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

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, to be published). 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. The Committee has provided comment on similar surveys in the past, with the most recent being a 2003 multi-element survey of infant foods[2] (COT, 2003a; FSA, 2003). The FSA has also completed a survey of metals in weaning foods and formulae for infants (FSA, 2006). 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

3. 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,

[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).
[2] COT (2003) 'Statement on a survey of metals in infant food' Available at: https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2003/statementmetals

such as nutrients and contaminants, to identify changes or trends in exposure and make assessments on the safety and quality of the food supply.

4. 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.

5. 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. The selection of 50 other foods was 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 other foods was a composite of 10 samples from different manufacturers and retailers.

Dietary exposure assessment

6. 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). These concentration data were used in conjunction with consumption data from the DNSIYC for exposure assessments. The DNSIYC was commissioned by the DH and the FSA to provide detailed information on the food consumption, nutrient intakes and nutritional status of infants and young children aged 4 up to 18 months living in private households in the UK. A total of 2683 individuals was surveyed. Consumption data for DNSIYC was collected from a 4 consecutive days estimated diary. Table 1 summarises the results of the exposure assessments carried out for each element in the three overarching food categories: infant formula, commercial infant foods and other foods.

Table 1. Summary of estimated chronic 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

Values are rounded to 2 significant figures (SF). Values are presented as estimates based on lower-bound (LB) to upper-bound (UB) concentration data. The

Food Category	Consumer (n = 2683*)	Dietary exposures in UK infants aged 4 to 18 months (µg/kg bw/day)															
		Essential elements						Non-essential elements									
		Cu	I	Fe	Mn	Se	Zn	Al	Sb	As	iAs	Cd	Cr	Pb	Hg	Ni	Sn
Infant Formula[(a)]	Mean	11	4.0	240	2.2	0.020-0.53	180	0.64-1.1	0-0.030	0-0.013	0-0.010	0-0.010	0.0029-0.10	0-0.015	0-0.0061	0.010-0.25	0-0.090
	97.5th percentile	37	14	760	6.9	0.060-1.8	600	2.0-3.6	0-0.10	0.012-0.040	0.010-0.030	0-0.022	0-0.32	0-0.046	0-0.020	0-0.90	0-0.31
Commercial Foods	Mean	5.7	0.28-0.33	81	19	0.14	51	12	0.010-0.020	0.13	0.04-0.062	0.06	0.30-0.39	0.030-0.040	0.0012-0.010	0.60-0.80	0.36-0.41
	97.5th percentile	26	1.6-1.7	370	78	0.67-0.70	250	54-55	0.040-0.10	0.58	0.19-0.26	0.27	1.4-1.8	0.13-0.17	0.010-0.030	2.6-3.6	1.9-2.1
Other Foods	Mean	16	5.3	160-170	63	0.8	160	19-20	0-0.050	0.78-0.79	0.090-0.10	0.19-0.20	0.26-0.48	0.040-0.070	0.020-0.030	0.92-1.5	38
	97.5th percentile	39	19	450-460	170	2.1	370	50-51	0-0.12	4.2	0.35-0.37	0.52	0.81-1.2	0.12-0.16	0.13-0.15	2.8-3.8	250
Total	Mean	37	11	550	85	1.1-1.6	440	33-34	0.0040-0.11	0.91-0.94	0.14-0.18	0.25-0.27	0.59-1.0	0.071-0.12	0.022-0.046	1.6-2.6	38
	97.5th percentile	69	23	1300	190	2.6-3.0	860	74-76	0.029-0.21	4.3-4.4	0.41-0.47	0.57-0.59	1.7-2.5	0.17-0.26	0.13-0.16	3.9-5.6	250

Cu: copper, I: iodine, Fe: iron, Mn: manganese, Se: selenium, Zn: zinc, Al; aluminium, Sb: antimony, As: arsenic (total), iAs: inorganic arsenic, Cd: cadmium. Cr, chromium, Pb: lead, Hg: mercury (total), Ni: nickel, Sn: tin

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.

(a) It should be noted that infant and follow-on formulae are supplemented with all of the essential elements measured in this survey. Minimum and maximum levels for each are detailed in an European Food Safety Authority (EFSA) Opinion (EFSA, 2014a).

