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

Third 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 draft statements in October 2012 (TOX/2012/36) and March 2013 (TOX/2013/12).

2. This third draft statement responds to the discussion of the second draft statement in March 2013. Levels of aluminium in soil are included. In addition the highest reported level of aluminium in water is taken into account in the exposure estimates and risk assessments. Renal excretion is still developing in infants and this is reflected in the conclusions.

3. Annex A contains a third 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
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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. Aluminum is the most commonly occurring metallic element, comprising eight percent of the earth's crust. The total aluminium content of food includes aluminium that is naturally present, aluminium as a contaminant, aluminium in food additives, and aluminium from food contact materials (FCM) (food containers such as cans, cookware, utensils and food wrappings). Additional exposure can come from drinking water used in food preparation, including reconstitution of infant formula, as well as water that is directly consumed. Aluminium has no known biological function.

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 evaluations, particularly the most recent, which was carried out by JECFA (FAO/WHO, 2012). In addition, a literature search was conducted to identify relevant papers not included in the previous reviews (Appendix A). The statement considers the toxic effects of aluminium, with particular focus on infants, and their potential dietary exposure, including from water. Data on concentrations of aluminium in water were provided by the Drinking Water Inspectorate (DWI) (for England and Wales), the Scottish Government and Northern Ireland Water. Data on levels of aluminium in infant formulae and complementary foods were obtained from the Food Standards Agency (FSA).

Absorption, distribution and excretion

Absorption

4. Aluminium entering the acidic environment of the stomach may be solubilised as the free ion, Al^{3+}, but as it passes into the duodenum, where the pH is higher, Al^{3+} is converted to insoluble aluminium hydroxide, most of which is excreted in the faeces. Thus, only a small proportion of ingested aluminium is available for absorption. (EFSA, 2008; Berthon, 2002; DeVoto and Yokel, 1994; Froment *et al*., 1989).

5. Following ingestion of various aluminium compounds by rats, measured absorption has generally been between 0.01% and 0.3%, the more water-soluble compounds (e.g. aluminium citrate, aluminium lactate) tending to be more bioavailable. However, because of limitations in the sensitivity of the analytical methods, inter-animal variation and methodological differences between studies, including the administered doses, it is not possible to draw firm conclusions on quantitative differences in absorption between different compounds. There are indications of increased absorption in female compared to male rats, and that the proportion of the dose absorbed is lower following repeated administration than following single administration (FAO/WHO, 2012).

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

Modulation of absorption

7. The bioavailability of aluminium depends not only on the form in which it is ingested, but also on the presence of dietary constituents with which the metal cation can complex. (EFSA, 2008).

8. Dietary constituents can have a marked effect on the absorption of aluminium. Some, such as citric acid, enhance its uptake by forming absorbable, soluble complexes. (Priest *et al.*, 1996; Harris *et al*., 2003).

9. Conversely, other compounds reduce the absorption of aluminium by forming insoluble complexes (e.g. phosphates and dissolved silicates) (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 also impacts on the absorption of aluminium. In iron deficiency, absorption of iron from food is increased, and if aluminium is available, its uptake may also increase (Winklhofer *et al.*, 2000; Cannata *et al.*, 1991). In addition, it has been observed that deficiency of calcium in the diet increased the absorption of aluminium from aluminium chloride in rats, leading to greater accumulation in tissues and associated neuropathology in rats (Provan and Yokel, 1990; Taneda, 1984). Conversely, higher calcium concentrations in the gastrointestinal tract have been found to decrease aluminium uptake from the

chloride, suggesting a shared mechanism for uptake of aluminium (when introduced as the chloride) and calcium (Cunat *et al.*, 2000; Feinroth *et al.*, 1982).

Distribution and excretion

10. Recent studies in rats have confirmed that absorbed aluminium can cross the placental barrier into the fetus and then enter the fetal brain, and that it is also transferred to the young via lactation. In addition, these studies have shown that administration of various aluminium salts to rats can lead to increased concentrations of aluminium in bone, kidney and spinal cord. (FAO/WHO, 2012). There is evidence that aluminium accumulates in humans, levels in tissues tending to increase with age (Slanina *et al.*, 1986; Priest, 2004). It has been estimated that approximately 60%, 25%, 10%, 3%, 1% and <1 % of retained aluminium is distributed to the skeleton, lung, muscle, liver, brain and blood, respectively. (Peto, 2010).

