TOX/2017/27

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

First draft statement on the results of the 2014 survey of metals and other elements in infant foods

Background

1. The Food Standards Agency (FSA) has completed a survey of 15 elements in the 2014 survey of metals and other elements in infant formula, commercial infant foods, and other foods (non-infant specific foods[1]) (FSA, 2016). The results of the survey provide information on the concentrations of aluminium, antimony, arsenic (including inorganic arsenic), cadmium, chromium, copper, iodine, iron, lead, manganese, mercury, nickel, selenium, tin and zinc in these foods. Estimates of dietary exposures have been calculated for each element for UK infants and young children aged 4 to 18 months using food consumption data taken from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013).

2. Details of the concentration data derived from this survey, and the subsequent exposure assessments, were presented to the Committee in discussion papers (TOX/2016/29) and (TOX/2017/18) at the July 2016 and March 2017 meetings. To aid the discussions, brief toxicology summaries for each of the elements surveyed were included in the discussion papers. The Committee commented on the concentration data and the results of the exposure assessments, and suggested some revisions to the wording of the toxicological summaries. This first draft statement (Annex A) contains updated toxicological summaries and conclusions.

3. Limits of detection and quantification were requested. These vary depending on the mass of sample analysed (Annex B).

4. A Food Surveillance Information Sheet (FSIS) will be drafted incorporating the conclusions of the Committee.

[1] Those which are not specifically manufactured or intended for infants, but are known to be or may be consumed by infants (e.g. bread, fruit and vegetables).

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Background

5. The Food Standards Agency (FSA) has completed a survey of 15 elements in the 2014 survey of metals and other elements in infant formula, commercial infant foods, and other foods (non-infant specific foods[2]) (FSA, 2016). The results of the survey provide information on the concentrations of aluminium, antimony, arsenic (including inorganic arsenic), cadmium, chromium, copper, iodine, iron, lead, manganese, mercury, nickel, selenium, tin and zinc in these foods. Estimates of dietary exposures have been calculated for each element for UK infants and young children aged 4 to 18 months using food consumption data taken from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013).

6. Details of the concentration data derived from this survey, and the subsequent exposure assessments, were presented to the Committee in a discussion paper (TOX/2016/29) and updated discussion paper (TOX/2017/18) at the July 2016 and March 2017 meetings. To aid the discussions, brief toxicology summaries for each of the elements surveyed were also included in the discussion papers. The Committee commented on the concentration data and the results of the exposure assessments, and suggested some revisions to the wording of the toxicological summaries. This discussion paper contains updated toxicological summaries and conclusions. A Food Surveillance Information Sheet (FSIS) will be drafted incorporating the conclusions of the Committee. It is anticipated that the toxicological summaries for each element will be included in an annex.

7. The Committee has provided comment on similar surveys in the past, with the most recent being a 2003 multi-element survey of infant foods[3] (COT, 2003a; FSA, 2003). The FSA has also completed a survey of metals in weaning foods and formulae for infants (FSA, 2006); however the COT did not

[2] Those which are not specifically manufactured or intended for infants, but are known to be or may be consumed by infants (e.g. bread, fruit and vegetables).
[3] COT (2003) 'Statement on a survey of metals in infant food' Available at: [4]There are 2683 respondents between the ages of 4 and 18 months in the DNSIYC survey. These exposure assessments and summary statistics are based on all responders (regardless of whether they ate the food or not)

provide comment on this survey. Although these surveys could provide a useful comparison of concentrations of different elements in specific foods, they cannot be directly compared to the current survey due to differences in the methodology of the survey itself (e.g. the grouping of certain foods) and in the exposure assessments.

The survey

4. Surveys such as this are carried out on a regular basis and are an important part of the UK Government's surveillance programme for chemicals in food. Survey results are used to estimate dietary exposures of the general UK population or specific sub-populations (e.g. infants) to chemicals in food, such as nutrients and contaminants, to identify changes or trends in exposure and make assessments on the safety and quality of the food supply.

5. A total of 47 samples of powdered and ready-to-feed infant formula (including follow-on formula and growing up milks, cow and goat milk-based and soya-based formulae), 200 samples of commercial infant foods, and 50 other foods were purchased from retail outlets throughout the UK during 2013 and 2014. All samples were analysed as sold (i.e. dry powdered infant formula and dried cereal products such as baby rice were not reconstituted prior to analyses), using Inductively Coupled Plasma Mass Spectrometry (ICP-MS) at the Food and Environment Research Agency for 15 metals and other elements.

6. The samples of formula-based products were representative of those on sale in the UK at the time of marketing, including the major brands and formula types. Samples of specific brands of commercial infant foods were collected in proportion to their market share. Selection of other foods were based on those that made the largest contribution to the infant diet, as recorded in the DNSIYC along with the Department of Health (DH) recommended first foods, next foods and foods from 8-9 months and 12 months (DH, 2015). Each of these 50 foods was a composite of 10 samples from different manufacturers and retailers.

Dietary exposure assessment

7. The concentration data from individual products were used to derive the overall mean concentration for each food group (e.g. a mean concentration for follow-on formula was calculated based on the results for each type of follow-on formula analysed). Food consumption data from the diet and nutrition survey of infants and young children[4] (DNSIYC) (DH, 2011) were used to calculate the exposure values of children aged 4 to 18 months. Table 1 below summarises the results of the exposure assessments carried

[4]There are 2683 respondents between the ages of 4 and 18 months in the DNSIYC survey. These exposure assessments and summary statistics are based on all responders (regardless of whether they ate the food or not)

out for each element in the three overarching food categories: infant formula, commercial infant foods and other foods.

