reports of acute effects in humans (despite levels of about 120 mg/kg in some home grown maize).

Risk assessment

3. One-off consumption of a product containing fumonisin levels resulting in exposures exceeding the TDI is unlikely to have an appreciable effect on health. However, the risks of consumption of products containing high levels of fumonisins sufficient to exceed the TDI for longer periods of time is uncertain.

4. Assessment of consumption of maize meal and consumer exposure to fumonisins is difficult. There are too few consumers of maize meal in the National Diet and Nutrition Survey (n=6) to derive reliable intake data.

5. The TDI set by the SCF earlier this year is 2μg/kg bw/day for total fumonisins. Using the data from the second analysis of the maize meal, which gave levels of total fumonisins of 4712 and 20435μg/kg the TDI would equate to an intake of 29 or 7g of these maize meal samples for adults and 17 or 3g for young persons (4-18yrs) for the 2 samples analysed. The SCF TDI used an uncertainty factor of 100 and was based on kidney and liver damage in rats from sub-chronic and long-term studies.

6. As the intake data are unreliable due to the small sample sizes, data on possible intakes can only be estimated from individual recipes (see Annex A). Maize meal is used as a thickening agent or an alternative to bleached cornflour, or in gluten-free foods, and it can also be used as part of some ethnic diets. Generally the recipes considered indicate intakes of maize meal of 5-20g/serving from foods such as tortillas, corn bread, muffins, scones etc. Intakes from dishes including polenta could be as high as 80-125g maize meal/serving but data from the survey have not found high levels of fumonisins in retail polenta products. We do not have any information on possible intakes of maize meal from ethnic diets, but it is known to be used to make a weaning porridge in some parts of Africa and could be used in the same way by some ethnic groups in the UK.

7. If it is assumed that one serving of breads, cakes etc might be consumed daily, this could lead to an intake of maize meal of up to 20g/day. This would equate to a fumonisins intake of 3xTDI for adults and 7xTDI for young persons consuming the most highly contaminated sample. However, it is unlikely that such consumption would be repeated on a daily basis.

Annex A

Maize Meal Consumption

1. There were too few consumers of maize meal (N=6) in the NDNS from which to derive reliable intake data and no suitable food substitutes were available in the programme, hence it was decided that the best way forward was to use consumption data from typical recipes.

2. The following information on the typical uses of the products has been sourced from the retailers:

   - Uses described over the phone: It is used mainly as a thickening agent, as an alternative to bleached cornflour, by consumers who require a gluten-free diet. It is used in desserts, soups and in Mexican foods such as tortillas.

   - Fresh and Wild Organic Maize Meal, uses described on the label: Muffins, tacos, breads, cakes and polenta. Use as a coating for fried foods. Do not confuse with cornflour/starch, which should only be used as a thickening agent.

3. Below we have provided a table of typical recipes that use maize meal. Most of these recipes were sourced from 'gluten-free' cookbooks designed for sufferers of Coeliac Disease. Those recipes sourced from the Sainsbury's recipe database are designed for individuals without specific dietary requirements, but may be consumed by Coeliacs if they are gluten-free.

4. Recipes quoted in the table below assume that corn meal and maize meal are synonymous. Recipes using just corn/maize flour (UK) or corn/maize starch (US) were not included (typically this is used as a thickening agent, a common use is in custard). An exception to this is the tortilla recipe, which contains masa harina (maize flour). This was included as the retailer suggested that the product might be used for tortillas. No other information on ethnic foods, such as maize meal used as a weaning porridge (typically eaten in certain parts of Africa), have been included.

5. The maize meal in a typical adult serving has been given for each recipe where that recipe specified the number of people it would serve. Where this information was not available an amount of maize meal per individual unit is given e.g. per muffin or slice. The recipes in the table below directly indicate the use of maize/corn meal. Maize meal may, however, be used as part of a gluten-free flour mix that can substitute for flour in any cake, bread or biscuit (resulting in a heavy texture). Maize flour or dry polenta typically makes up 38% of the mix. Many more polenta recipes are available on the Sainsbury's recipe database; here we have just given a couple of examples (including the recipe that used the highest serving of polenta in the database). Any other assumptions made are detailed in the notes section of the table (see below).