11. Following ingestion in humans, a small proportion of absorbed aluminium is excreted in bile, but the major route for elimination of aluminium is via the kidneys. (ATSDR, 2008). About 93 percent of Al^{3+} in plasma is bound to transferrin, and of the remaining 7 percent, approximately 88%, 8% and 2% is present as citrate, hydroxide and phosphate, respectively (Harris *et al*., 2003). Aluminium bound to these low molecular mass anions is filtered at the glomerulus, whereas that bound to transferrin is not. (Shirley and Lote, 2005). The elimination of aluminium from plasma appears to be polyexponential, and various half-lives have been reported, differing by species and by study (FAO/WHO, 2012).

12. Mitkus *et al.* (2011) have proposed that as glomerular filtration is not fully developed at birth, the rate at which aluminium is cleared from the blood of infants is likely to be slower than in adults, but that it would be expected to increase as renal function expanded during childhood. (Mitkus *et al.*, 2011).

Toxicity of aluminium in experimental animals

Acute and subchronic toxicity, genotoxicity and carcinogenicity

13. The potential toxicity of aluminium following dietary exposure was evaluated by both the EFSA (2008) and the JECFA (FAO/WHO, 2007 and 2012). The acute oral toxicity of those aluminium compounds for which data are available (bromide, nitrate, chloride and sulphate) is moderate to low. (EFSA, 2008).

14. When administered to rats, aluminium compounds (including aluminium nitrate, aluminium sulphate and potassium aluminium sulphate) have produced various effects, including decreased gain in body weight, and mild histopathological changes in the spleen, kidney and liver. Severity of effects increased with dose, and effects on nerve cells, testes, bone and stomach have been reported at higher doses. Sodium aluminium phosphate (SALP) acidic[1] produced no toxicologically

[1] SALP acidic is an approved food additive in the EU (E541).

relevant effects when administered to beagle dogs. However, administration of SALP basic resulted in decreased food consumption, decreased body and testis weight, hepatocyte vaccuolation and hypertrophy in the liver, and tubular and glomerular nephritis in the kidney. (FAO/WHO, 2007).

15. Aluminium compounds (including aluminium chloride, sulphate, nitrate, lactate, fluoride and pigments composed of potassium aluminium silicate) have been non-mutagenic when assessed in bacterial and mammalian cell systems and by an *in vivo* rat bone marrow micronucleus test. However, aluminium chloride produced some DNA damage and aluminium hydroxide, aluminium sulphate and aluminium chloride produced 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 give no indication of carcinogenic potential. (EFSA, 2008; FAO/WHO, 2012).

Reproductive and developmental toxicity

16. Studies of 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 cause testicular toxicity, decreased sperm quality and reduced fertility. No reproductive toxicity was seen in females given aluminium nitrate by gavage or dissolved in drinking water. Multi-generation reproductive studies in which aluminium sulphate and aluminium ammonium sulphate were administered to rats in drinking-water, showed no evidence of reproductive toxicity. (EFSA, 2008; FAO/WHO, 2012).

17. High doses of aluminium compounds given by gavage have induced signs of embryotoxicity in mice and rats – in particular, reduced fetal body weight or pup weight at birth and delayed ossification. (EFSA, 2008). Developmental toxicity studies in which aluminium chloride was administered by gavage to pregnant rats showed evidence of fetotoxicity, but it was unclear whether 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). (FAO/WHO, 2012).

18. Poirier *et al*. (2011) conducted a twelve-month neuro-developmental toxicity study of aluminium citrate administered via the drinking water to Sprague-Dawley rats, which was conducted according to Good Laboratory Practice (GLP). Aluminium citrate was selected for study since 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. An extensive functional observational battery of tests was performed at various times. Evidence of aluminium toxicity was demonstrated in the high (300 mg/kg bw/day of aluminium) and to a 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

SALP basic is a mixture of sodium aluminium phosphate with about 30% dibasic sodium phosphate. It is an approved food additive in some parts of the world, but not in the EU

neurobehavioural effects were observed, other than in the neuromuscular subdomain (reduced grip strength and increased foot splay). Thus, 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 was much lower than that of aluminium citrate. (Poirier *et al.*, 2011).

Observations in humans

19. Neurotoxicity (dialysis encephalopathy) has been reported in patients undergoing dialysis using water sources that contained high concentrations of aluminium (EFSA, 2008).