Table 1. Summary of estimated dietary exposures in UK infants aged 4 to 18 months to a selection of metals and other elements analysed in infant formula, commercial infant foods and other foods

Food Category	Consumer (n = 2683*)	Dietary exposures in UK infants aged 4 to 18 months (µg/kg bw/day)															
		Essential elements								Non-essential elements							
		Cr	Cu	I	Fe	Mn	Se	Sn	Zn	Al	Sb	As	iAs	Cd	Pb	Hg	Ni
Infant Formula	Mean	0.0029-0.10	11	4.0	240	2.2	0.020-0.53	0-0.090	180	0.64-1.1	0-0.030	0-0.013	0-0.010	0-0.010	0-0.015	0-0.0061	0.010-0.25
	High level	0-0.32	37	14	760	6.9	0.060-1.8	0-0.31	600	2.0-3.6	0-0.10	0.012-0.040	0.010-0.030	0-0.022	0-0.046	0-0.020	0-0.90
Commercial Foods	Mean	0.30-0.39	5.7	0.28-0.33	81	19	0.14	0.36-0.41	51	12	0.010-0.020	0.13	0.04-0.062	0.06	0.030-0.040	0.0012-0.010	0.60-0.80
	High level	1.4-1.8	26	1.6-1.7	370	78	0.67-0.70	1.9-2.1	250	54-55	0.040-0.10	0.58	0.19-0.26	0.27	0.13-0.17	0.010-0.030	2.6-3.6
Other Foods	Mean	0.26-0.48	16	5.3	160-170	63	0.8	38	160	19-20	0-0.050	0.78-0.79	0.090-0.10	0.19-0.20	0.040-0.070	0.020-0.030	0.92-1.5
	High level	0.81-1.2	39	19	450-460	170	2.1	250	370	50-51	0-0.12	4.2	0.35-0.37	0.52	0.12-0.16	0.13-0.15	2.8-3.8
Total	Mean	0.59-1.0	37	11	550	85	1.1-1.6	38	440	33-34	0.0040-0.11	0.91-0.94	0.14-0.18	0.25-0.27	0.071-0.12	0.022-0.046	1.6-2.6
	High level	1.7-2.5	69	23	1300	190	2.6-3.0	250	860	74-76	0.029-0.21	4.3-4.4	0.41-0.47	0.57-0.59	0.17-0.26	0.13-0.16	3.9-5.6

Values are rounded to 2SF. Values are presented as estimates based on lower-bound (LB) to upper-bound (UB) concentration data. The LB was calculated by treating concentration data < LOD as 0, while the UB was determined by treating values <LOD as equal to the LOD. If there is only one figure shown then all concentration data were above the LOD. *The exposure assessments are based on all 2683 responders, regardless of whether they ate the food or not.

Evaluation

8. Below are brief toxicological summaries and conclusions for each of the elements. Where possible, published health-base guidance values have been noted, and compared with the results of the current exposure assessments.

Essential elements

Chromium

9. Chromium is a metallic element that can exist in a number of oxidation states, the most common of which are: trivalent chromium (Cr (III)) and hexavalent chromium (Cr (VI)). Cr (III) is ubiquitous in nature and occurs in air, water, soil and biological systems. Most Cr (VI) is man-made and is not found naturally in the environment. Cr (III) has a normal role in potentiating the action of insulin and thereby influences carbohydrate and lipid metabolism. A deficiency of Cr (III), in humans, has only been observed in patients on long-term parenteral nutrition. The symptoms observed were impaired glucose tolerance and glucose utilisation, weight loss, neuropathy, elevated plasma fatty acids, depressed respiratory quotient and abnormalities in nitrogen metabolism. (EVM, 2003).

10. The toxicity of chromium varies depending on the valency state, with Cr (VI) being more toxic than Cr (III), which is an essential trace element. Most of the ingested Cr (VI) is considered to be reduced in the stomach to Cr (III), which is poorly bioavailable and presents low ability to enter cells. In contrast to Cr (III), Cr (VI) is able to cross cellular membranes. Ingested Cr (III) has a low level of toxicity, due partly to its poor absorption, while Cr (VI) and its compounds are oxidizing agents capable of directly inducing tissue damage, and epidemiological studies have found an association between exposure to Cr (VI) and lung cancer (EFSA, 2014a).

11. In 2014 the EFSA established a TDI for Cr (III) of 0.3 mg/kg bw based on the lowest NOAEL identified in a chronic oral toxicity study in rats. In their assessment, the EFSA assumed that all chromium in food was present as Cr (III); the EFSA noted that there was a lack of data on Cr (VI) in food and stated that this assumption was based on the outcome of recent speciation work, the fact that food is by-and-large a reducing medium, and that oxidation of Cr (III) to Cr (VI) would not be favoured in such a medium. The EFSA also assumed that all of the chromium present in drinking water was Cr (VI) (EFSA, 2014a), however as drinking water was not included in this survey, the TDI for Cr (III) has been used to assess the current dietary exposure estimates.

12. No speciation was performed as part of the current survey; therefore the subsequent dietary exposures are for total chromium, which, is assumed to be Cr (III) (EFSA, 2014a). For chromium, the total mean and high level exposures were 0.59-1.0 µg/kg bw/day and 1.7-2.5 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure

was the 'commercial infant foods' category, with total mean exposures ranging from 0.30-0.39 µg/kg bw/day. Overall, the current estimates of dietary exposure to chromium were well below the EFSA TDI at both mean and high level exposure.

13. The Committee concluded that the current estimated dietary exposures to chromium were not of toxicological concern.

Copper

14. Copper is an essential trace element and forms an essential component of many enzymes such as cytochrome c oxidase, amino acid oxidase, superoxide dismutase and monoamine oxidase. It is also thought to be essential for infant growth, host defence mechanisms, bone strength, red and white cell maturation, iron transport, cholesterol and glucose metabolism, myocardial contractility and brain development.