Evaluation

7. This evaluation considers only those reported levels of elements above those necessary for normal nutrition and not where potential deficiencies in the elements were observed, since this is outside of the remit of the COT. Below are brief toxicological summaries and conclusions for each of the elements. Where possible, published health-based guidance values (HBGV) have been noted, and compared with the results of the current exposure assessments.

Essential elements

Copper

8. Copper is an essential trace element and forms a necessary component of many enzymes such as cytochrome c oxidase, amino acid oxidase, superoxide dismutase and monoamine oxidase. There is also evidence that it plays an important role in infant growth, host defence mechanisms, bone strength, red and white cell maturation, iron transport, cholesterol and glucose metabolism, myocardial contractility and brain development.

9. Deficiency may lead to effects 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).

10. Some individuals have inborn errors of copper metabolism. Individuals with Wilson disease accumulate abnormal levels of copper in the liver and the brain. This is due to mutation of a gene responsible for excretion of copper into the hepatic biliary tract. Menkes disease is caused by mutations of another gene responsible for copper transport. Copper absorption from the intestine is impaired leading to low levels in the brain, plasma and liver, copper accumulation in certain tissues and reduced copper-dependent enzyme activity. (Kaler, 2013). Indian childhood cirrhosis (ICC) is a fatal disorder related to accumulation of high levels of copper in the liver. It has been attributed to the practice of storing and boiling water in copper-rich pans, but there also appears to be an element of genetic predisposition in some cases (EVM, 2003: EFSA, 2006).

11. 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. Liver toxicity may occur in humans who accumulate large quantities of copper in this organ but this is as a result of genetically determined conditions (paragraph 10) and is not relevant to the general population (EVM, 2003).

12. The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) has established a 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 16000 µg/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 1000 µg/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 5000 µg/day (equivalent to 71 µg/kg bw/day when using a default body weight of 70 kg) which was based on a NOAEL of 10000 µg/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).

13. For 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 HBGVs at both mean and high level exposure.

14. The Committee concluded that the current estimated dietary exposures did not indicate excessive copper intakes and were not of toxicological concern for the general population (in those without inborn errors of copper metabolism; no risk assessment has been performed for such individuals).

Iodine

15. 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[3] for iodine of 70 and 90 µg/day for 7 to 11 month olds and 1 to 3 year olds, respectively (EFSA, 2014c). These are equivalent to approximately 14 and 7.5 µg/kg bw/day when default body

[3] An adequate intake is the average nutrient level consumed daily by a typical healthy population that is assumed to be adequate for the population's needs. Available at: https://www.efsa.europa.eu/en/glossary-taxonomy-terms

weights of 5 and 12 kg are used for 7 to 11 month olds and 1 to 3 year olds, respectively.

16. 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 could possibly 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 µg/kg bw/day (equivalent to approximately 1800 µg iodide/day) in which no clinical thyroid pathology occurred; an uncertainty factor of 3 was applied to this (SCF, 2002).

17. 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 (~20 %) the SCF UL at both mean and high level exposure, and would thus not be of toxicological concern.

18. The Committee concluded that the current estimated dietary exposures did not indicate excessive iodine intakes and were not of toxicological concern.

Iron

19. 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 two of the groups that are particularly vulnerable to iron deficiency (EVM, 2003).

20. There are certain individuals with in-born errors of iron metabolism. For iron, hereditary or genetic haemochromatosis is one of the most common single gene disorders. It results in excessive absorption of dietary iron, causing high levels of iron to accumulate in the body. This may cause organ damage, leading to clinical manifestations including diabetes, arthritis and cirrhosis of the liver (Scientific Advisory Committee on Nutrition (SACN), 2010). In addition, hereditary anaemias, such as thalassaemia or sideroblastic anaemia, frequently require treatment by repeated blood transfusions, which may result in too much iron and consequently toxicity (EVM, 2003).

21. 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 developed 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 50000 and 220000 µg/day, the frequency increasing at higher dose levels. For guidance purposes, a supplemental intake of approximately 17000 µg/day (equivalent to 1700 µg/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 lowest observed adverse effect level (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).