20. It has been suggested that aluminium is implicated in the development of Alzheimer's disease and perhaps other neurodegenerative diseases in humans. In particular, aluminium has been shown to accumulate in the neurofibrillary tangles and senile plaques that are characteristic neuropathological features of Alzheimer's disease, although this does not necessarily imply a causal role. Epidemiological studies have focused mainly on the potential neurotoxicity of aluminium in drinking water or antacids, using various study designs. Associations of aluminium in drinking-water with dementia or Alzheimer's disease have been inconsistent, and none of the published studies has taken into account concomitant ingestion of aluminium in food. Studies of the use of antacids did not demonstrate an association with neurological conditions. (FAO/WHO, 2012).

21. In studies to date, occupational exposure to aluminium through welding and smelting processes has not had a demonstrable impact on cognitive performance, motor performance or reproductive outcomes (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 was inconsistent and did not support a causal association between aluminium exposure and Alzheimer's disease or other chronic neurological diseases. (EFSA, 2008; FAO/WHO, 2012).

23. There have been case reports of adults, infants and a child with normal renal function who experienced skeletal changes following frequent use of aluminium-containing antacids for the treatment of indigestion. (FAO/WHO, 2007). Moreover, neonates who were exposed to aluminium in solutions used for parenteral nutrition (315 µg/kg bw/week) had lower lumbar spine and hip bone mass in adolescence than neonates receiving aluminium-depleted solution (35 µg/kg bw/week) (possibly indicating a higher risk of hip fracture later in life). (Bishop *et al.*, 1997; Fewtrell *et al.*, 2009). However, in elderly people, the aluminium content of bones was not associated with higher risk of hip fractures (Hellström *et al.*, 2005).

24. Aluminium may cause allergic contact dermatitis (Siemund *et al*., 2012). No reports were identified describing allergenicity from dietary exposure to aluminium.

Lowermoor water pollution incident

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

26. 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).*" (COT, 2013)

Provisional tolerable weekly intake

27. 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).

28. JECFA concluded that the developmental and chronic neurotoxicity study of Poirier *et al*. (2011) demonstrating that aluminium citrate administered to rats in drinking-water resulted in renal damage and reduced grip strength, but not cognitive impairment in the pups (see paragraph 18) provided the most appropriate basis on which to establish a Provisional Tolerable Weekly Intake (PTWI)[2]. As the effect on grip strength was more pronounced in younger animals, exposure *in utero* and/or during lactation was considered likely to be more important than exposure at later stages. The NOAEL in this study was 30 mg/kg bw/day. (FAO/WHO, 2012).

29. In previous evaluations by both JECFA and EFSA (FAO/WHO, 2007; EFSA, 2008), it had been considered necessary to apply an additional uncertainty factor because of major gaps in the available 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. JECFA established a PTWI of 2 mg/kg bw (2000 µg/kg bw) by dividing the NOAEL of 30 mg/kg bw/day by an uncertainty factor of 100 for inter-species and intra-species differences, and converting to a weekly exposure, which was considered more appropriate in view of

[2] 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.

the cumulative retention of aluminium. The PTWI applied to all aluminium compounds in food, including food additives (FAO/WHO, 2012). The COT concluded that the derivation of this PTWI was sound and that it should be used in assessing potential risks from dietary exposure to aluminium.

30. Very young infants may be particularly sensitive to toxicants 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 than older children and adults. Therefore assessment of the risk of chemical toxicity for such infants should be considered on a case-by-case basis. (WHO, 2009).

Sources of aluminium exposure

31. In addition to aluminium in food and water, humans can be exposed to the metal and its compounds through inhalation, both in the workplace and the wider environment, and dermally through use of certain cosmetic products. The diet is the main source for individuals who are not exposed occupationally. Air concentrations vary between rural and urban settings, with higher levels in industrial areas. Exposure from this source 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). The typical range of aluminium concentrations in soils in the UK is from 2% to 12% (Rawlins et al., 2012), and this has the potential to be an additional source of exposure, particularly in young children. Aluminium chlorohydrate (ACH) is the active ingredient in some antiperspirants, and is thought to act by precipitating inside the eccrine sweat glands as insoluble aluminium hydroxide, which then plugs the glands 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 that from a daily dietary intake of 10 mg aluminium (Flarend *et al.*, 2001). This source of exposure is not relevant for infants.