15. Deficiency may include clinical features such as anaemia, neutropenia and bone abnormalities. Less common effects include hypopigmentation, impaired growth, increased incidence of infections, alterations of phagocytic capacity of neutrophils and abnormalities of glucose and cholesterol metabolism. (EVM, 2003; EFSA, 2006)

16. High levels of copper can cause acute gastrointestinal effects. This may be a direct irritant effect of copper in water and is not so apparent when copper is present in the food matrix (EVM, 2003). The JECFA has derived a provisional maximum tolerable daily intake (PMTDI) of 50-500 µg/kg bw on the basis of human epidemiological and nutritional data related to background exposure to copper (originally proposed in 1973) (FAO/WHO, 1982a). The Expert Group on Vitamins and Minerals (EVM) has set a safe upper level (SUL) for copper of 160 µg/kg bw/day based on a NOAEL of 16 mg/kg bw/day from a 13-week feeding study of copper sulphate in rats in which effects on the liver, kidney and forestomach were seen at higher doses (EVM, 2003). The Scientific Committee on Food (SCF) has set an upper level (UL) for copper of 1 mg/day for 1-3 year olds; this is equivalent to approximately 83 µg/kg bw/day based on the EFSA's default body weight of 12 kg for 1-3 year olds. This UL was extrapolated from an UL for adults of 5 mg/day (equivalent to 71 µg/kg bw/day when using a default body weight of 70 kg) which was based on a NOAEL of 10 mg/day from a 12 week supplementation study in 7 healthy adults for which the critical endpoint was adverse effects on liver function, an uncertainty factor of 2 was applied to account for potential variability within the normal population (SCF, 2003a).

17. Regarding copper, the total mean and high level exposures were 37 µg/kg bw/day and 69 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the 'other foods' category, with a total mean exposure of 16 µg/kg bw/day. Overall, the current estimates of dietary exposure to copper were below all of the available health-based guidance values at both mean and high level exposure.

18. The Committee concluded that the current estimated dietary exposures to copper were not of toxicological concern.

Iodine

19. Iodine is essential for the synthesis of thyroid hormones; through these hormones iodine has an important role in energy-yielding metabolism, integrity of connective tissue and is necessary for the development of the nervous system in the fetus and infant. Iodine deficiency is of particular concern in infants because of the risk of developmental brain damage, which can lead to physical and mental retardation and lower cognitive and motor performance in later life. In addition to this, chronic iodine deficiency may lead to compensatory thyroid hypertrophy/hyperplasia with goitre. The EFSA has recently proposed adequate intakes for iodine of 70 and 90 µg/day for 7 to 11 month olds and 1 to 3 year olds, respectively (EFSA, 2014b). These are equivalent to approximately 14 and 7.5 µg/kg bw/day when default body weights of 5 and 12 kg are used for 7 to 11 month olds and 1 to 3 year olds, respectively.

20. Chronic excessive iodine intake can also lead to goitre, and may accelerate the development of sub-clinical thyroid disorders to overt hypothyroidism or hyperthyroidism, increase the incidence of autoimmune thyroiditis, and increase the risk of thyroid cancer (EFSA, 2014b). The SCF has set an UL for iodine of 200 µg/day for 1-3 year olds (~ 16.7 µg/kg bw/day, based on a body weight of 12 kg). This UL was derived by adjustment of the adult UL of 600 µg/day (~ 8.6 µg/kg bw/day, based on a body weight of 70 kg) on the basis of body surface area (defined as body weight$^{0.75}$) since there was no evidence of increased susceptibility in children. The adult UL was based on a study covering a 5-year exposure at iodide intake levels of 30 mg/kg bw/day (equivalent to approximately 1800 mg iodide/day) in which no clinical thyroid pathology occurred, an uncertainty factor of 3 was applied to this (SCF, 2002).

21. For iodine, the total mean and high level exposures were 11 µg/kg bw/day and 23 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the ‘other foods’ category, with a total mean exposure of 5.3 µg/kg bw/day. Overall, the current estimates of dietary exposure to iodine were below or marginally greater than (~15%) the SCF UL at both mean and high level exposure, and would thus not be of toxicological concern.

22. The Committee concluded that at current estimated dietary exposures excessive iodine intake is unlikely to pose a risk to health.

Iron

23. Iron, a transition metal, is ubiquitous in biological systems. The majority of functional iron within the body is present in haem proteins, such as haemoglobin, myoglobin and cytochromes, which are involved in oxygen transport or mitochondrial electron transfer. Many other enzymes also contain

or require iron for their biological function. Iron deficiency generally develops slowly, and may not be clinically apparent until iron stores are exhausted and the supply of iron to the tissues is compromised, resulting in iron-deficiency anaemia. Infants over 6 months of age and toddlers are 2 of the groups that are vulnerable to iron deficiency (EVM, 2003).

24. Iron in foods occurs in two main forms: haem and non-haem. The major sources of haem iron in the diet are haemoglobin and myoglobin from meat, poultry and fish, while the major sources of non-haem iron consist mainly of iron salts, derived from plant and dairy products. Most of the non-haem iron present in foods is in the ferric form. Fortification of food with iron is common in developing countries, where deficiency of the element is widespread. The EVM has stated that overall there are insufficient appropriate data to establish a SUL for iron. Although many supplementation studies have been conducted, they have generally been in iron-deficient groups and none of them are applicable to the population as a whole. For iron-replete individuals in non-developing countries, the most common side effects reported are gastrointestinal in nature, and include constipation, nausea, vomiting, and epigastric pain. These effects are reported to follow supplemental doses of between 50 and 220 mg/day, the frequency increasing at higher dose levels. For guidance purposes, a supplemental intake of approximately 17 mg/day (equivalent to 1.7 mg/kg bw/day for a 10 kg infant) would not be expected to produce adverse effects in the majority of people. This was derived by dividing the lower end of the range found to have an effect by an uncertainty factor of 3 to allow for extrapolation from a LOAEL to a NOAEL. This was based on data referring to ferrous iron (Fe II), which is the form of iron generally used in supplements. No additional uncertainty factor was needed for inter-individual variation because the assessment was based on studies on large numbers of people. The EVM did not estimate a SUL for total iron as gastrointestinal effects are associated with iron in supplements rather than in foods (EVM, 2003).

