COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Second draft statement on the potential risks from high levels of aluminium in the infant diet

Introduction

1. The Committee on Toxicity (COT) has been asked to consider the toxicity of chemicals in the infant diet, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. An initial paper (TOX/2012/03), highlighting some of the areas for possible consideration was discussed by the COT in February, 2012, and Members concluded that there was a need for more detailed consideration of aluminium. A discussion paper on aluminium (TOX/2012/21) was presented to Members in June 2012 and a draft statement in October 2012 (TOX/2012/36). The minutes of the discussion from October are included in Annex A. COT toxicologists have confirmed that they are content with the Provisional Tolerable Weekly Intake (PTWI) established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

2. This second draft statement responds to the discussion of the first draft statement in October 2012. Further background information was added to provide the context of the statement, information about data sources drawn on, searches performed and an outline of the structure of the statement. Further information was provided on the dermal exposure to aluminium in addition to the potential exposure from drinking water. Conclusions from the subgroup report on the Lowermoor water pollution incident have also been included.

3. Annex B contains a second draft COT statement summarising the available information and the Committee's provisional conclusions on aluminium.

Questions on which the views of the Committee are sought

4. Members are invited to agree the text of the draft statement.

Secretariat
March 2013

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

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Minutes of the COT meeting of 30 October 2012:

Item 8: First draft statement on the potential risks from high levels of aluminium in the infant diet - TOX/2012/36

54. Interests were confirmed to be as previously declared for this topic.

55. Aluminium in the infant diet was discussed at the meeting in June 2012 and following on from this, Members were provided with a first draft statement on the potential risks from high levels of aluminium in the infant diet (TOX/2012/36). They were asked to comment on the structure of the statement, whether certain aspects needed further elaboration or could be shortened and whether they agreed that the Provisional Tolerable Weekly Intake (PTWI) established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) should be used in the risk characterisation of aluminium in the infant diet. Members were also asked to advise on conclusions they would like to see in the next draft.

56. Members requested that further background information be added to provide the context of the statement, information about data sources drawn on, searches performed and an outline of the structure of the statement.

57. The toxicologists from the Committee were asked to consider the derivation of the PTWI and confirm whether they were content with it.

58. Members requested that more information be provided on dermal exposure to aluminium through the use of antiperspirants. Further information was also requested on aluminium exposure through drinking water. Members asked that mean and median values be presented for aluminium concentrations in tap water in addition to 1st and 99th percentile values. They requested clarification regarding the apparent decrease in infant exposure to aluminium (Table 8 of TOX/2012/36).

59. Members concluded that the information provided so far did not indicate a concern for the health of infants.

60. Members agreed that they would finalise the statement and its conclusions after discussing the COT subgroup report on the Lowermoor water pollution incident, and when new consumption data from DNSIYC became available.

These minutes are available at: http://cot.food.gov.uk/pdfs/cotfinalmins30oct2012.pdf

Secretariat
March 2013

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Second draft statement on the potential risks from high levels of aluminium in the infant diet

Background

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that bears on the Government's dietary recommendations for infants and young children. The review will identify new evidence that has emerged since the Government's current recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years, but will be considered in two stages, focussing first on infants aged 0 – 12 months, and then on advice for children aged 1 to 5 years. SACN is examining the nutritional basis of the advice, and has asked that evidence on possible adverse effects of diet should be considered by other advisory committees with relevant expertise. In particular, SACN asked COT to review the risks of toxicity from chemicals in the infant diet.

2. This statement provides an overview of the potential risks from aluminium in the infant diet. The total aluminium content of food includes naturally present aluminium, aluminium as a contaminant, food additives and, aluminium from food contact materials (FCM) (food containers such as cans, cookware, utensils and food wrappings). Additional sources can come from drinking water used in food preparation, including reconstitution of infant formula, as well as water that is directly consumed.

3. Evaluations of aluminium in food have been conducted recently by the European Food Safety Authority (EFSA) (EFSA, 2008) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (FAO/WHO, 2007; FAO/WHO, 2012). This statement draws on information from those reviews, particularly the most recent, which was by JECFA (FAO/WHO, 2012). A literature search was conducted to identify additional papers not covered by these publications. The statement considers the toxicological effects of aluminium, with particular focus on infants, and their potential exposure from the diet including from water. Concentrations of lead in water were provided by the Drinking Water Inspectorate (DWI) for England and Wales, the Scottish government and Northern Ireland Water. Levels of lead in infant formulae and complementary foods were from the Food Standards Agency (FSA).

Hazard identification and characterisation

Absorption

4. Aluminium entering the acidic environment of the stomach is likely to be solubilised to the free ion (Al^{3+}). As the Al^{3+} moves into the duodenum it is converted to aluminium hydroxide as the pH is neutralised. Most of this will be expected to precipitate in the intestine, with subsequent faecal excretion, therefore only a small

amount of aluminium will be available for absorption. (EFSA, 2008; Berthon, 2002; DeVoto and Yokel, 1994; Froment *et al*., 1989).

5. Absorption of aluminium following the ingestion of various aluminium compounds by rats is generally in the region of 0.01− 0.3%, with the more water-soluble aluminium compounds being generally more bioavailable. However, as a result of limitations in the sensitivity of the analytical methods, inter-animal variation and methodological differences between studies, including the administered doses, it was not possible to draw firm conclusions on quantitative differences in absorption between different compounds. There were indications of increased absorption in female rats compared to males, and that the proportion of the dose absorbed was lower following repeated administration than following single administration (FAO/WHO, 2012).