Aluminium-containing food additives

32. 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; and dietary foods for infants and young children for special medical purposes as defined in Directive 1999/21/EC. However, it is possible that some infants might be given meals prepared from commercial foods, such as sponge cake, that could include aluminium-containing food additives. The COT statement on the 2006 UK Total Diet Study notes that the miscellaneous cereals group, which comprises cakes, scones, biscuits, breakfast cereals, flour and rice, was the principal dietary contributor to the population dietary aluminium exposure (42%)[3]. JECFA concluded that aluminium from the consumption of cereals and cereal-based products could reasonably be assumed to be mainly from food additive

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

sources (FAO/WHO, 2012). These products might occur in the diets of some infants, but no information is available on the extent to which they contribute to dietary exposure in infants.

Food contact materials

33. Aluminium is used as a packaging material because it is lightweight, and highly resistant to most forms of corrosion (Marsh and Bugusu, 2007). Migration of aluminium from foil into food depends on several factors, including the composition of the raw food, the duration and temperature of heating, the pH of the 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. Aluminium from food contact materials used during commercial food processing and storage will be included in the total aluminium measured in commercial infant foods, but no information is available on additional aluminium that might leach from food contact materials in the home.

Drinking water

34. The aluminium concentration in natural waters varies according to numerous physicochemical, mineralogical and geochemical factors. Moreover, water treatment in purifying plants includes a coagulation process that uses aluminium sulphate to remove organic matter. A residual quantity of this aluminium is then present in the drinking water. EC Directive 98/83 uses an indicator parameter value for aluminium of 200 µg/L. (Directive 98/83/EC).

35. Data on aluminium concentrations in drinking water were obtained from the Drinking Water Inspectorate (DWI) (for data from England and Wales, where testing is carried out by 29 water companies), the Scottish Government, and Northern Ireland Water. In 2011, aluminium concentrations in water in the UK ranged from <1 µg/L (England and Wales 1st percentile) to >205 µg/L (Northern Ireland 99th percentile), with median values between 6.6 and 28 µg/L (Table 1).

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

Water from England and Wales is analysed by 29 water companies. The limits of detection (LODs) are not the same for each company, which led to differing upper bound concentrations for the 1st and 25th percentiles.
*Assuming results lower than the (LOD) are equal to zero.
**Assuming results lower than the LOD are equal to the LOD.
¶Results lower than the LOD are reported as half of the LOD value.

Breast milk

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

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

37. 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.

38. A survey was conducted of metals in foods and formulae for infants that were sampled in the UK in 2004-2005 (FSA, 2006). Table 3 shows the mean, interquartile range (IQR) and range of aluminium concentrations measured in different types of infant formula (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) measured in infant formulae

Formula type	Number of samples	Average aluminium (µg/kg as sold)	IQR**	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[4]

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

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

Table 4. Aluminium concentrations (µg/kg as sold) measured in commercial infant foods

Food type	Number of samples	Average aluminium (µg/kg as sold)*	IQR**	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)

Dietary exposure to aluminium

40. In calculating dietary exposures, it is reasonable to assume values of 800 mL and 1200 mL for average and high-level daily consumption of breast milk or infant formula before weaning (e.g., EFSA, 2012). In its dietary exposure estimations, the COT has previously used bodyweight data from a relatively old survey (DH, 1994). Bodyweight data are now available from the recently published UK Dietary and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), with an average bodyweight of 7.8 kg for infants aged 4.0-6.0 months old. Since DNSIYC did not include infants younger than 4 months, in this statement the value of 5.9 kg for infants aged 0-3 months (DH, 1994), is applied to infants aged 0-4 months.

Breast milk

41. Only a small number of studies have measured the levels of aluminium in breast milk. The data from the study by Baxter *et al.* (1991) were from UK samples, but as the sample size was small, potential aluminium exposures were calculated using both the mean of measured concentrations (27 µg/L) and also the maximum value (79 µg/L). This was done separately for average (800 mL) and high-level (1200 mL) consumption by exclusively breastfed infants (Table 5). The estimated intakes are in the range of 19-75 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)			
	0-4.0 (800 mL)	0-4.0 (1200 mL)	>4.0-6.0 (800 mL)	>4.0-6.0 (1200 mL)
Mean - 27 µg/L	26	38	19	29
Maximum - 79 µg/L	75	112	57	85

* From Baxter *et al.* (1991)

Infant formulae and complementary foods

42. 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.