25. The United States Institute of Medicine (US IOM) has established a tolerable upper intake level (TUL) for supplemental non-haem iron of 40 mg/day for infants and children. This TUL is based on a NOAEL of 40 mg/day from epidemiological studies of supplementation with non-haem iron in infants and young children; an uncertainty factor of 1 was applied as there was little uncertainty regarding the range of intakes that is likely to induce gastrointestinal effects in infants and young children (IOM, 2001). If this TUL is applied to the age group assessed in this survey, then it is equivalent to approximately 4 mg/kg bw/day based on an average body weight of 10 kg for infants aged 4 to 18 months (DH, 2013).

26. Regarding iron, the total mean and high level exposures were 550 µg/kg bw/day and 1300 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the ‘infant formula’ category, with a total mean exposure of 240 µg/kg bw/day. Overall, the current estimates of dietary exposure to iron were below EVM’s guidance value for supplemental iron and the US IOM’s UL at both mean and high level exposure.

27. The Committee concluded that the current estimated dietary exposures to iron were not of toxicological concern.

Manganese

28. Manganese is an essential trace element that can exist in a variety of oxidation states. It is neurotoxic at high levels of occupational inhalation exposure, but there is limited evidence of neurological effects at lower doses. The extent of neurotoxicity is determined by the oxidation state, with Mn (III) being more toxic than Mn (II) (WHO, 2006). The dose response relationship in experimental animals has not been adequately clarified and the effects observed in animals may not reflect the subtle neurological effects reported in humans (EVM, 2003). Children might be particularly susceptible to the neurotoxicity of manganese. There is insufficient information to determine whether there are risks associated with dietary exposure to manganese and there are no reliable health-based guidance values available. In animals manganese-deficiency exhibits as skeletal abnormalities and poor growth, reproductive deficits and defects in lipid and carbohydrate metabolism. There is no evidence that manganese deficiency occurs normally in humans.

29. The EVM considered that, based on the results of epidemiological studies of neurological effects associated with concentrations of manganese in drinking water, total manganese intakes of 12.2 mg/day for the general population (equivalent to 1.22 mg/kg bw/day for infants aged 4 to 18 months) would not result in adverse health effects (EVM, 2003). This conclusion was based on a number of assumptions since neither of the two studies used to establish these guidance values recorded water consumption or dietary manganese intake. The WHO derived a TDI of 60 µg/kg body weight/day in the Guidelines for Drinking Water Quality (WHO, 2004). This was based on the upper range value of manganese intake of 11 mg/day, identified using dietary surveys, at which there were considered to be no observed adverse effects. An uncertainty factor of 3 was applied to take into consideration the possible increased bioavailability of manganese from water. No information was provided on how these reference doses were set in relation to speciation.

30. For manganese, the total mean and high level exposures were 85 µg/kg bw/day and 190 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the ‘other foods’ category, with a total mean exposure of 63 µg/kg bw/day.

31. The Committee concluded that it would not be appropriate to use the health-based guidance values that were currently available to characterise the potential risks from exposure to manganese as the way in which these values were derived was not considered sufficiently robust. The Committee is due to revisit the issue of manganese exposures in this age group in a statement at a later date.

Selenium

32. Selenium is an abundant element that can exist in 4 oxidation states (-2, +1, +2, and +6). Selenium is also an essential trace element and, in food, is generally present as the amino acid derivatives selenomethionine and selenocysteine. There are no typical symptoms of selenium deficiency but muscular pain and muscle and cardiac dysfunction have occurred in patients on parenteral nutrition without selenium added. Dietary deficiency of selenium is a contributing factor to Keshan disease; a congestive cardiomyopathy that can be fatal. The toxicity of selenium depends on the nature of the selenium compound, particularly its solubility; selenium sulphide is much less toxic than selenite, selenate and selenomethionine. Selenium toxicity is cumulative. In humans, the first signs of chronic toxicity appear to be pathological changes to the hair and nails, followed by adverse effects on the nervous system (EVM, 2003).

33. The EVM has derived a SUL of 7.5 µg/kg bw/day for selenium based on a lowest observed adverse effect level (LOAEL) of 0.91 mg/day, derived from an epidemiological dietary study in which signs of selenosis (prolonged prothombin time, morphological changes in the nails, and increased white blood cell count) were observed in individuals with selenium blood levels of 1.054 to 1.854 mg/L. These blood levels were calculated to represent a selenium intake of 0.91 mg/day, and an uncertainty factor of 2 was applied to extrapolate from the LOAEL to a NOAEL. A larger uncertainty factor was not considered necessary because the intake of 0.91 mg/day produced only slight effects and was close to a NOAEL (EVM, 2003).

34. The SCF has also set an UL for selenium of 60 µg/day for 1-3 year olds (~ 5 µg/kg bw/day, based on a 12 kg body weight) (SCF, 2000). This was derived from an adult UL of 300 µg/day (~ 4.3 µg/kg bw/day, based on a 70 kg body weight) on a body weight basis as there were no reports of increased susceptibility in children. The adult UL was established using a NOAEL of 850 mg/day for clinical selenosis in a study on 349 subjects. A follow-up study supported this NOAEL as 5 individuals recovered from selenosis when their selenium intake had been reduced to a mean of 819 mg/day. The NOAEL used was derived from a study on a large number of subjects and was expected to include sensitive individuals. An uncertainty factor of 3 was used to allow for the remaining uncertainties in the studies used in deriving the UL (SCF, 2000).

35. Regarding selenium, the total mean and high level exposures were 1.1-1.6 µg/kg bw/day and 2.6-3.0µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the ‘other foods’ category, with a total mean exposure of 0.8 µg/kg bw/day. Overall, the current estimates of dietary exposure to selenium were below the EVM and SCF’s upper levels at both mean and high level exposure.