6. The absorption of aluminium in human volunteers was similar to that observed in rats; calculated uptakes were 0.5%, 0.01% and 0.1% for aluminium citrate, aluminium hydroxide and citrate in combination with hydroxide (Priest *et al.*, 1996), with some indication of increased absorption in the elderly (FAO/WHO, 2012).

7. Despite the low oral bioavailability of aluminium, the use of ^{26}Al and accelerator mass spectrometry has enabled studies of aluminium toxicokinetics at low doses. Determination of aluminium absorption may be underestimated in a single blood/serum sample due to aluminium not yet absorbed, distributed out of the vascular compartment, or excreted. Urinary excretion compared to intake is commonly used to measure aluminium absorption, but offers no information about retention in tissues such as bone. Low aluminium bioavailability affects the accuracy of balance studies which estimate absorption based on the difference between intake and urinary plus faecal excretion. Comparison of the plasma aluminium concentration x time curve or area under curve after oral vs i.v. dosing is the generally accepted method for determining the oral bioavailability of most substances but requires repeated blood sampling. (EFSA, 2008; Krewski *et al.*, 2007).

Modulation of absorption

8. The bioavailability of aluminium is dependent on the form in which it is ingested and the presence of dietary constituents with which the metal cation can complex. (EFSA, 2008).

9. Ligands in food can have a marked effect on the absorption of aluminium. Some are able to enhance the uptake by forming absorbable complexes (e.g., with carboxylic acids such as citric and lactic acids, fluoride, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) (a metabolite of vitamin D_3 (cholecalciferol)), and parathyroid hormone). (Priest, 1993; Priest *et al.*, 1996; Harris *et al*., 2003; EFSA, 2008; Allain *et al.*, 1996; Varner *et al.*, 1998; Moon, 1994; Moon, Davidson and Bandy, 1992; Mayor *et al.*, 1980).

10. Conversely, other compounds are able to decrease the absorption of aluminium by forming insoluble complexes (e.g., with phosphate, dissolved silicate, phytate or polyphenols (Krewski *et al*.,2007; EFSA, 2008; Priest *et al.*, 1996; Birchall

et al., 1996; Taylor *et al.*, 1995; Edwardson *et al.*, 1993; Jugdaosingh *et al.*, 2000). Iron status of the body impacts on the absorption of aluminium and its accumulation in the brain. In iron deficiency, absorption of iron from food is increased, and if aluminium is available its uptake and storage may also increase. Iron sufficiency reduces iron absorption and may reduce aluminium absorption. (Winklhofer *et al.*, 2000; Cannata *et al.*, 1991). Calcium status in the gut impacts on aluminium absorption and accumulation. Dietary calcium deficiency increased the absorption of aluminium from aluminium chloride, and the extent of tissue aluminium accumulation, and aluminium-induced neuropathology in rats (Provan and Yokel, 1990; Taneda, 1984). Increased calcium concentrations in the gastrointestinal tract decreased aluminium uptake from the chloride, suggesting a common uptake mechanism for aluminium, introduced as the chloride, and calcium (Cunat *et al.*, 2000; Feinroth *et al.*, 1982).

Distribution, metabolism and excretion

11. Recent studies in rats have confirmed that absorbed aluminium is able to cross the placental barrier into the fetus and then into the fetal brain and that it is also transferred to the young via lactation. These studies have also confirmed that administration of a number of aluminium salts to rats can result in increased concentrations of aluminium in bone, kidney and spinal cord. (FAO/WHO, 2012). There is evidence to support the hypothesis that aluminium accumulates in humans (Slanina *et al.*, 1986; Priest, 2004). It has been observed that tissue aluminium levels are positively correlated with age, in humans. In humans aluminium is estimated to have a distribution of approximately 60, 25, 10, 3, 1 and <1 % in skeleton, lung, muscle, liver, brain and blood, respectively. (Peto, 2010).

12. Following ingestion in humans, a small amount of absorbed aluminium in the blood is excreted in bile, but the major route of aluminium elimination is by the kidneys. (ATSDR, 2008). Low molecular mass anions in plasma that could potentially bind aluminium are citrate, phosphate, hydroxide and silicate. Aluminium bound to these compounds will be filtered at the glomerulus, whilst aluminium bound to transferrin will not. (Shirley and Lote, 2005). Urinary excretion of aluminium in rats, mice, rabbits and dogs has been reported to have initial half-lives of 2-5 hours after intravenous administration and less than 1 day in humans. Multiple half-lives have been reported in different studies and species for a subsequent, slower phase of elimination, varying with the tissue, and with the calculated half-life generally increasing with the duration of sampling (FAO/WHO, 2012). About 93 percent of Al^{3+} in plasma is bound to transferrin, the remainder forms low molecular mass ligands. Of the remaining 7 percent, approximately 88%, 8% and 2% are present as citrate, hydroxide and phosphate, respectively (Harris *et al*., 2003).

13. Mitkus *et al.* (2011) summarised that glomerular filtration, the primary pathway of excretion of aluminium from the body as well as the main process of renal elimination of xenobiotics in newborns, is not fully developed at birth, it is expected that aluminium is not cleared from the blood of infants as quickly as that of adults. As a result the elimination rate would be expected to be lower in children than in adults, but would increase in time as renal function developed throughout childhood. (Mitkus *et al.*, 2011).

