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

Discussion paper on the potential risks from copper in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Introduction

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. The SACN is examining the nutritional basis of the advice. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants, most of which has been completed, and young children. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

2. This discussion paper provides estimated copper exposures for infants and young children in the UK aged 0 to 12 months and 1 to 5 years, respectively.

Background

3. Copper a malleable and ductile red-gold transition metal, atomic number 29, relative atomic mass 63.55, that exists in various mineral forms as Cu^{+} and Cu^{++} salts and is present throughout the environment. It has a wide range of uses including, the production of pesticides, ceramics and glass, plumbing , paints and pigments, and is present in a wide range of industrial and consumer products such as electrical equipment and coinage.

4. Copper is an essential trace element, being involved in a number of vital enzymes, such as cytochrome c oxidase, the final complex of the mitochondrial electron transport chain, and superoxide dismutase, involved in the reduction of oxygen free radicals and hence oxidative stress and other redox enzymes, including lysyl oxidase. Copper, complexed in ceruloplasmin, is involved in iron transport.

5. The general population is primarily exposed to copper via food and drinking water.

<u>Toxicokinetics</u>

Absorption

6. Copper in the lumen of the gut is largely bound to amino acids. Copper is taken up by cells of the gut wall by the action of the copper transporting protein Ctr1, for which the Cu(I) form is the substrate. (Nose *et al* 2006). Ctr1 expression appears to be regulated by hypoxia-inducible factor 2α (HIF 2α).(Pouvali *et al*,2012)

7. Copper , iron and zinc in the diet are known to interact with each other's intestinal absorption such that excessively high dietary levels, as may be caused by use of dietary supplements, may inhibit the uptake of one or more of these essential minerals (Arredondo *et al*, 2006)

Distribution

8. In the gut, the major pathway of transport into the portal circulation is via a p-type Cu-ATPase, ATP7A, in the Golgi apparatus. The Cu-ATP7A complex translocates to the epithelial basal membrane and delivers the copper into the portal vein. If ATP7A is deficient, copper is not released into the circulation, resulting in the systemic copper deficiency seen in Menkes disease. In the portal circulation, copper is bound to histidine, albumin or possibly transcuprein and transported to the liver. It is taken up into the liver through Ctr1 and incorporated into ceruloplasmin, which is then secreted into the systemic circulation. if it is not incorporated into ceruloplasmin, it is stored as metallothionein or incorporated in Cu-dependent enzymes.

9. ATP7A is poorly expressed in the liver so, in excess, copper binds to another p-type ATPase, ATP7B, which delivers copper into the biliary canalculi for excretion in the bile. If ATP7B is deficient then copper accumulates primarily in the liver (and also in the brain, where ATP7A is also poorly expressed), since translocation for excretion is inhibited, leading free copper accumulation and the symptoms of Wilson's disease. (EFSA 2015)

Metabolism

10. Copper is one of the metallic components in the cytochrome c oxidase complex in the mitochondrial inner membrane that is the final cytochrome complex that reduces oxygen to water. The property of copper to alternate between +1 and +2 oxidation states is also its function in redox enzymes such as amine oxidases, lysyl oxidases, dopamine β hydroxylase and superoxide dismutase.(EFSA 2015)

11. The protein ceruloplasmin, when fully activated by the binding of 6 copper atoms, acts as a ferredoxin, oxidising Fe^{++} in the blood to Fe^{+++}, for uptake into cells by transferrin. Thus deficiency in copper can also lead to iron deficiency.(Roeser *et al* 1970)

Excretion

12. Excess copper is bound to the ATPase ATP7B in the liver and is excreted mainly in the bile. Once in the bile, copper appears to be bound to bile salts and is no longer bioavailable.(ATSDR 2004)
https://www.atsdr.cdc.gov/toxprofiles/tp132.pdf

Toxicology

Acute toxicity

13. High levels of oral copper can cause acute gastrointestinal effects nausea, vomiting and diarrhoea. This may be a direct irritant effect of copper in water and is not so apparent when copper is present in the food matrix (SCF, 2003).

14. Intake of excess amounts of copper or its salts can also be through damaged skin. Higher doses can lead to haemolytic anaemia and anuria, which may be fatal. (EFSA 2015)
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Chronic effects

15. Copper is an essential trace element, showing detrimental effects at low and high chronic doses. Copper deficiency causes anaemia, low white blood cell count, muscle weakness, myopathy, damage to peripheral nerves and rarely optic neuropathy. Deficiency can be acquired by suffering from diseases affecting the GI tract, such as chronic diarrhoea or tropical sprue, high intake of zinc, gastric surgery or severe childhood protein deficiency. Deficiency can also be inherited in a condition called Menkes syndrome, where a mutation in the *ATP7A* gene on the X chromosome leads to reduced Cu uptake in 100,000 to 250,000 live births. Symptoms include muscle weakness, reduced growth, reduced intellectual capacity, pallor and characteristic kinked steely-textured hair.(EFSA 2015)

16. Acquired deficiency can be treated by dietary supplementation with copper sulphate and supportive measures. Menkes syndrome is treated with copper histidine but infants with this condition rarely survive past 3 years of age.