36. The Committee concluded that the current estimated dietary exposures to selenium were not of toxicological concern.

Tin

37. Tin is rarely found as the metallic element in nature but is more usually found combined with other substances, most commonly as the dioxide (EVM, 2003). It has oxidation states of II and IV. There is no proven biological function for tin. It has been suggested that, because of its coordination chemistry, it may contribute to macromolecular structure and function at the active site of metalloenzymes. Naturally occurring deficiency of tin in free-living humans or animal species has not been demonstrated. (EVM, 2003).

38. Inorganic tin is of low toxicity, whereas some organotin compounds are potent neurotoxicants, though these are not normally present in food, beverages or food supplements (EVM, 2003; WHO, 2006). Gastrointestinal effects are the main manifestation of toxicity associated with ingestion of foods or drinks contaminated with tin. These are caused by the irritant action of soluble inorganic tin compounds; recovery from the effects is rapid. Some sub chronic feeding studies have observed haematological changes in rats, but other chronic carcinogenicity studies and one multi generation reproduction study did not record any such effects, or noted that the observed changes were transient. Pancreatic atrophy has also been observed in sub chronic studies in rats (EVM, 2003).

39. The JECFA established a PTWI of 14 mg/kg bw for tin in 1988 but later stated that the basis for this PTWI was unclear and that it may have been derived from intakes associated with acute effects (FAO/WHO, 2006). The EVM has established a guidance level of 220 µg/kg bw/day based on sub-chronic toxicity studies in rats that showed pancreatic atrophy occurring at doses of about 240 mg/kg bw/day. In addition, changes to liver cells and anaemia were observed in a study in which a NOAEL of 22-33 mg/kg bw/day could be derived. Applying uncertainty factors of 10 for inter-species variation and 10 for inter-individual variability to this NOAEL, gave a daily intake of about 0.2-0.3 mg/kg bw/day. The EVM suggested that the lower end of this range, 0.22 mg/kg bw/day, could be used for guidance purposes only and would be expected not to produce adverse effects in humans (EVM, 2003).

40. For tin, the total mean and high level exposures were 38 µg/kg bw/day and 250 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the ‘other foods’ category, with total mean exposures ranging from 38 µg/kg bw/day. Overall, the total mean exposure estimates to tin were well below EVM guidance level, and would therefore not be of toxicological concern. Although the total high level estimate was approximately 10% above the EVM guidance level, this is only a minor exceedance and would be unlikely to result in adverse effects.

41. The Committee concluded that the current estimated dietary exposures to tin were not of toxicological concern.

Zinc

42. Zinc is an essential trace element, occurring in nature as the sulphide, the silicate, and the oxide. Deficiency in zinc can result in retardation of growth and delay in sexual maturation, dermatitis, diarrhoea and increased

susceptibility to infections. Excessive zinc intake interferes with the gastrointestinal absorption of copper, potentially leading to secondary copper deficiency, which can result in conditions such as anaemia and bone abnormalities (EVM, 2003). The JECFA has established a PMTDI for zinc of 0.3-1.0 mg/kg bw; clinical studies in which up to 600 mg of zinc sulphate (equivalent to 200 mg elemental zinc) had been administered daily in divided doses for a period of several months were used as the basis for deriving the PMTDI (FAO/WHO, 1982b). The EVM has derived a SUL of 25 mg/day (equivalent to 2.5 mg/kg bw/day for a 10 kg infant) based on a LOAEL of 50 mg/day from epidemiological studies assessing the impact of zinc supplementation, and an uncertainty factor of 2 (to extrapolate from the LOAEL to a NOAEL) (EVM, 2003). The SCF has extrapolated an UL of 7 mg/day for 1 to 3 year olds (~ 580 µg/kg bw/day, based on a 12 kg body weight) from an adult UL of 25 mg/day (~ 360 µg/kg bw/day, based on a 70 kg body weight) on the basis of body surface area (defined as body weight$^{0.75}$) since there was no evidence of increased susceptibility in children. The adult UL was based on a NOAEL of 50 mg/day from epidemiological studies assessing the impact of zinc supplementation; an uncertainty factor of 2 was applied owing to the small number of subjects included in relatively short-term studies but acknowledging the rigidly controlled metabolic experimental conditions that had been employed (SCF, 2003b).

43. Regarding zinc, the total mean and high level exposures were 440 µg/kg bw/day and 860 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the ‘infant formula’ category, with total mean exposures ranging from 180 µg/kg bw/day. Overall, the current estimates of mean dietary exposure to zinc were below all of the available health-based guidance values. The current estimates of high level dietary exposure were greater than the SCF guidance values (~50%) but below the JECFA and EVM values.

44. The Committee concluded that the current estimated dietary exposures to zinc were not of toxicological concern.

Non-essential elements

Aluminium

45. In 2011, the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) revised their provisional tolerable weekly intake (PTWI) for aluminium. Based on new data that had addressed some of the research needs that they had identified in previous assessments, the JECFA withdrew their PTWI of 1 mg/kg bodyweight (bw)/day, and established a new PTWI of 2 mg/kg bw/day. This new PTWI was derived using a no observed adverse effect level (NOAEL) of 30mg/kg bw/day taken from a developmental and chronic neurotoxicity study in rats, and an uncertainty factor of 100 for inter-species and intra-species differences. The JECFA also converted the NOAEL to a weekly exposure, as this was considered more appropriate in view of the cumulative retention of aluminium (FAO/WHO, 2012).

46. For aluminium, the total mean and high level exposures were 33-34 µg/kg bw/day and 74-76 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the 'other foods' category, with total mean exposures ranging from 19-20 µg/kg bw/day. Overall, the current estimates of dietary exposure to aluminium were well below the JECFA PTWI (equivalent to 286 µg/kg bw/day) at both mean and high level exposure.