Toxicity of aluminium in experimental animals

Acute and subchronic toxicity, genotoxicity and carcinogenicity

14. The potential toxicity of aluminium through exposure in the diet has been recently evaluated by both the EFSA (2008) and the JECFA (FAO/WHO, 2007 and 2012). Acute oral toxicity of those aluminium compounds for which data were available (bromide, nitrate, chloride and sulphate) is moderate to low. (EFSA, 2008).

15. Aluminium compounds (including aluminium nitrate, aluminium sulphate or potassium aluminium sulphate) administered to rats produced a variety of effects including mild histopathological changes in the spleen, kidney and liver, decreased body weight gain. Severity of effects increased with dose and effects on nerve cells, testes, bone and stomach were reported at higher doses. Sodium aluminium phosphate (SALP) acidic administered to beagle dogs., produced no toxicologically relevant effects. SALP basic, administration resulted in decreased food consumption, decreased body and testis weight and histopathological changes in liver and kidney of male dogs. (EFSA, 2008).

16. Aluminium compounds (including aluminium chloride, sulphate, nitrate, lactate, fluoride and pigments composed of potassium aluminium silicate) tested were non-mutagenic in bacterial and mammalian cell systems and in an *in vivo* rat bone marrow micronucleus test. There was some DNA damage and effects on chromosome integrity and segregation *in vitro*. Several indirect mechanisms of genotoxicity have been proposed, which are considered unlikely to be of relevance for humans exposed to aluminium via the diet. The available studies showed no signs of carcinogenic potential. (EFSA, 2008; FAO/WHO, 2012).

Reproductive and developmental toxicity

17. Studies on the reproductive toxicity in male mice (intraperitoneal or subcutaneous administration of aluminium nitrate or chloride) and rabbits (administration of aluminium chloride by gavage) have demonstrated the ability of aluminium to produce testicular toxicity, decreased sperm quality and reduced fertility. No reproductive toxicity was seen in females administered aluminium nitrate by gavage or dissolved in drinking water. Multi generation reproductive studies conducted with aluminium sulphate and aluminium ammonium sulphate administered to rats in the drinking-water did not provide evidence of reproductive toxicity. (EFSA, 2008; FAO/WHO, 2012).

18. In general, high doses of aluminium compounds given by gavage were able to induce some signs of embryotoxicity in mice and rats, in particular, reduced fetal body weight or pup weight at birth and delayed ossification. (EFSA, 2008). The available developmental toxicity studies involving dosing of aluminium chloride by oral gavage to pregnant rats provided evidence of fetotoxicity, but it was unclear if the findings were secondary to maternal toxicity. There were no effects on pregnancy outcome in a developmental study of “basic aluminium chloride” (17% aluminium oxide, 9% aluminium and 19.9% chlorine in aqueous solution). In a developmental and chronic neurotoxicity study of aluminium citrate administered to rats in drinking-water, the major treatment-related effects were renal damage (hydronephrosis, urethral dilation, obstruction and/or presence of calculi) and

reduced grip strength, but not cognitive impairment, in the pups (Poirier *et al.*, 2011). As the effect on grip strength was more pronounced in younger animals, exposure *in utero* and/or during lactation is likely to be more important than exposure during the later stages. (FAO/WHO, 2012).

Observations in humans

19. Neurotoxicity (dialysis encephalopathy) has been reported in patients undergoing dialysis where insufficiently purified water was used, and the patients were therefore parenterally exposed to high concentrations of aluminium (EFSA, 2008).

20. In addition to bone changes observed in patients on dialysis, osteomalacia has been observed in several patients on long-term parenteral nutrition who had a variety of gastrointestinal illnesses with malabsorption. There have also been case reports of adults, infants and a child with normal renal function who experienced skeletal changes from frequent use of antacids for the treatment of indigestion. (FAO/WHO, 2007). Neonates who were exposed to aluminium from solutions for parenteral nutrition had reduced lumbar spine and hip bone mass in adolescence, potential risk factors for later osteoporosis and hip fracture. (Fewtrell *et al.*, 2009). However, in elderly people, the aluminium content in bones was not associated with increased risk of hip fractures (Hellström *et al.*, 2005).

21. It has been suggested that aluminium is implicated in the aetiology of Alzheimer's disease and associated with other neurodegenerative diseases in humans. Most of the available epidemiological studies have addressed the potential neurotoxicity of aluminium in drinking water or antacids, by means of different designs: experimental, prospective cohort, or case-control studies or ecological studies. Some of the drinking-water studies showed an association of aluminium with dementia or Alzheimer's disease, whereas others reported an absence of neuropsychological effects measured in several ways. None of these studies took into account the ingestion of aluminium in food. The coincidental observation of neuropathological features of Alzheimer's disease and aluminium in brain reported in some cases does not demonstrate a causal role of aluminium in Alzheimer's disease. Occupational exposure to aluminium through welding, smelting and electrolysis in aluminium smelters and automobile and train and truck construction does not seem to have an impact on cognitive performance, motor performance or adverse reproductive outcomes in exposed workers (EFSA, 2008; FAO/WHO, 2012; Sakr *et al*, 2010; Meyer-Baron *et al*, 2007; Kiesswetter *et al*, 2007; Kieswetter *et al*, 2009).

22. Both EFSA and JECFA concluded that the information available remains inconsistent and does not support a causal association between aluminium exposure and Alzheimer's disease or other neurological conditions. (EFSA, 2008; FAO/WHO, 2012).