17. Wilson's disease, a copper storage disease caused by a mutation in the *ATP7B* gene, reduces copper excretion and causes deposition of the metal in the tissues, notably the iris, liver and brain, and can lead to cirrhosis. If Wilson's disease is diagnosed early and treatment with a copper chelating agent such as D-penicillamine is begun and continued then patients improve and may be without lifelong symptoms. (Coffey *et al* 2013)

18. Other characterised copper-related diseases include Indian Childhood Cirrhosis and Childhood Idiopathic Copper Toxicosis, both of which appear to be largely linked to inadvertent excess intake, although there may be some genetic predisposition in the former (SCF, 2003)

19. Copper binding to the Huntington's disease-associated protein huntingtin has been proposed as participating in the cytotoxic effects of this protein and hence affecting the severity of the disease in predisposed individuals.(Fox *et al* 2007)

20. Copper has been suggested as a participant in the oxidation of polychlorinated biphenyls (PCBs) to produce toxic and carcinogenic metabolites (Oakley *et al*, 1996).

Oxidative stress

21. Free copper ions are toxic by virtue, like other metals, of initiating oxidative stress by the generation of reactive oxygen species through the Haber-Weiss reaction (Gaetke, 2003):

$^{*}O_2^{-}$ (superoxide) + Cu^{2+} -> O_2.+ Cu^{+}

$Cu^{+} + H_2O_2 \rightarrow Cu^{2+} + OH^{-} + OH\cdot$

The hydroxyl radical then initiates the oxidative damage.

22. Conversely, since copper in required for the activity of superoxide dismutase, deficiency of copper may also indirectly lead to oxidative stress and the development of diseases such as non-alcoholic fatty liver disease (Antonucci *et al*, 2017)

Carcinogenicity

23. The IARC evaluation (1987) on copper (II) 8-hydroxyquinoline allocated it to Group 3: "Not classifiable as to their carcinogenicity to humans", based on inadequate evidence in experimental animals". Magaye *et al* (2012) reviewed the evidence for carcinogenicity of copper nanoparticles. Although DNA damage was noted when cells were exposed to copper particles in the nm size range *in vitro* and a variety of degenerative and inflammatory effects were observed in the lungs, liver, kidneys and spleen of rodents exposed to Cu-nanoparticles by various routes, none of the *in vivo* studies reported carcinogenicity.

Expert opinions

24. An expert opinion on exposure to copper in food and drinking water has been published by the European Food Safety Authority's (EFSA) Panel on Contaminants in the Food Chain (CONTAM) (EFSA, 2015). The EFSA Scientific Committee on

Food (SCF) derived an upper limit in their review of 2003. The EVM reviewed copper in their report on metals in the diet (2003). The World Health Organization (WHO) has reviewed exposures to copper via drinking water as part of the development of their ‘Guidelines for Drinking Water Quality’ (WHO, 1982).

The EFSA Scientific Committee on Food (SCF)

25. *SCF* has set an upper level (UL) for copper of 1 mg/day for 1-3 year olds; if applied to the age group assessed in their survey, this is equivalent to approximately 100 µg/kg bw/day based on an average body weight of 10 kg for infants aged 4 to 18 months (DH, 2013). This UL was extrapolated from an UL for adults of 5 mg/day 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, 2003).

http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf

WHO

26. The Joint FAO/WHO Committee on Food Additives (JECFA, 1982) stated that *“…the level of copper in food meets the nutritional requirements (2-3 mg/day for adults; 0.5-0.7 mg/day for infants). Copper is not carcinogenic in either humans or animals, and copper salts are not embryotoxic in rodents. Highly-exposed populations do not appear to be adversely affected, nor does copper appear to be a cumulative toxic hazard for man, except for individuals with Wilson's disease. On this basis, the previous tentative evaluation of a maximum daily load of 0.5 mg/kg bw was reaffirmed as a provisional value for a maximum tolerable intake of 0.5 mg/kg bw per day from all sources. “*

A Provisional Maximum Tolerable Daily Intake: (PMTDI) of 0.5 mg/kg bw per day was derived

EVM

27. The Expert Group on Vitamins and Minerals stated in their statement of 2003 (https://cot.food.gov.uk/sites/default/files/vitmin2003.pdf):

“*A NOAEL of 16 mg/kg bw/day was identified in a well-reported sub-chronic toxicity study in rats. Higher doses resulted in damage to the forestomach, kidney and liver. If uncertainty factors of 10 for inter-species variation and 10 for intra-individual variation (total 100) are applied to this, a Safe Upper Level of 0.16 mg/kg bw day for total intake of copper is derived. This is equivalent to 10 mg/day in a*

60 kg adult. This is consistent with the data from small scale human studies which suggest that up to 10 mg/day supplemental copper may be without adverse effect. The worst-case maximum estimated daily exposure from food and water is 9 mg/day copper suggesting that there is a margin of 1 mg/day for supplementation or other additional intake."