47. The Committee concluded that the current estimated dietary exposures to aluminium were not of toxicological concern.

Antimony

48. The World Health Organization (WHO) has set a tolerable daily intake (TDI) of 6 µg/kg bw (WHO, 2003). This was based on a NOAEL of 6 mg/kg bw for decreased body weight gain and reduced food and water intake in a 90-day drinking water study in rats; and an uncertainty factor of 1000 (10 for inter-species, 10 for intra-species and 10 for the use of a sub-chronic study). The toxicity of antimony is a function of the water solubility and the oxidation state of the species, with antimony (III) being more toxic than antimony (V), and inorganic compounds being more toxic than organic compounds. No information was provided regarding how the TDI was established in relation to the speciation, although, the WHO noted that antimony leached from antimony-containing materials would be in the form of the antimony (V) oxo-anion, which is the less toxic form (WHO, 2003).

49. For antimony, the total mean and high level exposures were 0.0040-0.11 µg/kg bw/day and 0.029-0.21 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the 'other foods' category, with total mean exposures ranging from 0-0.050 µg/kg bw/day. Overall, the current estimates of dietary exposure to antimony were well below the WHO TDI at both mean and high level exposure.

50. The Committee concluded that the current estimated dietary exposures to antimony were not of toxicological concern.

Arsenic

51. The toxicity of arsenic is dependent on the form, organic or inorganic, and the oxidation state of arsenical compounds. It is generally accepted that inorganic arsenic compounds are more toxic than the organic arsenic compounds that are commonly found in fish, seafood and other marine organisms (EFSA, 2009a). For this reason, the Committee has previously recommended that surveys such as this one should measure both total and inorganic arsenic (COT, 2003b).

52. The COT has commented on arsenic in food a number of times in the past. In general the conclusions have been that dietary exposure to organic arsenic was unlikely to constitute a risk to health, but that dietary exposure to inorganic arsenic should be as low as reasonably practicable (ALARP) and

that efforts to reduce the levels of inorganic arsenic in food and water should continue, because it is genotoxic and a known human carcinogen (COT, 2008; COT, 2016).

53. For total arsenic, the total mean and high level exposures were 0.91-0.94 µg/kg bw/day and 4.3-4.4 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the 'other foods' category, with total mean exposures ranging from 0.78-0.79 µg/kg bw/day. However, the focus of the current risk characterisation is on inorganic arsenic since this is the form that is carcinogenic and is of most concern.

Inorganic arsenic

54. The main adverse effects associated with long-term ingestion of inorganic arsenic in humans are skin lesions, cancer, developmental toxicity, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism, and diabetes (EFSA, 2009a). The International Agency for Research on Cancer (IARC) has reviewed arsenic on a number of occasions, concluding that it is a group 1 carcinogen that causes cancer of the lung, urinary bladder, and skin in humans (IARC, 2012). There are a number of proposed mechanisms of carcinogenicity of inorganic arsenic, including oxidative damage, epigenetic effects and interference with DNA damage repair, but not direct reaction with DNA (EFSA, 2009a; FAO/WHO, 2011a; IARC, 2012).

55. The European Food Safety Authority (EFSA), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) have published risk assessments on exposure to inorganic arsenic in food. Based on the available epidemiological studies, the EFSA calculated a range of values for the 95% lower confidence limit of the benchmark dose ($BMDL_{01}$) of 0.3 to 8 µg/kg bw/day, this range was identified for cancers of the lung, skin and urinary bladder, as well as skin lesions (EFSA, 2009a). Using a different approach to modelling the dose-response data, and studies that had been published after the EFSA assessment, the JECFA calculated a BMDL of 3.0 µg/kg bw/day for a 0.5% increased incidence of lung cancer (FAO/WHO, 2011a).

56. The COT has concluded that the JECFA $BMDL_{0.5}$ of 3.0 µg/kg bw/day identified for lung cancer should be used in the characterisation of the potential risks from exposure to inorganic arsenic. This was because the JECFA risk assessment was based on more robust and recent evidence than that available to the EFSA (COT, 2016). A margin of exposure (MOE) approach should be used to compare exposure estimates to the BMDL.

57. The COT also noted that as there was no precedent for interpreting MOEs that have been calculated based on a BMDL derived from an epidemiological study and relating to a low cancer incidence, such interpretation must be done on a case-by-case basis. As the JECFA BMDL used in this case was based on human data and a 0.5% increased incidence of lung cancer in a well-conducted prospective cohort study, and as inorganic arsenic does not appear to be directly genotoxic, the COT concluded that an MOE of 10 or above could be considered a low concern (COT, 2016).

58. The total mean exposures to inorganic arsenic were 0.14-0.18 µg/kg bw/day. This range of exposures generates an MOE of 20 (rounded to 1 significant figure (SF)), as this is greater than 10, these exposures would be considered a low concern. The total high level exposures were 0.41-0.47 µg/kg bw/day and generate MOEs of 6-7 (rounded to 1 SF). As these MOEs are marginally less than 10 there could be a small risk to high level consumers. The highest contributing food category to total mean exposure was the 'other foods' category, with total mean exposures ranging from 0.090-0.10 µg/kg bw/day.

59. The Committee concluded that, although the current average dietary exposures to inorganic arsenic would be considered a low concern, the high level exposures could present a small risk to consumers; the Committee therefore reiterated that efforts to reduce the levels of inorganic arsenic in food should continue.