22. The United States Institute of Medicine (US IOM) has established a tolerable upper intake level (TUL) for supplemental non-haem iron of 40000 µg/day for infants and children. This TUL is based on a NOAEL of 40000 µg/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 4000 µg/kg bw/day based on an average body weight of 10 kg for infants aged 4 to 18 months (DH, 2013).

23. For 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.

24. The Committee concluded that the current estimated dietary exposures did not indicate excessive iron intakes and were not of toxicological concern (in those without inborn errors of iron metabolism; no risk assessment has been performed for such individuals).

Manganese

25. 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, and 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 characterised 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 available HBGVs are not considered reliable. In animals, manganese-deficiency exhibits as skeletal abnormalities and poor growth, reproductive deficits and defects in lipid and carbohydrate metabolism.

26. The EVM was unable to establish a safe upper level (SUL) for manganese. However they noted that for guidance purposes, based on the results of epidemiological studies of neurological effects associated with concentrations of manganese in drinking water, total manganese intakes of 12200 µg/day for the general population (equivalent to 1220 µg/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 derive these indicative reference intakes recorded water consumption or dietary manganese intake. The WHO established a TDI of 60 µg/kg body weight in the Guidelines for Drinking Water Quality (WHO, 2004). This was based on the upper range value of manganese intake of 1100 µg/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 established in relation to speciation.

27. 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.

28. The COT considered that the way in which the currently available HBGVs for manganese had been derived was not sufficiently robust for the risk characterisation of dietary exposure to this metal. Hence, the Committee concluded that, although exposure values were far below the HBGVs, whilst reassuring this was not an appropriate basis on which to conclude on the safety of such exposures. The Committee is due to revisit the issue of manganese HBGVs and exposures in this age group in a statement at a later date.

Selenium

29. 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 signs or 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).

30. The EVM has derived a SUL of 7.5 µg/kg bw/day for selenium based on a LOAEL of 910 µg/day, derived from an epidemiological dietary study in which signs of selenosis (prolonged prothrombin 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. 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 910 µg/day produced only slight effects and was close to a NOAEL (EVM, 2003).

31. 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 µg/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 µg/day. The NOAEL used was obtained 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).

32. For selenium, the total mean and high level exposures were 1.1-1.6 µg/kg bw/day and 2.6-3.0 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 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.

33. The Committee concluded that the current estimated dietary exposures did not indicate excessive selenium intakes and were not of toxicological concern.

Zinc

34. 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. Acrodermatitis enteropathica is a rare inherited condition which can result in severe zinc deficiency. The deficiency is caused by the inability to absorb zinc from the intestine. The symptoms are similar to those of dietary zinc deficiency (NHS, 2017).

35. 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 300-1000 µg/kg bw; clinical studies in which up to 600000 µg of zinc sulphate (equivalent to 200000 µg elemental zinc) had been administered daily in divided doses for a period of several months were used as the basis for establishing the PMTDI (FAO/WHO, 1982b). The EVM has derived a SUL of 25000 µg/day (equivalent to 2500 µg/kg bw/day for a 10 kg infant) based on a LOAEL of 50000 µg/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 7000 µg/day for 1 to 3 year olds (~ 580 µg/kg bw/day, based on a 12 kg body weight) from an adult UL of 25000 µg/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 50000 µg/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).

36. For 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.

37. The Committee concluded that the current estimated dietary exposures did not indicate excessive zinc intakes and were not of toxicological concern.

Non-essential elements

Aluminium

38. In 2011, 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 1000 µg/kg bodyweight (bw), and established a new

PTWI of 2000 µg/kg bw. This new PTWI was established using a NOAEL of 30000 µg/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).

39. For aluminium, the total mean and high level exposures were 33-34 µg/kg bw/day (231-238 µg/kg bw/week) and 74-76 µg/kg bw/day (518-532 µg/kg bw/week), 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 (133-140 µg/kg bw/week). Overall, the current estimates of dietary exposure to aluminium were well below the JECFA PTWI at both mean and high level exposures.

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

Antimony

41. The WHO has establised a TDI of 6 µg/kg bw (WHO, 2003). This was based on a NOAEL of 6000 µg/kg bw/day 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).