The tolerable Upper Level (UL) of 100 µg/kg bw/day derived by SCF and the Safe Upper Level (SUL) of 0.16 mg/kg bw/day or 160 µg/kg bw/day, derived by the EVM, have been used in this discussion paper for comparison with one another.

Copper exposures in infants aged 0 to 12 months and young children aged 1 to 5 years

Sources of copper exposure

Human breast milk

28. Dorea (2000) reported concentrations ranging from about 200 to 1 000 µg/L over the course of lactation, with most values in the order of 300–400 µg/L. (cited by EFSA, 2015).

29. As part of the 2004 SUREmilk study, levels of copper were measured in breast milk from t women in the UK. In 113 samples, copper was determined at levels ranging from 68 to 896 µg/kg (Woolridge *et al*., 2004).

30. The COT[1] noted that the SUREmilk samples were collected primarily to explore the viability of breast milk collection methods and did not constitute a rigorous survey. Nevertheless, it was possible to draw the conclusion that the estimated intakes of metals and other elements associated with the highest detected concentrations in the breast milk samples did not raise toxicological concerns. From reports from other countries, average values vary over three orders of magnitude, from approximately130 µg/l to 830 g/l; reported maximum values range from 209 to 895µg/l Cu. Table 1 gives a range of recent measured levels of Cu in breast milk.

Table 1. Concentrations of copper in breast milk available from the published literature

Country	Number of	Average concentration	Minimum concentration	Maximum concentration	Reference

[1] http://cot.food.gov.uk/sites/default/files/cot/cotsuremilk.pdf

	samples	(µg/L)	(µg/L)	(µg/L)	
UK	104	-	68	896	Woolridge *et al.*(2004)
USA	20	169.5±63.1	71.5	317.1	Klein *et al (2017)*
Namibia	6	130.9±63.5	55.6	208.8	Klein et al (2017)
Poland	23	186.9±48.1	83.0	252.4	Klein et al (2017)
Argentina	21	211±99.5	89.5	419.1	Klein et al (2017)
France	100	451 ± 102			Pineau *et al* (2015)
Sweden	60	471±75	327	670	Björklund *et al* (2012)
Poland	323	137±92	25	455	Winiarska-Mieczan (2014)

31. In the absence of a suitable UK study of copper in breast milk, the Swedish study of Björklund *et al* (2012) has been used in exposure assessment and risk characterisation in this paper since it gives the most conservative values.

Infant formulae and food

32. Concentrations of copper have recently been measured in an FSA survey of metals and other elements in infant formulae and foods (e.g. commercial infant foods) (referred to as the Infant Metals Survey, FSA 2016a), and in the composite food samples of the 2014 Total Diet Study (TDS), FSA 2016b.

Food contact materials

33. The migration of copper from food contact materials could represent an additional source for the presence of this metal in food and drinking water.

34. Demont *et al (*2012) studied the influence of the pigments used and the extraction technique (effect of temperature, pH and type of extracting acid) on the migration of copper and 17 other metals from the surface of glazed ceramic pots (volume 650±50ml). Copper migration increased with increasing temperature (20 – 85^{o}C), time of exposure (0 – 3 hours) and with increasing basicity of the extracting acid (acetic < malic< citric).

35. Copper migration from copper carbonate pigment into 4% acetic acid was linear at 20^{o}C and became increasingly biphasic with rising temperature with a sharp increase up to 30 minutes and thereafter a slower rise. Three hours at 20^{o}C led to a

final concentration of approximately 4 mg/l and at 85^{o}C approximately 14 mg/l in the acid.

Drinking water

36. The primary source of copper in drinking water is leaching from copper plumbing. The UK Drinking Water Authority says that in general the concentration of copper in domestic drinking water is low and within the limit set by the EU and WHO (see below). Over time of use a layer of copper oxide forms on the inner surface of the pipes (red cuprous oxide in cold conditions, black cupric oxide in hot conditions), which is overlaid by a layer of green copper hydroxycarbonate. These layers reduce the release of copper into the water. http://www.fwr.org/copper.pdf

37. In houses with new pipes that have not developed a passivating layer of oxide on their surface, levels after a period of inactivity, such as overnight or over a week end, may exceed the guidance level. Where such an effect may occur it is recommended that the water in the pipes is flushed out for a few minutes before it is taken for drinking. If the pH of the water falls then the protective oxide layer is corroded away and the concentration of free copper in the water increases. http://dwi.defra.gov.uk/consumers/advice-leaflets/copper.pdf

38. EU legislation sets a value of 2 mg/L for copper in water intended for human consumption (Directive 98/83/EC). The WHO has also established a guidance level of 2 mg/L for copper in drinking water (WHO, 2004).

http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:330:0032:0054:EN:PDF

http://www.who.int/water_sanitation_health/dwq/chemicals/copper.pdf

39. Levels of copper in drinking water in 2016/2017 from England and Wales, Northern Ireland and Scotland were provided by the Drinking Water Inspectorate (DWI), Northern Ireland Water and the Drinking Water Quality Regulator (DWQR) for Scotland, respectively. Median and 97.5th percentile values calculated from these data are shown in Table 2. These values have been used to calculate exposures to copper from drinking water in combination with exposures from food.