Cadmium

60. Cadmium is primarily toxic to the kidney, especially to the proximal tubular cells where it accumulates over time and may cause renal dysfunction. Cadmium can also cause bone demineralisation, either through direct bone damage or indirectly as a result of renal dysfunction. Using benchmark dose modelling the EFSA derived a critical urinary cadmium concentration of 1 µg/g creatinine after 50 years of exposure, and estimated that in order to remain below this level in 95% of the population by age 50, the average daily dietary cadmium intake should not exceed 0.36 µg/kg bw, corresponding to a weekly dietary intake of 2.52 µg/kg bw. The EFSA noted that because of the long half-life of cadmium in the human body, a health-based guidance value should be set on weekly rather than daily basis, and hence established a tolerable weekly intake (TWI) of 2.5 µg/kg bw. The EFSA also noted that some subgroups such as children may exceed the TWI by about two-fold, and stated that although on an individual basis exceeding the TWI by about two-fold is unlikely to lead to adverse effects on the kidney, it clearly demonstrates the need to reduce exposure to Cd at the population level (EFSA, 2009b).

61. In contrast to the EFSA TWI, the JECFA, using the same data as EFSA, has established a provisional tolerable monthly intake (PTMI) for cadmium of 25 µg/kg bw (equivalent to ~6 µg/kg bw/week or 0.8 µg/kg bw/day). This PTMI was based on data on urinary cadmium levels in humans and a point of departure of 5.24 µg/g creatinine which corresponded to a dietary intake of 0.8 µg/kg bw/day; the JECFA considered that a monthly guidance value was more appropriate than a daily or weekly value due to cadmium's exceptionally long half-life (FAO/WHO, 2011b). Following the publication of the JECFA PTMI, EFSA compared the approaches taken by EFSA and JECFA to establish an HBGV for cadmium (EFSA, 2011a). Following this evaluation a statement (EFSA, 2011b) was produced by EFSA concluding that the approach adopted in its Opinion (2009b) was appropriate. In this risk characterisation the EFSA TWI, which is the lower of the health-based guidance values, has been used to assess the current exposures

following the rigorous statistical review by EFSA of the derivation of its HBGV compared with that of JECFA.

62. For cadmium, the total mean and high level exposures were 0.25-0.27 µg/kg bw/day and 0.57-0.59 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the 'other foods' category, with total mean exposures ranging from 0.19-0.20 µg/kg bw/day. Overall, the total mean exposure estimates were approximately 70% of the TWI and would thus not be of toxicological concern. The total high level estimates were approximately 60% above the EFSA TWI. Such exposures are unlikely to lead to adverse effects on the kidney, although it is important to consider whether the potential vulnerability of the infant kidney would be increased due to its immaturity. It should be noted that food is unlikely to be the only source of exposure to cadmium in this age group; other potentially important sources of exposure include water, soil and dust.

63. Although the EFSA TWI of cadmium was exceeded by infants in some cases, these exceedances were small in magnitude (260% maximum) and were only relevant over a short period of life, not over the 50 years of bioaccumulative exposure considered by EFSA in setting the HBGV. The Committee decided that this was therefore not a major cause for concern, However, considering the cumulative nature of cadmium toxicity, any exceedance of the HBGV, no matter how small, is undesirable and dietary exposure of infants to cadmium should be kept as low as reasonably practicable.

Lead

64. Exposure to lead is associated with developmental neurotoxicity in infants and young children, a sub-group of the population who are particularly vulnerable to its adverse effects as their brain is still developing and because they absorb a higher percentage of ingested lead (COT, 2016b). To assess the potential risks of exposure to lead, the EFSA has derived a $BMDL_{01}$ of 12 µg/L from blood lead levels associated with a decrease of 1 Intelligence Quotient (IQ) point; this decrease is considered to be relevant at the population level. The BMDL corresponds to a dietary intake value of 0.5 µg/kg bw/day (EFSA, 2010); this value can be used in an MOE approach to assess exposures to lead.

65. The COT has previously concluded that "*as the BMDL was for a small effect (a one-point difference in IQ), derived from pooled analysis of multiple cohort studies of exposures in infants and children, and is likely to be conservative, an MOE of >1 can be taken to imply that at most, any risk is likely to be small. MOEs <1 do not necessarily indicate a problem, but scientific uncertainties (e.g. because of potential inaccuracies in the assessment of exposures, failure to control completely for confounding factors, and the possibility that the samples of children studied have been unrepresentative simply by chance) mean that a material risk cannot be ruled out. This applies particularly when MOEs are substantially <1*" (COT, 2016b).

66. For lead, the total mean and high level exposures were 0.071-0.12 µg/kg bw/day and 0.17-0.26 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the 'other foods' category, with total mean exposures ranging from 0.040-0.070 µg/kg bw/day. Overall, the current estimates of dietary exposure to lead generated ranges of MOEs of 4-7 and 2-3 (rounded to 1 SF) for mean and high level exposures, respectively. It should be noted that food is not the only source of exposure to lead in this age group; other potentially important sources of exposure include water and soil.

67. The Committee concluded that any risk posed by the current estimated dietary exposures to lead were small. There are other potentially more important sources of exposure to lead such as water and soil.

Mercury

68. Mercury exists in multiple forms and in three oxidation states (elemental mercury, mercurous mercury, and mercuric mercury). The properties and chemical behaviour of mercury strongly depend on its oxidation state and its chemical form. Mercurous and mercuric mercury form numerous inorganic and organic chemical compounds. Organic forms of mercury, such as methylmercury, are the most toxic following ingestion as they are absorbed more effectively in the gastrointestinal tract than elemental mercury or inorganic mercury compounds (WHO, 2006).

69. Food is the major source of exposure to mercury in the general population, particularly methylmercury in fish. The EFSA has established TWIs of 4 µg/kg bw and 1.3 µg/kg bw for inorganic mercury and methylmercury, respectively. The EFSA TWI for inorganic mercury was in line with that established by the JECFA, which was based on the lowest $BMDL_{10}$ of 0.112 mg/kg bw/day, expressed as mercuric chloride, for an increase in relative kidney weight in rats. After correcting this value for the amount of mercury in mercuric chloride (73.9 %), and adjusting to account for 5 days per week dosing, rather than 7 days per week dosing, this value resulted in a $BMDL_{10}$ of 0.06 mg/kg b.w. per day, expressed as mercury. After application of a 100-fold uncertainty factor, and conversion to a weekly basis, this gave a TWI of 4 µg/kg bw (EFSA, 2012).