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)			
	0-4.0 (800 mL)	0-4.0 (1200 mL)	>4.0-6.0 (800 mL)	>4.0-6.0 (1200 mL)
Powdered cows' – 106 µg/L	101	151	76	114
Powdered goats' – 148 µg/L	140	211	106	159
Powdered soy-based – 293 µg/L	278	417	210	316
Ready-to-consume (cows' –based) – 58 µg/L	55	83	42	62

*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.

43. 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 the

median and 99th percentile values for aluminium concentrations in drinking water from England and Wales (paragraph 34) water used to reconstitute infant formula might contribute a further 67 µg/kg bw/week to total aluminium exposure As a worst case, the highest 99th percentile value (205 µg/L in Northern Ireland) could lead to additional exposure of 248 µg/kg bw/week in exclusively formula-fed infants aged 0-3 months consuming high levels of reconstituted milk (Table 7).

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

Aluminium concentration in drinking water (µg/L)	Age of infant (months)			
	0-4.0 (800 mL)	0-4.0 (1200 mL)	>4.0-6.0 (800 mL)	>4.0-6.0 (1200 mL)
Median (England and Wales) – 7.3	5.9	8.8	4.5	6.7
99th percentile (England and Wales) – 55	44	67	34	50
99th percentile (Northern Ireland) - 205	165	248	125	188

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.

44. In 2003, the COT[5] 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 likely to underestimate exposures, but allowed direct comparison of the data with results from a previous food survey conducted by the Ministry of Agriculture, Fisheries and Food (MAFF) (MAFF, 1999). Estimated high-level (97.5th percentile) exposure to aluminium at age 7-12 months was 532 µg/kg bw/week compared to 686 µg/kg bw/week from the 1999 survey. In addition, estimates were made using manufacturers' feeding instructions, and these indicated mean dietary exposures of some 1225 - 1554 µg/kg bw/week. (Table 8). The COT considered that these two approaches provided a range within which actual exposures were likely to lie.

45. 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

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

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 suggest reductions in dietary exposure of infants to aluminium from between 1997 and 2005. This contrasts with the position for the wider population. A COT statement[6] on the 2006 UK Total Diet Study (TDS) of metals and other elements, noted 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]
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 represent commercially available foods and do not include the contribution of drinking water in reconstitution, or offered separately.
Bodyweights used in these surveys are as used in COT[7] and are 5.9, 7.7, 8.9 and 9.8 kg, respectively for infants aged 0-3, 4-6, 7-9 and 10-12 months.
[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.

46. The exposure estimates in table 8 do not take into account water used in reconstitution of infant formula, or drinking water that might be consumed separately. No direct data are available on the amounts that are likely to be used. However the calculated figures in paragraph 42 and table 7 indicate that exposure from water is likely to be less than the maximum from other dietary sources.

[6] http://cot.food.gov.uk/pdfs/cotstatementtds200808.pdf
[7] http://cot.food.gov.uk/pdfs/statement.pdf

47. The COT has previously noted that estimates of dietary exposure in infants from the United Kingdom (UK) have relied on survey data that may have been outdated, leading to underestimation of exposure, or on assumptions about feeding patterns from manufacturers' instructions that may have overestimated 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 and may help refine estimates of exposure from commercial infant foods and possibly other foods consumed by infants.

Risk characterisation

48. Humans can be exposed to aluminium compounds through inhalation, both in the workplace and the wider environment, and dermally through use of certain cosmetic products. The diet is likely to be the main source for infants. Based on the exposure estimates in this statement, food is likely to be the dominant source of exposure, although there are uncertainties regarding exposure to food additives from foods not intended for consumption by infants, from use of food contact materials in the home, and from soil.

49. Based on the maximum reported concentration of aluminium in breast milk, exposures of exclusively breastfed infants may be up to 6% of the PTWI of 2 mg/kg bw (2000 µg/kg bw), with the highest exposure in high level consumers aged 0-3 months. In infants fed exclusively with ready-to-eat formulae, exposures to aluminium may be 4% of the PTWI. In those fed exclusively with powdered formulae, the exposure to aluminium could be up to 8, 11 and 21% of the PTWI, respectively from cows' milk-, goats' milk- and soya based products. In addition, the water used to reconstitute the infant formula could give further exposure of up to some 248 µg/kg bw/week aluminium (12% of the PTWI) (paragraph 43), resulting in total exposure of up to 33% of the PTWI.