23. Aluminium may have immunotoxicological effects predominantly in the form of allergic contact dermatitis (Siemund *et al*., 2012). Injection of aluminium–containing vaccines has been shown to cause persistent itching nodules (Netterlid *et al*., 2004). Conversely, some aluminium compounds have been shown to reduce

allergic responses (Wilcock *et al.*, 2004; Smith *et al.*, 2006). No reports of allergenicity from dietary exposure to aluminium were identified.

Lowermoor water pollution incident

24. A subgroup of the COT has advised on the possible long term health effects arising from a 1988 water pollution incident at Lowermoor water treatment works near Camelford, North Cornwall, in which 20 tonnes of aluminium sulphate was accidentally put into the water supply at the works. Water supplies to an estimated 20,000 people were polluted with aluminium, sulphate and other metals dissolved from the pipework and plumbing materials. (COT, 2013)

25. The COT subgroup report concluded for aluminium that

- "*Immediately after the incident, there was no, or at most, very low Margins of Exposure but they rose to pre-incident levels within one month. Taking into account the fact that the Margins of Exposure were below pre-incident levels for only a short period, on the basis of the current evidence, it is unlikely that the short period of increased exposure to aluminium would have caused, or would be expected to cause, delayed or persistent harm to health. However, infants are a potentially vulnerable group and, therefore, the possibility of delayed or persistent harm to health should be explored further in those who were infants at the time of the incident (i.e. below one year of age). Consumption of the contaminated water by pregnant women may have led to exposure of the developing fetus. Although the period of exposure to increased levels of aluminium was short, in view of the neurodevelopmental effects seen with aluminium in animal studies, we consider that the possibility of delayed or persistent harm to health should be explored also in those who were in utero at the time of the incident.*" (COT, 2013)

Provisional tolerable weekly intake

26. In its most recent evaluation, JECFA concluded that it was not possible to draw conclusions on quantitative differences in the overall toxicokinetics of different aluminium-containing food additives or between experimental animals and humans. The recent evidence supported previous observations of neurodevelopmental effects in experimental animals, but there were some limitations to all of the studies (FAO/WHO, 2012).

27. JECFA concluded that the study of Poirier *et al*. (2011) provided the most appropriate basis for establishing a Provisional Tolerable Weekly Intake (PTWI)[1]. This was a twelve-month neuro-developmental toxicity study of aluminium citrate administered via the drinking water to Sprague-Dawley rats, conducted according to Good Laboratory Practice (GLP). Aluminium citrate was selected for the study as it is the most soluble and bioavailable aluminium salt. Pregnant rats were exposed to aluminium citrate from gestational day 6 through lactation, and then the offspring were exposed post-weaning until postnatal day 364, with an extensive functional observational battery of tests performed at various times. Evidence of aluminium toxicity was demonstrated in the high (300 mg/kg bw/day of aluminium) and to a

[1] For contaminants that may accumulate within the body over a period of time, JECFA has commonly used the PTWI as the most appropriate health-based guidance value.

lesser extent, the mid-dose groups (100 mg/kg bw/day of aluminium). In the high dose group, the main effect was renal damage, resulting in high mortality in the male offspring. No major neurological pathology or neurobehavioural effects were observed, other than in the neuromuscular subdomain (reduced grip strength and increased foot splay). Thus in this study the lowest observed adverse effect level (LOAEL) was 100 mg/kg bw/day and the no observed adverse effect level (NOAEL) was 30 mg/kg bw/day. Bioavailability of aluminium chloride, sulphate and nitrate and aluminium hydroxide were much lower than the aluminium citrate. (Poirier *et al.*, 2011).

28. The JECFA used the NOAEL of 30 mg Al/kg bw/day from the study by Poirier *et al.* for establishing a PTWI for aluminium compounds. In previous evaluations of both JECFA and EFSA (FAO/WHO, 2007; EFSA, 2008), it had been considered necessary to include an uncertainty factor for major gaps in the database in addition to the default factor of 100 for inter- and intra-species differences. However, because long-term studies on the relevant toxicological end-points had become available since the previous evaluations, JECFA concluded that this was no longer needed. The JECFA established a PTWI of 2 mg/kg bw by dividing the NOAEL of 30 mg/kg bw/day by the uncertainty factor of 100 for inter-species and intra-species differences, and converting to a weekly basis in view of the cumulative properties of aluminium. The PTWI applies to all aluminium compounds in food, including food additives (FAO/WHO, 2012). The COT concluded that the derivation of this PTWI is sound and that it can be used in assessing dietary exposure to aluminium.

29. Very young infants are a particularly sensitive subgroup because their metabolic capacities are not yet fully developed. In general, health-based guidance values are not considered applicable to infants under the age of 12 weeks who might be at risk at lower exposure levels. Therefore risk characterisation of exposure of such infants to chemicals (e.g. in infant formula or occurring as contaminants) has to be considered on a case-by-case basis. (WHO, 2009).

Sources of aluminium exposure

30. In addition to aluminium present in food, humans can be exposed to aluminium through inhalation, dermally and occupationally. The diet is the predominant route for non-occupationally exposed individuals. Air concentrations vary between rural and urban settings, with higher levels in industrial areas. Exposure in this way could contribute up to 0.04 mg/day (EFSA, 2008; WHO, 1997). Dermal exposure occurs mainly through the use of antiperspirants (Yokel and McNamara, 2001). Aluminium chlorohydrate (ACH) is the active ingredient in some antiperspirants and is thought to act by precipitating inside the eccrine sweat glands to produce insoluble aluminium hydroxide, which then plugs the gland and blocks the secretion of sweat. The average rate of absorption through the skin was calculated as 0.25 µg/day, equivalent to 2.5 % of a diet containing 10 mg aluminium per day (Flarend *et al.*, 2001). This exposure route is not relevant for infants.