Table 2. Median and 97.5th percentile concentrations (µg/L) of copper in water across the UK for 2016/2017

Country	Number of samples	Limit of Detection (mg/L)	Median concentration (mg/L)	97.5th Percentile concentration (mg/L)
England and Wales	12812	<0.0006 - <1*	0.0143	0.28
Northern Ireland	393	0.001	0.005	0.08
Scotland	16638	0.004	0.01	0.22

* The DWI noted that the water companies had reported a range of LODs that varied with the analytical method used, and clarified that the relevant drinking water regulations specify that the LOD must not be more than 10% of the prescribed value (2 mg/L for copper).

Environmental

Soil

40. Copper is present at about 0.1 mg/kg in the Earth's upper continental crust (Rawlins et al., 2012). It occurs naturally at high levels in some types of rock, and is released to soils from anthropogenic activities such as smelting. A total concentration of 10 mg/kg (for sandy loam soil) was adopted as the Soil Guideline value for residential soils (Environment Agency, 2009) and is well above the concentration found in most soils.

41. Concentrations of copper were measured in 5,670 topsoil (from a depth of 0 to 15 cm) samples collected between 1978 and 1982 in England and Wales. Samples were analysed 30 years later (Rawlins et al., 2012). The median and 90th percentile concentrations were reported as 19 and 38 mg/kg, respectively.

42. In 2012 and 2013, Defra published normal background concentrations (NBCs) for copper in soil in England and Wales (Defra, 2012 and 2013). An NBC is the 95th percentile upper confidence interval of the available data; it is defined as a contaminant concentration that is seen as typical and widespread in top-soils (depth 0 - 15 cm). In order to establish meaningful NBCs, the available soil data were grouped in domains (e.g. principal, urban, and ultrabasic) that were defined by the most significant controls on a contaminant's high concentrations and distribution. The NBCs for each domain in England and Wales were published following a Defra-commissioned BGS project to define the typical background concentrations for soil contaminants.

43. As part of the BGS project, summary statistics were derived from topsoil data from 2 or 3 core datasets held for England and Wales (Ander et al., 2012 and 2013). Although the NBCs and summary statistics were derived for several domains for England and Wales, the most significant domain for each country was the principal

domain. The principal domains are areas which do not contain significantly elevated levels of copper. Overall, for England and Wales, the area covered by the principal domains constitutes approximately 99% and 94% of each country respectively. The summary statistics reported for the principal domain in England were a median of 21 mg/kg and a 95th percentile of 62 mg/kg (n = 34504 samples). The statistics reported for the same domain in Wales were a median of 22 mg/kg and a 95th percentile of 43 mg/kg (n = 966 samples).

44. Between 2004 and 2006, 6,862 samples of rural surface soil (depth 5 - 20cm) were collected from sites in Northern Ireland as part of the Tellus survey. The samples were collected on a systematic basis and following the protocols set out in the BGS's Geochemical Baselines Survey of the Environment (G-BASE) programme. The median and 95th percentile concentrations derived from the data are 32 and 105 mg/kg, respectively.

45. The median value of 32 mg/kg and the highest 95th percentile concentration value for copper in soil from the Tellus survey (105 mg/kg) have been used to estimate exposures to soil in this assessment.

Air

46. Data from 25 air sampling sites across the UK have been collected by Defra (https://uk-air.defra.gov.uk/data/non-auto-data?uka_id=UKA00168&view=data&network=metals&year=2016&pollutant=262#view)..The data for 2016 have yielded lowest and highest median values of 0.43 and 54 and lowest and highest 99th percentiles of 0.77 and 160 ng copper/m^3 across the sites.

Dust

47. Harrison (1979) determined the levels of copper and other metals in outside and domestic dust samples collected in Lancaster, UK. "Available" copper levels in domestic dust, i.e. those extractable from the dust by 0.07N HCl to mimic gastric acid, were 151 ± 72 μg/g (Mean ± SD, n = 4, range 94 – 253 μg/g).

48. Culbard *et al* (1988) determined levels of copper and other metals in dust from various environments, including domestic dust from seven London boroughs (N = 683, geometric mean = 208 mg/kg, range = 9 – 5300 mg/kg), the Cu-Sn mining towns of Camborne and Hayle (N = 72, geometric mean = 662 mg/kg, range = 99 – 8000 mg/kg) and other geochemical hotspots across England and Wales (N = 494, geometric mean = 254 mg/kg, range = 33 – 74400 mg/kg).