50. Exposures to aluminium from infant formulae in combination with commercial infant foods (based on 2004-5 survey data, Table 8) are expected to be <776 µg/kg bw per week (39% of the PTWI). This does not take into account water used in reconstitution of foods and formulae, or offered separately, but even unusually high water concentrations of aluminium (a 99th percentile value of 205 µg/L in Northern Ireland) would not take total intake above the PTWI. No information is available that would allow assessment of the contribution from foods not specifically marketed for infants, some of which could include aluminium-containing food additives.

51. In principle the PTWI does not apply to infants aged 0-12 weeks. However the estimated exposures of infants at this age based on the worst case scenario of soy formula reconstituted with water containing a high concentration of aluminium could be up to 665 µg/kg bw/week. This is 33% of the PTWI, and although capacity for renal excretion is still developing in the newborn, an exposure at this level would not be a concern. The worst case estimated dietary exposure is approximately twice the dose of aluminium (315 µg/kg bw/week as a standard parenteral solution) given to neonates that was associated with reduced lumbar spine and hip bone mass in adolescence (Bishop *et al.*, 1997; Fewtrell *et al.*, 2009) However, taking into account that the absorption of aluminium compounds in food is generally less than 0.3%, and

for some insoluble compounds is likely to be very much less than this, there is a margin of more than 150 between the estimated dietary exposure and this parenteral dose indicating a concern.

52. Exposure of very young infants fed exclusively on soy-based formula is higher than for others of the same age. 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). Estimates of dietary aluminium exposure for infants aged 4-12 months are below the PTWI and do not indicate a toxicological concern.

Conclusions

53. Infants may be exposed to aluminium compounds through inhalation of particulate matter in the air and from the diet. Use of aluminium-containing cosmetic products is unlikely in this age group. The diet is likely to be the main source.

54. Aluminium in the infant diet results from its natural occurrence in foods, its presence in drinking water (either naturally or from water treatment) that is used to reconstitute infant formula or consumed directly, and possible leaching from food containers such as cans, cookware, utensils and food wrappings. Analysis of aluminium in commercial foods for infants does not distinguish between its natural occurrence and anthropogenic sources (e.g. from environmental contamination or food contact materials). In addition, although aluminium-containing food additives are not permitted in infant formulae and processed foods for infants, they may be present in some foods fed to infants, and additional aluminium may derive from use of aluminium-containing food contact materials in the home.

55. 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. No empirical data are available on absorption of aluminium in infants specifically.

56. Urinary excretion is the primary route by which aluminium is eliminated from the body. Since glomerular filtration is not fully developed at birth, lower rates of elimination would be expected in infants than in adults.

57. The main toxic effects of aluminium that have been observed in experimental animals are neurotoxicity and nephrotoxicity. Neurotoxicity has been described in patients dialysed with water containing high concentrations of aluminium, but epidemiological data on possible adverse effects in humans at lower exposures are inconsistent. Based on a neuro-developmental toxicity study of aluminium citrate administered via 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 considers that the derivation of this PTWI was sound and that it should be used in assessing potential risks from dietary exposure to aluminium.

58. From the limited data that are available on levels of aluminium in breastmilk of UK mothers, it appears that exposure to aluminium in exclusively breastfed infants is less than 10% of the PTWI.

59. Exposure of infants fed exclusively with infant formula is similar to, or higher than that of exclusively breastfed infants, the highest potential exposure being from soy-based formula. This could amount to some 21% of the PTWI, and in the worst case, the water used in reconstitution of powdered formulae could contribute a further 12% of the PTWI.

60. 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, even unusually high water concentrations of aluminium are unlikely to take total intake above the PTWI. The possible contribution from foods not specifically marketed for infants, which may contain aluminium-based food additives is currently unknown. Further information on this might become available when the full analysis of the DYNSYIC data is possible.

61. In principle the PTWI does not apply to infants aged 0-12 weeks. However the estimated exposures of infants at this age could be up to 33% of the PTWI, and although capacity for renal excretion is still developing in the newborn, an exposure at this level would not be a concern.

62. Overall, the estimated exposures of infants to aluminium from the dietary sources that have been considered do not indicate toxicological concerns or a need for modified Government advice.

May 2013

Abbreviations

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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Appendix A

Search strategy

General aluminium exposure search

Databases interrogated –

- EFSA
- COT
- FSA
- JECFA
- British Geological Survey

Scientific publications literature search in Pubmed

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

- Studies which did not provide estimates for aluminium leaching from food contact materials

The above mentioned terms were also searched in Google™. It identified latest government advice and opinions.