Aluminium-containing food additives

31. Certain aluminium compounds are permitted for use as food additives in the European Union (EU). Aluminium containing food additives are not permitted in the following: Infant formulae for infants in good health: follow-on formulae for infants in good health; processed cereal-based foods and baby foods for infants and young children in good health; dietary foods for infants and young children for special medical purposes as defined in Directive 1999/21/EC. Home-prepared infant foods could contain aluminium-containing food additives. Data from the 2006 UK Total Diet Study showed groups of foods most likely to contain aluminium were bread, miscellaneous cereals, vegetables (not potatoes or green vegetables), sugars and preserves, meat products and potatoes. The aluminium present in bread and miscellaneous cereal products is likely to come from aluminium-containing food additives. (Rose *et al.*, 2010) These products could potentially be found in the diets of some infants.

Food contact materials

32. Aluminium is used as a packaging material as it is lightweight, and highly resistant to most forms of corrosion; its natural coating of aluminium oxide provides a highly effective barrier to the effects of air, temperature, moisture, chemical attack, light and microorganisms (Marsh and Bugusu, 2007). Migration of aluminium from foil into food depends on several factors such as the composition of the raw food, the duration and temperature of heating, the composition and the pH-value of food, and the presence of other substances (e.g. organic acids, salt, sugar and other ions). (Ranau *et al.*, 2001; Turhan, 2006). Cooking of acidic foods in aluminium saucepans or foil can result in leaching of the metal (Ranau *et al.*, 2001). Aluminium and aluminium compounds are also permitted for use as additives in plastic food contact materials under Commission Regulation (EU) 10/2011.

Drinking water

33. The aluminium concentration in natural waters varies significantly depending on numerous physicochemical, mineralogical and geochemical factors. Water treatment in purifying plants includes a coagulation process using aluminium sulphate to remove organic matter. However, a residual amount is present in the drinking water. EC Directive 98/83 uses an indicator parameter value for aluminium of 200 µg/L. (Directive 98/83/EC).

34. Data on aluminium concentrations in drinking water were obtained from the Scottish government, Northern Ireland Water and the Drinking Water Inspectorate (DWI) for data from England and Wales. Water testing in England and Wales is performed by 29 water companies. Aluminium concentrations in water in the UK ranged from less than 1 (England and Wales 1st percentile) to 205 (Northern Ireland 99th percentile) µg/L, with median values in the range of 6.6 to 28 µg/L for England and Wales and Northern Ireland, respectively (Table 1). The concentrations of aluminium in the water, when tested, may be higher than in water consumed as samples are taken prior to water being flushed through the tap.

Table 1. Aluminium concentrations (µg/L) in tap water

	England and Wales	Northern Ireland	Scotland
1st percentile	0* – 1**	4	4
25th percentile	0* – 6**	19	16
Mean	9.0* – 11**	38	31
Median	6.6* – 7.3**	28	25
75th percentile	13	45	38
99th percentile	55	205	134
Number of samples	42400	1730	5020

*Assuming results lower than the limit of detection are equal to zero.
**Assuming results lower than the limit of detection are equal to the limit of detection.

Breast milk

35. Concentrations of aluminium have been measured in human milk in a number of studies (Table 2). The data from the UK are from a small study published in 1991, but the relevance of these data is supported by more recent studies elsewhere. The women participating in these studies were from the normal population within the specified country.

Table 2. Concentrations of aluminium measured in human breast milk

Country	Number of samples	Mean (± SD) aluminium levels (ug/L)	Median aluminium levels (ug/L)	Range of aluminium levels (ug/L)
Australia[1]		30		
UK[2]	8	27	15	3-79
Spain[3]	45	23.9 (± 9.6)	25.0	7-42
Austria[4]	27		67	<10 - 380
Morocco[6]	396	17.3 (± 13.9)		1.3 – 62.2

[1]Weintraub *et al*., (1986), [2]Baxter *et al*., (1991), [3]Fernandez-Lorenzo *et al*., (1999), [4]Krachler *et al.*, (2000), [6]Zaida *et al.,* (2007)

Infant formulae

36. Aluminium concentrations in infant formulae have been measured in a number of studies (Baxter *et al*., 1991; Fernandez-Lorenzo *et al.*, 1999; Krachler *et al.*, 2000; Ikem *et al*., 2002; Navarro-Blasco and Alvarez-Galindo, 2003; FSA, 2006; Zaida *et al*., 2007; Boa Morte *et al*., 2008; Kazi *et al*., 2009; Burrell and Exley, 2010; Dabeka *et al*., 2011) and in a variety of formulae including cow's milk-based, soy-based, special dietary and powdered or liquid formulations.

37. A survey has been conducted of metals in foods and formulae for infants sampled in the UK in 2004-2005 (FSA, 2006). Table 3 shows the average, standard deviation and range of aluminium concentrations measured in different types of infant formulae (for infants aged 0-12 months old) in the survey. Soy-based infant formulae showed higher average aluminium levels than the animal milk varieties and

powdered formulae (µg/kg as sold) showed higher levels than ready-to-use infant formulae.