49. Data from the London boroughs will be used in this discussion paper.

Exposure assessment

50. Consumption data (on a bodyweight basis) from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), and the National Diet and

Nutrition Survey Rolling Programme (NDNS) (Bates *et al.*, 2014) have been used for the estimation of dietary exposures for ages 4 to 18 months, and 18 to 60 months respectively. Bodyweight data used in the estimation of other copper exposures are shown in Table 3 below.

51. Thorough exposure assessments have been performed for the dietary sources of exposure to copper. The assessments for the non-dietary sources of exposure (i.e. dust, soil and air) have been included to give a more holistic view of exposures, but are not as thorough as the focus of this statement is the diet of infants and young children.

Table 3. Average bodyweights used in the estimation of copper exposures

Age group (months)	Bodyweight (kg)
0 to <4	5.9[a]
4 to <6	7.8[b]
6 to <9	8.7[b]
9 to <12	9.6[b]
12 to <15	10.6[b]
15 to <18	11.2[b]
18 to <24	12.0[c]
24 to <60	16.1[c]

[a] DH, 1994
[b] DH, 2013
[c] Bates *et al*., 2014

Infants (0 to 12 months)

52. No consumption data were available for exclusive breastfeeding in infants aged 0 to 6 months. Therefore, the default consumption values used by the COT in other evaluations of the infant diet of 800 and 1200 mL for average and high level consumption have been used to estimate exposures to copper from breastmilk. These estimates were based on minimum and maximum copper concentrations of 327 and 670 µg/L, respectively. The ranges of exposure to copper in exclusively breastfed 0 to 6 month olds were 37 to 67 and 69 to 140 and µg/kg bw/day in average and high level consumers respectively (Table 4).

Table 4. Estimated copper exposure from exclusive breastfeeding in 0 to 6 month old infants, with breast milk containing copper at 3.1 or 19.4 µg/L.

Copper concentration (µg/L)	Exposure (µg/kg bw/day)			
	Average consumer (800 mL/day)		High consumer (1200 mL/day)	
	0 to <4 months	4 to <6 months	0 to <4 months	4 to <6 months
327	44	34	67	50
670	91	69	140	100

Values rounded to 2 significant figures (SF)

53. Data on breast milk consumption for infants aged 4 to 18 months were available from the DNSIYC and the NDNS and have been used to estimate exposures at these ages (Table 5), based on a minimum and maximum concentration of 3.1 and 19.4 µg/L, respectively . There were too few records of breast milk consumption for children older than 18 months in the NDNS to allow a reliable exposure assessment, and breast milk is expected to contribute minimally in this age group.

54. Mean exposures to copper for 4 to 18 month olds were 0.078 to 1.8 µg/kg bw/day, and 97.5th percentile exposures were 0.16 to 3.0 µg/kg bw/day (Table 5).

Table 5. Estimated copper exposure in 4 to 18 month old infants from breast milk, containing copper at 327 and 19.4 µg/L.

Exposure (µg/kg bw/day)	Age group (months)				
	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18
Mean @ 327 µg/L	30	22	12	10	8.3
97.5th percentile @ 327 µg/L	51	52	38	25	17
Mean @ 640 µg/L	59	43	24	19	16
97.5th percentile @ 640 µg/L	99	100	74	48	33

Values rounded to 2 SF

Infant formulae and complementary foods

55. Copper exposure estimates for this category were derived using occurrence data from the Infant Metals Survey (FSA, 2016a). Exposure estimates for 0 to 6 month olds were calculated for exclusive feeding on infant formulae using the default consumption values of 800 and 1200 mL (Table 6). Consumption data from the DNSIYC were used to estimate exposures for 4 to 12 month olds (DH, 2013)

56. In 0 to 6 month olds, exposures to copper from ready-to-feed formula were 39 to 51 µg/kg bw/day in average consumers, and 58 to 76 µg/kg bw/day in high level consumers. Exposures to copper calculated for reconstituted formula incorporating the water concentration from the TDS, and the highest median and 97.5th percentile concentrations for copper in water reported in Table 6 were 47 to 93 µg/kg bw/day in average consumers, and of 70 to 140 µg/kg bw/day in high level consumers (Table 6).

Table 6. Estimated average and high level exposures to copper from exclusive feeding on infant formulae for 0 to 6 month olds.