42. 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.

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

Arsenic

44. 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).

45. 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, albeit indirectly, and a known human carcinogen (COT, 2008; COT, 2016).

46. 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

47. 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).

48. EFSA, and JECFA have published risk assessments on exposure to inorganic arsenic in food. Based on the available epidemiological studies, 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, JECFA calculated a BMDL of 3.0 µg/kg bw/day for a 0.5% increased incidence of lung cancer in humans (FAO/WHO, 2011a).

49. 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.

50. 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 of low concern (COT, 2016).

The total mean exposures to inorganic arsenic were 0.14-0.18 µg/kg bw/day. 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. This range of exposures results in an MOE of 20 (rounded to 1 significant figure (SF)). As this is greater than 10, these exposures would be considered of low concern. The total high level exposures were 0.41-0.47 µg/kg bw/day, resulting in 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.

51. The Committee concluded that, although the current average dietary exposures to inorganic arsenic would be considered of low concern, high level exposures could present a small risk to consumers.

Cadmium

52. 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 (BMD) modelling 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. EFSA noted that because of the long half-life of cadmium in the human body, an HBGV should be set on a weekly rather than a daily basis, and hence established a tolerable weekly intake (TWI) of 2.5 µg/kg bw. 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 such exceedances are unlikely to lead to adverse effects on the kidney, this clearly demonstrates the need to reduce exposure to cadmium at the population level (EFSA, 2009b).

53. In contrast to the EFSA TWI, 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; 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 the present risk characterisation the EFSA TWI, which is the lower of the HBGVs, 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.

54. 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.

55. Although the EFSA TWI of cadmium was exceeded by infants in some cases, these exceedances were small in magnitude (by 60% maximum) and would not be expected to remain at this level over the decades of bioaccumulative exposure necessary to reach the reference value used by EFSA in setting the HBGV. This was therefore not a major cause for concern. However, considering the cumulative nature of cadmium toxicity, it would be prudent to minimise the exposure of infants to as low a level as is reasonably practicable.

Chromium

56. 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 anthropogenic 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 signs observed were impaired glucose tolerance and glucose utilisation, weight loss, neuropathy, elevated plasma fatty acids, depressed respiratory quotient and abnormalities in nitrogen metabolism (Expert Group on Vitamins and Minerals (EVM), 2003).

57. The toxicity of chromium varies with its 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 is not readily sequestered into cells. In contrast to Cr (III), Cr (VI) is able to cross cellular membranes. 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, 2014b).

58. In 2014 EFSA established a TDI for Cr (III) of 300 µg/kg bw based on the lowest NOAEL identified in a chronic oral toxicity study in rats. In their assessment, EFSA assumed that all chromium in food was present as Cr (III); 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. EFSA also assumed that all of the chromium present in drinking water was Cr (VI) (EFSA, 2014b), 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.

59. Speciation was not determined 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.

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

Lead

61. 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.

62. 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).

63. 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 resulted in 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.

64. 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

65. 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 and distributed more widely in the body (WHO, 2006).

66. 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 112 µmg/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 the fact that dosing was for only 5 days per week, this value resulted in a $BMDL_{10}$ of 60 µg/kg bw/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).

67. The TWI for methylmercury was based on a methylmercury concentration in maternal hair of 11500 µg/kg, that was the mean of the apparent no observed effect level (NOEL) from a Seychelles nutrition cohort at 9 and 30 months (11000 µg/kg maternal hair), and the $BMDL_{05}$ from a Faroese cohort at age seven years (12000 µg/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 for inter-individual variability, resulting in a TWI of 1.3 µg/kg bw. In their assessment, 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 the present assessment, total dietary exposures have been compared to the TWI of 4 µg/kg bw for inorganic mercury. Exposures for fish-based categories have been compared to the methylmercury TWI of 1.3 µg/kg bw.

68. For mercury, the total mean and high level exposures were 0.022-0.046 and 0.13-0.16 µg/kg bw/day (0.15-0.32 and 0.91-1.1 µg/kg bw/week), 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 (0.14- 0.21 µg/kg bw/week). 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.