Table of typical gluten free recipes using maize/corn meal[1,2,3,4,5]

Recipe	Amount of cornmeal per single serving (g)	Notes
Hard polenta and grilled courgettes[1]	125	Per adult serving Highest single adult serving from Sainsbury's database polenta recipes
Polenta sandwich[1]	83	Per adult serving
Grilled vegetable pizza[2]	19	Per adult serving
Corn Tortillas[1*]	17	Per tortilla
Cheese and onion corn bread[2]	16	Per 1 slice, assuming each slice is 85g (approximated to banana loaf slice – MAFF portion sizes)[4] Recipe specifies 175g maize meal per 900g loaf
Apricot and orange muffins[2]	14	Per muffin
Scones made with cornmeal[5]	10	Approximate cornmeal per 50g scone (approximated to wholemeal scone – MAFF portion sizes)[4]
Wild mushroom and broccoli flan[2]	9	Per adult serving
Corn crisp bread[3]	8	Per crisp bread
Corn, Buckwheat and Rice Bread[2]	5	Per 1 slice, assuming each slice is 85g (approximated to banana loaf slice – MAFF portion sizes)[4] Recipe specifies 50g maize meal per 900g loaf

1 Sainsbury's recipe database: http://recipe.sainsburys.co.uk/recipe/search

2 Anne Sheasby 'Gluten Free Cooking' 2000, Annes Publishing Ltd.

3 Peter Thompson 'Gluten-free cookery' 2001, Hodder and Stoughton.

4 MAFF 'Food Portion Sizes' 1998, 2nd Ed. The Stationery Office.

5 Marilyn Le Breton 'The AiA Gluten and Dairy Free Cookbook' 2002, Jessica Kingsley Publishers, London and Philadelphia.

* This recipe is not gluten free.

Nickel leaching from kettle elements into boiled water

Background

1. The Committee was asked for urgent advice on the health implications of nickel leaching from kettle elements into boiled water, based upon results of a study commissioned by the Drinking Water Inspectorate (DWI). Members were provided with the full DWI study report, a summary of the data drafted by the Secretariat, the draft risk assessment of nickel from the Expert Group on Vitamins and Minerals (EVM) and an opinion previously provided by a COT expert to support the EVM evaluation.

2. Seven Members were able to provide written comments in the time available. The following summary of the comments was drafted by the Secretariat and approved by the Chairman.

Nickel in boiled water

3. The new data show that boiling of water in some types of exposed element kettle results in an increase in the nickel content. This is consistent with the results of previous studies reviewed in the DWI report.

4. There is no statistical analysis of the data in the DWI report and it is therefore not possible to draw conclusions with respect to possible effect of water filtration. The study design involved 3 types of filter, 8 models of kettle, 4 kettles per model, 2 samples of water, which were sometimes but not always pooled for analysis, with 8 sampling days. Specialist statistical expertise is required to analyse these data.

5. The data indicate that there might be a difference between filtered and unfiltered water. However this depends on a number of factors such as the age of both the kettle and the filter, type of kettle, whether the water is hard or soft, and how long the water is allowed to stand in the kettle after boiling. In practice, it is likely that kettles are often boiled containing appreciable amounts of water from previous use. The results of repeated boiling studies are odd since the nickel content of the water appears to decrease. The limited study of water boiled under "domestic conditions" indicates that if there is a difference it is much less marked when the kettle and filter are older.

6. The data only address water from two specific locations and it is not possible to determine whether these are representative of all water supplies, or how variable the results would be using water from other areas. Potential variables include the presence of organic compounds (e.g. in peaty water), differences in reservoir conditions, distance water has been piped and types of piping used.

7. In considering the nickel levels that should be used in a risk assessment, Members concluded that it would be preferable to have more complete data on boiled water corresponding to normal usage of kettles. Members considered that if it is necessary to conduct a risk assessment on the currently available data, then since the leaching declines rapidly during the first seven uses, it would be more relevant to use the data from the later sampling points.

Health risks associated with ingestion of nickel

8. As noted by the EVM, ingestion of nickel may result in an elicitation or exacerbation of allergic reactions in individuals who already have allergic sensitisation to nickel. Nickel-sensitised individuals should therefore be considered to be at greater risk; nickel sensitisation is more prevalent in women than in men. There is limited evidence that atopic dermatitis sufferers may have a higher rate of nickel sensitisation (Cronin *et al*., 1993). An allergic skin reaction may result from single exposure to pre-sensitised individuals, but is not considered to be a serious health risk.