Infant Formula	Copper Exposure (µg/kg bw/day)			
	0 to <4 months		4 to <6 months	
	Average consumer (800 mL/day)	High level consumer (1200 mL/day)	Average consumer (800 mL/day)	High level consumer (1200 mL/day)
Ready-to-Feed [a]	51	76	39	58
Dry Powder [b, c]	61	92	46	69
Dry Powder [c] + TDS water of 20 µg/L [d]	63	95	48	72
Dry Powder [c] + median water of 10 µg/L [d]	62	94	47	70
Dry Powder [c] + 97.5th percentile water of 280 µg/L [d]	93	140	70	110

Values rounded to 2 SF
[a] Exposure based on first milk infant formula copper concentrations of 376 µg/L
[b] Exposure does not include the contribution from water
[c] Exposure based on first milk dry infant formula using copper concentrations of 3007 µg/kg
[d] Calculated assuming reconstituted formula comprises 85% water

57. Total upper-bound (UB) mean exposures (excluding water) to copper from infant formulae, commercial infant foods, and other foods, for 4 to 12 month olds were 37 to 40 µg/kg bw/day, and 97.5th percentile exposures were 62 to 72 µg/kg bw/day. Detailed exposure assessments for 4 to 18 month old infants and young children are provided in Annex A. Total mean and 97.5th percentile exposures were also calculated using the highest median and 97.5th percentile concentrations for copper in water reported in Table 7. The resulting total mean and 97.5th percentile exposures indicated that levels of copper in water made a minimal contribution (< 5%) to total exposure (Table 7).

Table 7. Estimated exposures to copper from infant formulae, commercial infant foods and other foods for 4 to 12 month olds.

Food	Copper Exposure (µg/kg bw/d)					
	4 to <6 Months (n=116)		6 to <9 Months (n=606)		9 to <12 Months (n=686)	
	Mean	97.5th	Mean	97.5th	Mean	97.5th
Infant formula	24	53	19	41	14	30
Commercial infant foods	5.7	21	8.3	29	7.7	31
Other foods	5.1	24	11	34	16	40
UB Total (excl. water)	37	72*	40	68*	38	62*
Total, inc. tap water+ at highest Median conc. 10 µg/L	37	72	40	68	38	62
Total, inc. tap water+ At highest 97.5th percentile conc. 280 µg/L	38	73	43	71	41	65

Values rounded to 2 SF
+Exposure assessments taking account of contribution of drinking water were derived by multiplying mean water consumption for age by either the highest median or highest 97.5th percentile copper concentration from Table 2
* Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories

Children aged 12 to 18 months

58. Estimated exposures to copper from food for children aged 12 to 18 months were calculated using occurrence data from both the Infant Metals Survey (FSA, 2016a), and the 2014 TDS (FSA, 2016b). The exposure data derived from the Infant Metals Survey allow estimation of copper exposure in infant formula, commercial infant foods and the most commonly consumed adult foods (‘other foods’) as sold, whereas the results from the TDS are based on analysis of food that is prepared as for consumption. In addition, the Infant Metals Survey included analysis of infant formulae and commercial infant foods which are not included in the TDS.

59. The consumption data from the DNSIYC were used for the estimation of exposure for children aged 12 to 18 months (DH, 2013).

Exposure estimates based on the Infant Metals Survey

60. The ranges of total mean and 97.5th percentile exposures (excluding water) to copper from infant formula, commercial infant foods and other foods were 26 to 29 and 49 to 55 µg/kg bw/day, respectively. Total mean and 97.5th percentile exposures were also calculated using the highest median and 97.5th percentile concentrations for copper in water reported in Table 8. The resulting total mean and 97.5th percentile exposures indicated that levels of copper in water made a minimal contribution (< 10%) to total exposure (Table 8).

Table 8. Estimated exposures to copper from infant formulae, commercial infant foods and other foods in children aged 12 to 18 months.

Food	Copper Exposure (µg/kg bw/d)			
	12 to <15 Months (n=670)		15 to <18 Months (n=605)	
	Mean	97.5th	Mean	97.5th
Infant formula	5.3	24	2.9	17
Commercial infant foods	4.4	21	2.4	13
Other Foods	19	39	21	40
Total (excl. water)	29	55*	26	49*
Total, inc. tap water+ at highest Median conc. 10 µg/L	29	55	26	49
Total, inc. tap water+ At highest 97.5th percentile conc. 280 µg/L	33	59	30	53

Values rounded to 2 SF
+Exposure assessments taking account of contribution of drinking water were derived by multiplying mean water consumption for age by either the highest median or highest 97.5th percentile copper concentration from Table 2
* Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories

Exposure estimates based on the TDS

61. Table 9 shows the estimated copper exposures calculated using the TDS data for children aged 12 to 18 months. The copper concentration for the tap water group in the TDS was reported to be 20 µg/l (close to the LOQ). This value is within the range of LODs reported by different water authorities across the UK (Table 2). The

calculation was therefore also performed using the highest median (10 µg/L) and 97.5th percentile (280 µg/L) copper concentration in tap water reported in Table 2

62. Total mean and 97.5th percentile exposures to copper from a combination of all food groups are in the region of 32 to 40 and 60 to70 µg/kg bw/day, respectively (Table 9). These are higher than those estimated from the Infant Metals Survey due to the inclusion of a greater number of foods in the exposure estimate for the TDS. Overall the figures in Table 10 demonstrate that the copper content of water, even when present at the highest 97.5th percentile value results in a minimal increase (<10%) in total dietary exposure in young children in the UK.