Table 3. Aluminium concentrations (µg/kg as sold) in infant formulae

Formula type	Number of samples	Average aluminium (µg/kg as sold)	SD**	Range* (µg/kg as sold)
Powdered				
All formulae	32	899**	623	<100 – 2423
Cows' milk-based	27	817**	572	<100 - 2423
Goats milk-based	3	878*	596	235 - 1412
Soy-based	2	2027*	310	1808 - 2246
Ready-to-use				
cows' milk-based	14	84**	43	<17 - 162

*Data published in FSA (2006)
**Calculated from data published in FSA (2006)

Complementary foods[2]

38. Table 4 shows the average and range of aluminium concentrations measured in 153 samples of commercial infant foods measured in the FSA survey of metals in foods and formulae for infants (FSA, 2006).

Table 4. Average and range (µg/kg as sold) of aluminium concentrations measured in commercial infant foods

Food type	Number of samples	Average aluminium (µg/kg as sold)*	Standard deviation (SD)**	Range (µg/kg as sold)*
Baby rice	8	780	804	203 - 2284
Biscuits	8	4571	6206	1021 - 19715
Breakfast foods	27	1024	980	71 - 4288
Cereal bars/rice cakes	9	7205	8236	834 - 25388
Desserts	12	1690	3527	127 - 12744
Fish	7	470	488	129 - 1475
Fruit puree	7	1529	1336	402 - 4406
Meat	45	1074	1094	113 - 4097
Pasta/dairy	16	914	1032	95 - 3928
Rusks	7	2612	1678	763 - 4455
Vegetables	7	1419	1573	111 - 4621

*Data published in FSA (2006)
**Calculated from data published in FSA (2006)

[2] Solid foods introduced into the diet of infants to complement the milk feed, which remains the predominant part of the diet for the majority of the first year of life.

Dietary exposure to aluminium

39. Reasonable estimates of average and high-level daily consumption of breast milk or infant formula before weaning are 800 mL and 1200 mL (e.g., EFSA, 2012). The mean bodyweights used for calculation of exposures are those previously used by the COT[3] as these included weights for infants younger than 6 months, required for infant formula, complementary food and breast milk exposure estimates. These bodyweights were 5.9 kg, 7.7 kg, 8.9 kg and 9.8 kg for infants aged 0-3, 4-6, 7-9 and 10-12 months old respectively.

Breast milk

40. There were only a small number of studies that had measured the levels of aluminium in breast milk. The data from the study by Baxter *et al.* (1991) were from UK samples. As the sample number was small both the reported mean (27 µg/L) and the upper end of the range (79 µg/L) of reported aluminium levels, were used to calculate possible aluminium exposure levels for average (800 mL) and high-level (1200 mL) consumption by exclusively breastfed infants (Table 5). The estimated intakes are in the range of 20-75 µg/kg bw/week for average consumption and 29-112 µg/kg bw/week for high level consumption.

Table 5. Aluminium exposure (µg/kg bw/week) from exclusive breastfeeding estimated for average and high level consumption

Aluminium concentration in breast milk *	Age in months (consumption volume)			
	0-3 (800 mL)	0-3 (1200 mL)	4-6 (800 mL)	4-6 (1200 mL)
Mean - 27 µg/L	26	38	20	29
Maximum - 79 µg/L	75	112	57	86

* From Baxter *et al.* (1991)

Infant formulae and complementary foods

41. In the FSA 2006 survey, levels of aluminium were measured in powdered and ready-to-eat infant formulae as sold. From the data for formulae consumed by infants aged 0-6 months old, infant aluminium exposure was calculated based on average and high level consumption for infants exclusively fed on formula (Table 6). These values do not take into account aluminium from water used in reconstitution. The estimated intakes are in the order “ready-to-consume” formula < cows’ milk powdered formula < goats’ milk powdered formula < soy-based powdered formula.

[3] http://cot.food.gov.uk/pdfs/statement.pdf

Table 6. Aluminium exposure (µg/kg bw/week) from exclusive feeding of infant formulae estimated for average and high level consumption

Mean aluminium concentration in infant formula*	Age in months (consumption volume)			
	0-3 (800 mL)	0-3 (1200 mL)	4-6 (800 mL)	4-6 (1200 mL)
Powdered cows' – 106 µg/L	101	151	77	116
Powdered goats' – 148 µg/L	140	211	108	161
Powdered soy-based – 293 µg/L	278	417	213	320
Ready-to-consume (cows' –based) – 58 µg/L	55	83	42	63

*From FSA (2006). Excludes contribution of aluminium from water in reconstituted powdered formulae.

For each powdered infant formula the manufacturers' instructions provided the volume of feed to be prepared a day and the mass of powder required. From this, the mass of powder per litre was calculated in order to calculate the concentration of aluminium in reconstituted formula. These values were averaged for the different samples of cows' milk-, goats' milk- and soya-based formulae to obtain the mean aluminium concentration in reconstituted formula. Infant exposure is based on consumption of 0.8 L or 1.2 L per day, expressed on a bodyweight (5.9 kg for infants aged 0-3 months and 7.7 kg for infants aged 4-6 months) and per week basis. Aluminium measured in the ready-to-use formulae was averaged and this provided the mean aluminium concentration in the infant formulae.

42. The exposure from drinking water used to reconstitute infant formula will vary with the level of aluminium in drinking water. Water accounts for approximately 85% of the total volume of formula preparation, i.e. 680 and 1020 ml per day, respectively for average and high level consumption of formula. Based on median and 99th percentile data for aluminium concentrations in drinking water from England and Wales (para 34) water used to reconstitute infant formula could potentially contribute up to 67 µg/kg bw/week of total aluminium exposure (Table 7). However aluminium levels may be higher in some instances. A higher concentration of aluminium (205 µg/L (Northern Ireland, 99th percentile) could lead to exposures of 248 µg/kg bw/week in exclusively formula-fed infants aged 0-3 months consuming high levels.