9. Oral exposure is not considered to cause skin sensitisation in the absence of prior exposure via jewellery or other skin contact. Oral exposure to nickel at an early age (prior to ear piercing) may inhibit subsequent development of allergic hypersensitivity to nickel (Todd *et al*., 1989; Van Hoogstraten *et al*., 1991; Vreeburg *et al*., 1984). Therefore infants are not considered to be at greater risk that adults. In addition, there is some evidence that oral exposure to nickel may reduce sensitisation in those who already have contact hypersensitivity (e.g. Jovall *et al*., 1987; Panzani et al., 1995).

Information needs for risk assessment

10. Since absorption of nickel from beverages such as tea or ingested with food is greatly reduced compared with absorption from water alone, information is required on the ways in which boiled water may be consumed, and the amounts consumed.

11. More information is required on the factors influencing leaching, using water samples that are representative of different supplies. A study with distilled water would be useful for comparison. More information is needed on different types of filter and kettle, on the time-course of changes in nickel leaching with the age of the kettle used, frequency and effects of descaling and how frequently consumers replace their kettles. Exposure data to be used in a risk assessment should be based on water boiled under conditions similar to those used in homes, the work-place and catering establishments.

Conclusions

12. The Committee concluded that the results of the DWI report support previous observations that boiling water in some types of kettle may result in elevated levels of nickel in the water. No other conclusions could be reached in the absence of statistical analysis of the data.

13. Individuals with prior allergic sensitisation to nickel are at greatest risk of adverse effects arising from nickel ingestion. A single exposure to high levels of nickel in food or water may result in exacerbation or elicitation of an allergic skin reaction in these individuals. This is not considered to be a serious health risk. Infants are not considered to be at greater risk than adults.

14. In order to assess the risks associated with nickel in boiled water, more information is needed on the possible exposure resulting from use of different types of filter and kettle under normal conditions of use.

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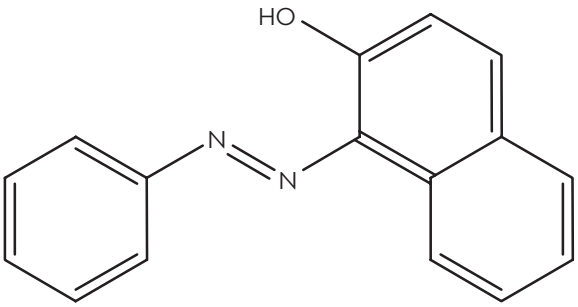
Sudan 1 found in chilli powder

Risk Assessment of Sudan I



1-phenylazo-2-naphthol
Major synonyms: Sudan I, C.I. Solvent Yellow 14

1. In 1975 the International Agency for Research on Cancer (IARC) reviewed the available data on Sudan I. It placed Sudan I in Group 3[§] based on the limited data available at that time (IARC 1975). IARC also cited an evaluation carried out by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), which concluded that on the basis of toxicological evidence, Sudan I is considered to be unsafe for use in food. Subsequent to the IARC evaluation further data have become available on Sudan I.

In vitro genotoxicity data

2. Garner and Nutman (1977) reported a negative result in the Ames test with concentrations up to 100mg/plate. Cameron *et al.* (1987) reported that Sudan I induced revertants in *S. typhimurium* TA1538 in the presence of hamster liver S9, with a concentration related response from 3333mg/plate. There was also an apparent concentration-related response with rat liver S9, but it did not reach the level of twice the spontaneous revertants, which was a specified criterion for a positive response at that time. No increase in revertants was seen in the absence of S9. Tennant *et al.* (1987) reported Sudan I as being positive with metabolic activation in the Ames test with a lowest positive concentration 0.3 μg/plate, but insufficient detail is available to judge the validity of this result.

3. In Chinese Hamster Ovary (CHO) cells, Sudan I induced sister chromatid exchange in the presence and absence of metabolic activation, but did not induce chromosome aberrations (Tennant *et al.,* 1987); Ivett *et al.,* 1989). It has also given positive results in the mouse lymphoma assay (Tennant *et al.,* 1987; Cameron *et al.*, 1987; McGregor *et al.,* 1991).

[§] Group 3: The agent (the mixture, the circumstances surrounding exposure) may not be classed in terms of its carcinogenicity for man. This category groups those agents for which proof of carcinogenicity is insufficient for man and insufficient or too limited for laboratory animals.

4. Stibovora *et al.* (2002) reported that metabolism of Sudan I by CYP1A1 (and possibly CYP3A4) in human microsomes produces a product that can form DNA adducts. This compound exhibited the same chromatographic properties as the 8-(phenylazo)deoxy-guanosine DNA adduct produced following metabolism of Sudan I by rat microsomal enzymes.