Table 9. Estimated dietary exposure to copper based on the TDS data in children aged 12 to 18 months.

Copper concentration in the water µg/L	Copper Exposure (LB-UB Range) (µg/kg bw/day)			
	12 to <15 Months (n=670)		15 to <18 Months (n=605)	
	Mean	97.5th	Mean	97.5th
20 (TDS)	32-33	60-61	36-37	63-64
10(highest median)	32-33	60-61	36-37	63-64
280 (highest 97.5th percentile)	35-36	66-67	39-40	69-70

Values rounded to 2 SF

63. In general, the food groups making the highest contribution to copper exposure were miscellaneous cereals, bread and fresh fruits (FSA, 2016b).

Children aged 18 months to 5 years

64. Exposure estimates for these age groups were derived using occurrence data from the 2014 TDS, and consumption data from the NDNS (Bates *et al*., 2014).

65. Table 10 shows the copper exposures that were calculated using the TDS data for children aged 18 months to 5 years. Detailed exposure assessments are presented in Annex B As described in paragraph xx, the exposures have been estimated using the TDS water concentration 20 µg/L), and the highest median 0.0143 µg/L) and 97.5th percentile (0.28 µg/L) copper concentrations in water reported in Table 2. This results in total mean and 97.5th percentile exposures to copper from a combination of all food groups of 35 to 44 and 57 to 65 µg/kg bw/day, respectively (Table 10). Overall the figures in Table 10 demonstrate that the copper content of tap water results in a minimal increase (<10%) in total dietary exposure to copper of young children in the UK.

Table 10 Estimated dietary exposure to copper in children aged 18 months to 5 years.

Copper concentration in water µg/L	Copper Exposure (LB-UB Range) (µg/kg bw/day)			
	18 to <24 Months (n=70)		24 to <60 Months (n=429)	
	Mean	97.5th	Mean	97.5th
20 (TDS)	40-41	60-61	35-36	57-58
10 (highest median)	40-41	60-61	35-36	57-58
280 (highest 97.5th percentile)	43-44	65	38	61-62

Values rounded to 2 SF

66. As with the younger children, the food groups making the highest contribution to copper exposure in the TDS were miscellaneous cereals, bread and fresh fruits (FSA, 2016b).

Environmental

Dust

67. Potential exposures of UK infants aged 6 to 12 months and young children aged 1 to 5 years to copper in dust were calculated assuming ingestion of 30 or 60 mg/day, respectively (US EPA, 2011a). Younger infants, who are less able to move around and come into contact with dust, are likely to consume less dust than children of these age groups. Mean and maximum copper concentrations in dust of 208 and 5300 mg/kg, respectively, were used to estimate average and high level exposures (paragraph 49) (Table 11).

Table 11. Possible copper exposures from dust in infants and young children aged 6 months to 5 years.

Copper concentration (mg/kg)	Exposure (µg/kg bw/day)					
	Age (months)					
	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
208 (Mean)	0.72	0.65	1.2	1.1	1.0	0.78
5300 (Maximum)	18	17	30	28	27	20

Values rounded to 2 SF

Soil

68. Potential exposures of UK infants aged 6 to 12 months and young children aged 1 to 5 years to copper in soil were calculated assuming ingestion of 30 or 50 mg/day, respectively (US EPA, 2011a). Younger infants, who are less able to move around and come into contact with soil, are likely to consume less soil than children of these age groups. Median and 95th percentile soil concentrations of 32 and 105 mg/kg respectively were used in these exposure estimations (paragraph 45) (Table 12). The data show that copper in soil at a concentration of 105 mg/kg (95th percentile value from the from the Tellus Survey, paragraph 45) leads to exposure of up to 0.49 µg/kg bw/day. Exposure from this source is at least an order of magnitude below those from the diet.

Table 12. Possible copper exposures from soil in infants and young children aged 6 months to 5 years.

Copper concentration (mg/kg)	Exposure (µg/kg bw/day)					
	Age (months)					
	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
32 (Median)	0.11	0.10	0.15	0.14	0.13	0.099
105 (95th percentile)	0.36	0.33	0.49	0.47	0.44	0.33

Values rounded to 2 SF

Air

69. Potential exposures of UK infants aged 0 to 12 months and young children aged 1 to 5 years to copper in air were estimated using the body weights shown in Table 3, and by assuming the mean ventilation rates presented in Table 13; these rates have been derived from the US EPA exposure factors handbook (US EPA, 2011b). The resulting exposures are presented in Table 14.

Table 13. Mean ventilation rates used in the estimation of copper exposures from air (derived from US EPA, 2011b)

Age group (months)	Ventilation rate (m^3/day)
0 to <4	3.5
4 to <6	4.1
6 to <9	5.4
9 to <12	5.4
12 to <15	8.0
15 to <18	8.0
18 to <24	8.0
24 to <60	10.1

70. The copper concentrations used in the exposure calculations were the lowest and highest median values and lowest and highest 99th percentile values of 0.43 54, 0.77 and 160 ng/m^3, respectively, from monitoring sites in the UK (see paragraph 47).