69. The mean and high level exposure estimates for the fish-based groups of the 'commercial infant foods' ('*meat and fish based foods and dishes*') were 0- 0.0030 and 0- 0.020 µg/kg bw/day (0- 0.021 and 0- 0.14 µg/kg bw/week), respectively. In the 'other foods' ('*fish*') categories the mean and 97.5th percentile exposures were 0.020 and 0.13 µg/kg bw/day (0.14 and 0.91 µg/kg bw/week), respectively. These values were all below the TWI for methylmercury.

70. The Committee concluded that the current estimated dietary exposures to inorganic mercury and methylmercury were not of toxicological concern.

Nickel

71. 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, acute oral absorption of nickel is able to elicit eczematous flare-up reactions in the skin of nickel-sensitized individuals.

72. The TDI value used by the COT in its risk characterisation of nickel was established by Haber *et al.,* 2017 and was established 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 establishment of the TDI. 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 establish a TDI of 22, rounded to 20 µg/kg bw/day.

73. 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.

74. The Committee concluded that the current estimated chronic dietary exposures to nickel were not of toxicological concern for the general population.

75. It is not possible to determine whether there is a risk of sensitisation to nickel in infants and young children exposed to nickel through the diet. The effect from ingestion of an acute exposure of nickel in sensitised individuals could be a dermal reaction, which although unpleasant is not life-threatening.

Tin

76. 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).

77. 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. In some sub-chronic feeding studies haematological changes have been observed in rats, but no such effects were recorded in chronic carcinogenicity studies and in one multi-generation reproduction study, or it was noted that the observed changes were transient. Pancreatic atrophy has also been observed in sub-chronic studies in rats (EVM, 2003).

78. 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 based on 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 identified. 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).

79. 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 the 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.

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

Overall conclusion

81. The Committee assessed the chronic dietary exposures calculated for the 15 metals and other elements measured in a range of foodstuffs for infants and ‘other foods’ eaten by infants and young children.

82. The Committee concluded that the current estimated dietary exposures did not indicate excessive intakes of copper, iodine, iron, selenium, or zinc, and that intakes of these and of chromium, aluminium, antimony, mercury, nickel and tin were not of toxicological concern.

83. Although manganese exposures were below the available HBGVs the Committee considered that the way in which the HBGVs were derived was not robust. Therefore, it would not be appropriate to use these HBGVs to characterise the potential risks from exposure to manganese.

84. Not all calculated exposures for all elements were below an HBGV. In some instances cadmium exposures exceeded the TWI, but these were small in magnitude and would not be expected to remain at these levels over the decades of bioaccumulative exposure necessary to reach the reference value used by EFSA in setting the HBGV. On the basis of the MOEs calculated, the Committee considered that current average dietary inorganic arsenic exposures would be of low concern but high level exposures could present a small risk to consumers. The Committee also 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.

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Abbreviations:

Al	aluminium
ALARP	as low as reasonably practicable
As	arsenic (total)
BMD	benchmark dose
BMDL	95% lower confidence limit of the BMD
bw	bodyweight
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Cd	cadmium
Cr	chromium
Cu	copper
DH	Department of Health
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
FAO	Food and Agriculture Organization
Fe	Iron
FSA	Food Standards Agency
FSIS	Food Surveillance Information Sheet
HBGV	health based guidance value
Hg	mercury (total)
I	iodine
IARC	International Agency for Research on Cancer
iAs	inorganic arsenic
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IQ	Intelligence quotient
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
LOAEL	lowest observed adverse effect level
mg	milligram
Mn	manganese
MOE	margin of exposure

NHS	National Health Service
Ni	nickel
NOAEL	no observed adverse effect level
NOEL	no observed effect level
Pb	lead
PMTDI	provisional maximum tolerable daily intake
PTMI	provisional tolerable monthly intake
PTWI	provisional tolerable weekly intake
SACN	Scientific Advisory Committee on Nutrition
Sb	antimony
SCF	Scientific Committee on Food
Se	selenium
SF	significant figure
Sn	tin
SUL	safe upper level
TDI	tolerable daily intake
TUL	tolerable upper level
TWI	tolerable weekly intake
UL	upper level
US IOM	United States Institute of Medicine
WHO	World Health Organization
Zn	zinc

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