In vivo genotoxicity data

5. Oral administration of Sudan I has been reported to induce micronuclei in rat and mouse bone marrow (Elliot *et al.,* 1997). In both rat studies, there was a significant increase in micronuclei at 24 and 48h harvest times at the only dose tested, 5000 mg/kg, which was reported as clear positive result. In mice, there were some inconsistencies between the two experiments with respect to results at the different harvest times and depending on the number of cells scored. Positive results were obtained at a dose of 5000 mg/kg at both harvest times, and also at 2000 mg/kg when 6000 cells at the 24 h harvest. The authors reported this as a weak effect because the fold increases above control were less than for rat. There were no signs of toxicity in either rats or mice, but an orange coloration of urine and faeces indicated that Sudan I was absorbed.

6. Westmoreland and Gatehouse (1991) reported a dose-related increase in bone marrow cell micronuclei in male PVG rats 24 hours after a single oral dose of 250, 500 or 1000 mg/kg. Administration of 1000 mg/kg Sudan I induced micronucleus formation in bone marrow cells and peripheral blood reticulocytes of F344 rats (Wakata *et al.* (1998). In contrast, Westmoreland and Gatehouse reported a negative response in a bone marrow micronucleus assay in male CRH mice at single doses of either 500, 1000 or 2000 mg/kg.

7. Negative results have been reported for induction of rat liver unscheduled DNA synthesis assay (UDS) at doses of up to 2000 mg/kg (Mirsalis *et al*., 1989; Elliot *et al.,* 1997; Westmoreland and Gatehouse, 1991). Mirsalis *et al*. (1989) and Westmoreland and Gatehouse (1991) reported negative or equivocal responses in the induction of S-phase DNA synthesis.

8. Tsuda *et al.* (1999) reported that oral administration of 1000 mg/kg Sudan I to male ddY mice produced a positive result in a Comet assay in stomach and colon 8, but not 3 or 25 hours after dosing. No evidence of genotoxicity was seen in kidney, liver, bladder, lung, brain or bone marrow.

Carcinogenicity data

9. Since the IARC evaluation, the carcinogenicity of Sudan I has been investigated as part of the National Toxicology Programme (NTP, 1982). Groups of 50 male and 50 female F344/N rats were fed diets containing 0, 250 or 500ppm Sudan for 103 weeks. These diets provided doses of 0, 13-36 and 26-73 mg Sudan I/kg bw/day to the males and 0, 12-32 and 25-68 mg/kg bw/day to the females. Groups of 50 male and 50 female B6C3F1 mice were fed diets containing 0, 500 or 1000ppm Sudan I for 103 weeks, providing doses of 0, 115-198 and 243-405 mg Sudan I/kg bw/day to the males and 0, 116-208 and 226-416 mg/kg bw/day in the females.

10. No compound-related clinical signs or effects on survival were observed. Neoplastic nodules of the liver occurred in rats of both sexes with a significant dose-related trend (male, $P<0.001$; female, $P=0.005$), which was not associated with non-neoplastic pathology in the liver. The authors concluded that the study provided unequivocal evidence of carcinogenicity following dietary administration in both sexes of F344 rats.

11. Lymphomas or leukemias occurred in the low-dose female mice at an incidence significantly ($P<0.05$) higher than that in the controls (control, 12/50; 500ppm, 23/50; 1000ppm, 17/50). However, because of the lack of a dose-related trend and because the incidence in the 1000ppm group was not significantly increased, an association between the incidence of hematopoietic tumors and the administration of Sudan I was not clearly established. The incidence of lymphomas or leukemias in male mice was not significantly increased (control, 5/49; 500ppm, 10/50; 1000ppm, 10/50). The authors concluded that Sudan I was not considered to be carcinogenic for B6C3F1 mice of either sex.

12. Hepatomas have been reported in mice following subcutaneous administration (IARC, 1975).

Additional data

13. There is evidence that Sudan I can cause allergenicity in the form of contact dermatitis following its use as a red dye in "kumkum" (an Indian cosmetic) at concentrations ranging from 2.8 mg/g to 8.7 mg/g (Kozuka *et al*., 1988). Additional evidence of allergenicity is reported by Kato *et al* (1986) who demonstrated that a metabolite of Sudan I (4'-hydroxy-1-phenylazo-2-napthol) elicited a positive allergenic response in guinea pigs sensitised to Sudan I. The authors concluded that the *para*-hydroxylation of the phenyl group of Sudan I may play an important role in its allergenicity

Conclusions

14. The Chairman of COT, COC and COM noted that, although there are as always some incomplete and possibly equivocal results, overall the azo structure, the genotoxicity data and the carcinogenicity data lead to the conclusion that it is prudent to assume that Sudan I is a genotoxic carcinogen. Dietary exposure should therefore be as low as reasonably practicable (ALARP).