70. The TWI for methylmercury was based on a methylmercury concentration in maternal hair of 11.5 mg/kg, this was the mean of the apparent no observed effect level (NOEL) from a Seychelles nutrition cohort at 9 and 30 months (11 mg/kg maternal hair), and the $BMDL_{05}$ from a Faroese cohort at age seven years (12 mg/kg in maternal hair). By application of a maternal hair to maternal blood ratio of 250, the mean maternal hair concentration was converted into a maternal blood concentration (46 µg/L); this concentration was converted to a daily dietary mercury intake of 1.2 µg/kg bw by using a one-compartment toxicokinetic model. A factor of 2 was applied to account for variation in hair to blood ratio, and when converting the steady state concentration of mercury in blood to an estimated daily intake, a factor

of 3.2 was applied, resulting in a TWI of 1.3 µg/kg bw. In their assessment, the EFSA regarded total mercury as inorganic mercury for all food categories apart from 'Fish and other seafood', and stated that because this approach was chosen, total mercury dietary exposure could not be derived by adding inorganic and methylmercury dietary exposure together (EFSA, 2012). For the purposes of this assessment, total dietary exposures will be compared to the TWI of 4 µg/kg bw for inorganic mercury (equivalent to ~0.57 µg/kg bw/day).

71. Regarding mercury, the total mean and high level exposures were 0.022-0.046 µg/kg bw/day and 0.13-0.16 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the 'other foods' category, with total mean exposures ranging from 0.020-0.030 µg/kg bw/day. Overall, the current estimates of dietary exposure to mercury were well below the EFSA TWI for inorganic mercury at both mean and high level exposure. The mean and high level exposure estimates for the fish-based groups of the 'commercial infant foods' ('*meat and fish based foods and dishes*') and 'other foods' ('*fish*') categories were also below the TWI for methylmercury (equivalent to 0.19 µg/kg bw/day) (see Tables 3 to 6 in Annex B).

72. The Committee concluded that the current estimated dietary exposures to mercury were not of toxicological concern.

Nickel

73. The EFSA has recently published an opinion on nickel in food (EFSA, 2015). Although the IARC has classified nickel and nickel compounds as human carcinogens, the EFSA considered it unlikely that dietary exposure to nickel results in cancer in humans, and concluded that dietary exposure likely represents the most important contribution to the overall exposure to nickel in the general population. The non-carcinogenic adverse effects of oral exposure to nickel in humans include effects on the gastrointestinal, haematological, neurological and immune systems. Following acute exposure, the most reported effects were on the gastrointestinal and neurological systems. Exposure through skin or by inhalation may lead to nickel sensitization, and, although oral exposure is not known to lead to sensitization, oral absorption of nickel is able to elicit eczematous flare-up reactions in the skin of nickel-sensitized individuals.

74. The TDI value used by the COT in its risk characterisation of nickel was established by Haber *et al.,* 2017 and was derived specifically for the toddler population. A NOAEL of 2.2 mg/kg bw for pup bodyweight in the F1 generation was selected as the point of departure for derivation of a TDI. The default uncertainty factors of 10, each for interspecies and intraspecies differences, were selected and applied to the NOAEL of 2.2 mg/kg bw/day to derive a TDI of 22, rounded to 20 µg/kg bw/day.

75. For nickel, the total mean and high level exposures were 1.6-2.6 µg/kg bw/day and 3.9-5.6 µg/kg bw/day, respectively. The highest contributing food category to total mean exposure was the 'other foods' category, with total

mean exposures ranging from 0.92-1.5 µg/kg bw/day. All exposures were below the toddler-specific TDI of 20 µg/kg bw/day.

76. The Committee concluded that the current average and high level chronic dietary exposure estimates to nickel are unlikely to be of concern for UK infants and young children.

Secretariat

June 2017

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

First draft statement on the results of the 2014 survey of metals and other elements in infant foods

Limits of detection and limit of quantification (µg/kg) for each element and the various sample weights

1. Table 1 shows the LOD and LOQ for each element and various sample weights. The LOD was defined as three times the standard deviation of the signal from reagent blanks (taken through the entire analytical procedure) when subsequently corrected for sample weight and dilution. The LOQ was defined as ten times the standard deviation of the signal from reagent blanks (taken through the entire analytical procedure) when subsequently corrected for sample weight and dilution (FERA, 2014).

Table 1. LOD's and LOQ's (µg/kg) for each element and the various sample weights

LOD	Al	Cr	Mn	Fe	Ni	Cu	Zn	As	Se	Cd	Sn	Sb	Hg	Pb	I	iAs
0.25 g																6
0.5 g	100	20	20	300	40	20	160	1	2	1	16	5	1	2	10	
1.0 g	50	10	10	150	20	10	80	0.5	1	0.5	8	2.5	0.5	1	5	
2.0 g	25	5	5	75	10	5	40	0.3	0.5	0.3	4	1.3	0.3	0.5	2.5	
3.0 g	17	3	3	50	7	3	27	0.2	0.3	0.2	3	0.8	0.2	0.3	2	

LOQ	Al	Cr	Mn	Fe	Ni	Cu	Zn	As	Se	Cd	Sn	Sb	Hg	Pb	I	iAs
0.25 g																20
0.5 g	333	67	67	1000	133	67	533	3.3	6.7	3.3	53	17	3.3	6.7	33	
1.0 g	167	33	33	500	67	33	267	1.7	3.3	1.7	27	8.3	1.7	3.3	17	
2.0 g	83	17	17	250	33	17	133	1.0	1.7	1.0	13	4.3	1.0	1.7	8.3	
3.0 g	57	10	10	167	23	10	90	0.7	1.0	0.67	10	2.7	0.67	1.0	6.7	

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