Table 7. Possible additional aluminium exposure of exclusively formula fed infants through drinking water (England and Wales) used to reconstitute infant formula (µg/kg bw/week).

Aluminium concentration in drinking water (µg/L)	Age of infant (months)			
	0-3 (800 mL)	0-3 (1200 mL)	4-6 (800 mL)	4-6 (1200 mL)
Median – 7.3	5.9	8.8	4.5	6.8
99th percentile – 55	44	67	34	51

The exposure is calculated assuming that water accounts for approximately 85% of the total volume of formula preparation for 0-3 and 4-6 month age ranges. The exposure volumes used in the calculations were 680 and 1020 mL instead of 800 and 1200 mL, respectively.

43. In 2003, the COT[4] considered the results of an FSA survey of elements, including aluminium, in commercial infant food and formulae (FSA, 2003). In the absence of recent consumption data for infants aged 6-12 months old, different approaches were used for estimation of the dietary exposure. Consumption data from the 1986 survey of British Infants for age 6-12 months (Mills and Tyler, 1991) were considered probably an underestimation of consumption but allowed direct comparison of the data with results of a previous food survey conducted by the Ministry of Agriculture, Fisheries and Food (MAFF) (MAFF, 1999). The high level (97.5 percentile) estimated exposure at age 7-12 months was 532 µg/kg bw/week compared to 686 µg/kg bw/week from the 1999 survey. In addition, manufacturers' feeding instructions were used, which indicated mean dietary exposure in the region of 1225 - 1554 µg/kg bw/week. (Table 8). The COT considered that these two approaches provided a range within which the actual exposures were likely to be found.

44. Manufacturers' feeding instructions and recommendations were also used to estimate exposure based on the results of a subsequent FSA survey of metals in commercial infant foods and formulae (FSA, 2006). The estimated mean aluminium exposures ranged from 104 to 776 µg/kg bw/week for infants. (Table 8). Overall, although the data relate to different surveys, with different foods sampled, the estimates in Table 8 indicate reductions in dietary exposure of infants to aluminium from 1997-2005. In a COT statement[5] on the 2006 UK Total Diet Study (TDS) of metals and other elements, the results show an apparent increase in dietary exposure to aluminium for the general population.

Table 8. Estimated dietary exposure of infants to aluminium from infant formulae and foods.

Year survey published	Survey dates	Diet	Mean exposures calculated using manufacturers' consumption guidelines (µg/kg bw/week)				Mean (and 97.5th percentile) exposures calculated using 1986 survey (µg/kg bw/week)
			Age (months)				Age (months)
			0-3	4–6	7-9	10-12	7 – 12
1999[a]	1997 - 1999	Normal					273 (686)
2003[a]	2001 - 2002	Normal	98	994	1225	1239	154 (532)
		Soy	574	1694	1554	1526	[c]

[4] http://cot.food.gov.uk/pdfs/statement.pdf

[5] http://cot.food.gov.uk/pdfs/cotstatementtds200808.pdf

2006[b]	2004 - 2005	Normal	104	200	424	776	[c]

Manufacturers' feeding guidelines, as detailed on each product label, were used as the source of consumption data for formulae. For weaning foods 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. The mean concentration of aluminium was calculated from its concentration in every eligible food for a particular age group (using a dilution factor for samples of dried food).
These results only represented commercially available foods and do not include the contribution of drinking water in reconstitution, or offered separately.
[a] Data taken from the COT statement on a survey of metals in infant food (2003)
[b] Data taken from FSA (2006) [c] Exposures were not calculated using the 1986 consumption data (Mills and Tyler, 1991) for the 2006 FSA survey.

45. The exposure estimates in table 8 do not take into account water used in reconstitution of infant formula, or on drinking water that might be consumed separately, due to the lack of data on the amounts likely to be used. However the data in paragraph 42 and table 7 indicate that exposure from water is likely to be less than from other dietary sources.

46. The COT has previously noted that the estimates of dietary exposure by infants from the United Kingdom (UK) relied on survey data that may have been outdated or on assumptions about feeding patterns that may represent an overestimate of food consumption. More relevant data will be provided by the Diet and Nutrition Survey of Infants and Young Children (DNSIYC), which will be available for use later in 2013. Furthermore, there is a lack of information on exposure from home prepared foods.

Risk characterisation

47. Based on median and maxiumum reported concentrations of aluminium in breast milk, exposure of exclusively breast fed infants are up to 2% and 6% of the PTWI of 2 mg/kg bw (2000 µg/kg bw), respectively, with the highest exposure in high level consumers aged 0-3 months. Aluminium exposure from infant formulae for exclusively formula-fed infants are up to 4% of the PTWI for ready-to-eat formulae. From powdered formulae the exposure to aluminium could be up to 8, 11 and 21% of the PTWI, respectively for cows' milk-, goats' milk- and soya based formulae. The water used to reconstitute infant formula could potentially add up to approximately 248 µg/kg bw/week aluminium (12% of the PTWI), resulting in infant formula and water comprising up to 34% of the PTWI.

48. The highest average exposure to aluminium from infant formulae and commercial food (based on 2004-5 survey data, Table 8) relative to the PTWI was in high level consumers aged 10 to 12-months (39% of the PTWI). This does not take into account water used in reconstitution of foods and formulae, or offered separately. The food groups containing the highest levels of aluminium (µg/kg as sold) were cereal bars/rice cakes, biscuits and rusks. The available data indicate a reduction in aluminium exposure from infant formulae and commercial food at all infant age ranges. No information was available that would allow assessment of the contribution of home-prepared food, some of which could contain aluminium-containing food additives, to infants' dietary exposure to aluminium.