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Declaration of COT members' interests during the period of this report

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Professor I Hughes (Chairman)	Pfizer	Education Adviser	Archives of Disease in Childhood	Commentary Editor
	BP Amoco	Shares	Academy of Med Sciences	Fellow
	BP Amoco	Daughter is an employee of this company	Soc for Endocrinology Royal College of Paediatrics and child Health	Member
	Topical Endocrinology	Editorial Board Member	Medical Res Council	Fellow, Senior Examiner, Regional Academic Adviser Member of Advisory Board
			Pfizer Aventis NovoNordisk Diabetes UK Wellcome Trust Juvenile Diabetes Fund	Funds received from all these sources for Departmental research and education in medicine and health related topics
Professor Alan Boobis	NONE	NONE	GlaxoSmithKline	Support by industry
			Servier Pharmaceuticals	Support by industry
Dr P Carthew	Unilever	Employee	NONE	NONE
	Provalis	Share Holder		
Professor J K Chipman	Sequani	Training	AstraZeneca	Research Support
		Consultancy	Glaxo Smith Kline	Research Support
	AstraZeneca	Consultancy	ICI	Research Support
	Inamed	Consultancy	HSE	Research Support
	Unilever	Consultancy	CEFIC-LRI	Research Support
	Syngenta	Lecture fee	Dept of Health	Research Support
			Inamed	Research Support

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Dr J Hinson	GlaxoSmithKline	Shareholder	NONE	NONE
Dr P Jackson	Bristol Myers Squibb	Lecture fees	Novartis	Research grant
	Merck Sharp Dohme	Lecture fees	Merck Sharp Dohme	Research grant
	British Heart Foundation	Lecture fees	Servier	Research grant
			Bristol Myers Squibb	Research grant
			Pfzier	Research grant
			AstraZeneca	Research grant
			Bohringer Ingelheim	Research grant
			Medtronic AVE	Research grant
			Department of Health	Research grant
Dr M Joffe	NONE	NONE	NONE	NONE
Professor J Lunec	NONE	NONE	Scilucent LLC. USA	Funding research group to investigate toxicology of soya-bean oil implants
Dr A Piersma	NONE	NONE	NONE	NONE
Professor D Ray	CEFIC (European chemical industry body)	Advisory panel fee	NONE	NONE
Professor I R Rowland	Colloids Naturels International Rouen (CNI)	Consultancy	Various	Departmental teaching and research funded by various food companies
	Cerestar	Consultancy		
	Halifax	Shares		
	Woolwich	Shares		
Dr L Rushton	Institute of Petroleum	Consultancy, Contracts and Grants – Completed	Concawe	Contracts to Institute for Environment and Health (IEH) Now Completed
	Transport and Geneal Workers Union	consulancy – Completed	European Silica Industry	Ongoing Cohort Study, Contract to IEH
	Friends Provident	Shares	International Manganese Institute	Contract to IEH to prepare criteria document
	Northern Rock	Shares	American Chemistry Council	Contract to IEH for systematic review and meta-analysis
	Unilever	Consultancy – advice on design of an epidemiological survey relating to dermatitis		

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Ms J Salfield	NONE	NONE	NONE	NONE
Dr A Smith	Abbey Natiional	Share Holder	Rhone Poulenc	Past Research
	British telecom	Share Holder	Glaxo Wellcome	Support
	MMO2	Share Holder	CEFIC – LRI	Past Research
	HBOS	Share Holder		Support
	Latham & Watkins	Consultancy		Research Support
Dr L Stanley	CXR Biosciences	Salary	Cyclacel	Company contract
			Euro Chlor	Company contract
			Halogenated Solvents Industry Alliance	Company contract
			Association of Plastics Manufacturers, Europe	Company contract
			Astra Zeneca	Company contract
Professor S Strobel	NONE	NONE	Syngenta	Research Grannt
			FSA	Contract Research
Professor S Strobel	NONE	NONE	Syngenta	Research Grant
			FSA	Contract Research
Dr M Tucker	Zeneca	Pension	NONE	NONE
Miss A Ward	NONE	NONE	NONE	NONE