49. In principle the PTWI does not apply to infants aged 0-12 weeks, since their metabolic capacities are not yet fully developed. However the estimated exposures of infant of this age are less than 10% of the PTWI, and do not indicate a specific concern. Exposure of infants exclusively fed on soy-based formula is higher than for other very young infants. JECFA has noted a need for studies to identify the forms of aluminium present in soy-based formula and their bioavailability. (FAO/WHO, 2012). However, current UK government advice is that infants should not be fed soy formula unless it has been prescribed or recommended by a general practitioner (GP). Soy infant formula contains phytoestrogens which could affect infants' reproductive development. Soy-based infant formula also contains glucose which is more harmful to the teeth of infants than the lactose present in infant formula made from cows' milk. (NHS Choices, 2013). The estimates of aluminium exposure of infants aged 4-12 months are below the PTWI and do not indicate a toxicological concern

Conclusions

50. The presence of aluminium in the infant diet results from naturally occurring aluminium, possible contamination from the environment, and possible leaching from food containers such as cans, cookware, utensils and food wrappings. Additional sources can come from drinking water used in food preparation, including reconstitution of infant formula, and water that is directly consumed. The diet is the predominant route.

51. The absorption of aluminium from food is low (generally 0.5% or less). The presence of citrate, a common constituent of some foods, increases absorption. There is no specific information relating to absorption of aluminium in infants.

52. Urine is the primary route of aluminium excretion. Since glomerular filtration is not fully developed at birth, the elimination rate would be expected to be lower in infants than in adults, but would increase in time as renal function developed throughout childhood.

53. The toxicological effects of aluminium observed in experimental animals are neurotoxicity and nephrotoxicity. Based on a neuro-developmental toxicity study of aluminium citrate administered via the drinking water to rats the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a Provisional Tolerable Weekly Intake (PTWI) of 2 mg/kg bw (expressed as aluminium) for all aluminium compounds in food, including food additives. The COT concluded that the derivation of this PTWI is sound and that it can be used in assessing dietary exposure to aluminium.

54. From the limited available data on levels of aluminium in breastmilk of UK mothers, the aluminium exposure of exclusively breastfed infants is less than 10% of the PTWI.

55. Exposure of infants exclusively fed on infant formula is similar to, or higher than that of exclusively breastfed infants, with the highest from soya based formula, at up to about 21% of the PTWI before taking into account water used in

reconstitution of powder formula. Such water could contribute up to approximately 248 µg/kg bw/week aluminium, an additional 12% of the PTWI.

56. Estimates of exposure to aluminium from infant formula and commercial infant foods are up to 39% of the PTWI, without taking into account water used in reconstitution or consumed separately. However, exposure from water is likely to be less than from food. The highest estimated exposure is in the 10-12 month age group.

57. Overall, the COT concluded that the estimated exposures of infants to aluminium do not indicate toxicological concerns or a need for Government advice in this area.

Secretariat
March 2013

Abbreviations

$1,25(OH)_2D_3$	1,25-dihydroxyvitamin D_3
AUC	Area under the curve
Al	Aluminium
COT	Committee on Toxicity
DH	Department of Health
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
DWI	Drinking Water Inspectorate
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization
FCM	Food contact materials
FSA	Food Standards Agency
GLP	Good Laboratory Practice
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Lowest-observed-adverse-effect level
MAFF	Ministry of Agriculture, Fisheries and Food
NOAEL	No-observed-adverse-effect level
PTWI	Provisional tolerable weekly intake
SACN	Scientific Advisory Committee on Nutrition
SALP	Sodium aluminium phosphate
SD	Standard deviation
UK	United Kingdom
WHO	World Health Organization

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Search strategy

General aluminium exposure search

Databases interrogated –

- EFSA
- COT
- FSA
- JECFA

Scientific publications literature search

Specific search terms:

Aluminium AND Breast milk
Search Dates (From/To) - to present
Exclusion Criteria –

- Studies without aluminium levels in breast milk

Aluminium AND Infant formula
Search Dates (From/To) - to present
Exclusion Criteria –

- Studies without aluminium levels in infant formula

Aluminium AND Baby food
Search Dates (From/To) - to present
Exclusion Criteria –

- Studies without aluminium levels in baby food
- Childrens diet (above >2 years)

Aluminium AND Infant food
Search Dates (From/To) - to present
Exclusion Criteria –

- Studies without aluminium levels in infant food
- Childrens diet (above >2 years)

Aluminium AND Infant toxicity
Search Dates (From/To) - to present
Exclusion Criteria –

- Aluminium toxicity in adults

Aluminium AND Absorption
Search Dates (From/To) - to present
Exclusion Criteria –

- Studies in patients with renal disease

Aluminium AND Citrate
Search Dates (From/To) - to present
Exclusion Criteria –

- Studies not using aluminium and citrate

Aluminium AND Silicon

Search Dates (From/To) - to present
Exclusion Criteria –

- Studies using silicon alone
- Studies of silicon not relating to bioavailability or toxicology

Aluminium AND Fluoride
Search Dates (From/To) - to present
Exclusion Criteria –

- Studies using fluoride alone
- Studies of fluoride not relating to bioavailability or toxicology

The above mentioned search terms were also used in google. It identified latest government advice and opinions.

Secretariat
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