Table 14. Possible exposures to copper in infants and young children from air

Copper concentration (ng/m^3)	Exposure (µg/kg bw/day)							
	Ages (months)							
	0 to <4	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
0.43 (lowest median value)	0.00026	0.00023	0.00027	0.00024	0.00032	0.00031	0.00029	0.00027
54 (highest median)	0.032	0.028	0.034	0.030	0.041	0.039	0.036	0.034
0.77(lowest 99th percentile value)	0.00046	0.00040	0.00048	0.00043	0.00058	0.00055	0.00051	0.00048
160(highest 99th percentile value)	0.095	0.084	0.099	0.090	0.12	0.11	0.11	0.10

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Risk characterisation

Breast milk

71. Exposure data were compared with the SCF and EVM Upper Levels, as shown in the following tables.

72. No consumption data were available for exclusive breastfeeding in infants aged 0 to 6 months. Therefore, the default consumption values used by the COT in other evaluations of the infant diet of 800 and 1200 mL for average and high level consumption have been used to estimate exposures to copper from breastmilk. These estimates were based on a mean and 97.5th percentile copper concentrations of 327 and 670 µg/L. The ranges of intakes of copper in exclusively breastfed 0 to 6 month olds were 34 to 91 and 50 to 140% of the SCF UL in the average and high level consumers respectively (Table 15).Using the EVM SUL, intakes ranged from 21 to 57 and 31 to 88% of the SUL in the average and high level consumers respectively (Table 16).

Table 15. Estimated copper intake from exclusive breastfeeding in 0 to 6 month old infants, with breast milk containing copper at 327 or 670 µg/L as a percentage of the SCF UL.

Copper	Copper intake as percentage of SCF UL (100 µg/kg

concentration (µg/L)	bw/day)			
	Average consumer (800 mL/day)		High consumer (1200 mL/day)	
	0 to <4 months	4 to <6 months	0 to <4 months	4 to <6 months
327	44	34	67	50
670	91	69	140	100

Values rounded to 2 significant figures (SF)

Table 16. Estimated copper intake from exclusive breastfeeding in 0 to 6 month old infants, with breast milk containing copper at 327 and 670 µg/L as a percentage of the EVM SUL..

Copper concentration (µg/L)	Copper intake as percentage of EVM SUL (160 µg/kg bw/day)			
	Average consumer (800 mL/day)		High consumer (1200 mL/day)	
	0 to <4 months	4 to <6 months	0 to <4 months	4 to <6 months
327	28	21	42	31
670	57	43	88	63

Values rounded to 2 significant figures (SF)

73. From the above table it appears that the copper intake of average consuming infants.is well below the SCF UL for copper but slightly exceeded the UL in high level consumers. Using the EVM SUL, both average and high level consumers were within the SUL.

74. The ranges of intakes of copper in 4 to 18 month old infants from breast milk were 8.3 to 59 and 17 to 100% of the SCF UL in the average and high level consumers respectively (Table 17).Using the EVM SUL, intakes ranged from 5.2 to 37 and 11 to 63% of the SUL in the average and high level consumers respectively (Table 18).

Table 17. Estimated copper intake in 4 to 18 month old infants from breast milk, containing copper at 327 and 19.4 µg/L. as a percentage of the SCF UL.

Exposure (µg/kg bw/day)	Age group (months)				
	Copper intake as percentage of SCF UL (100 µg/kg bw/day)				
	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18
Mean @ 327 µg/L	30	22	12	10	8.3
97.5th percentile @ 327 µg/L	51	52	38	25	17
Mean @ 640 µg/L	59	43	24	19	16

97.5th percentile @ 640 µg/L	99	100	74	48	33

Values rounded to 2 SF

Table 18. Estimated copper intake in 4 to 18 month old infants from breast milk, containing copper at 1.2 µg/L as a percentage of the EVM SUL.

Exposure (µg/kg bw/day)	**Age group (months)**				
	Copper intake as percentage of EVM SUL (160 µg/kg bw/day)				
	4 to <6	**6 to <9**	**9 to <12**	**12 to <15**	**15 to <18**
Mean @ 327 µg/L	19	14	7.5	6.3	5.2
97.5th percentile @ 327 µg/L	32	33	24	16	11
Mean @ 670 µg/L	37	27	15	12	10
97.5th percentile @ 670 µg/L	62	63	46	30	21

Values rounded to 2 SF

Infant formulae and complementary foods

75. In 0 to 6 month olds, intakes of copper from ready-to-feed formula were 39 to 51% of the SCF UL in the average consumers, and 58 to 76% of the UL in high level consumers. Mean and high-level intake of copper from infant formula reconstituted with water containing copper up to 280 µg/L (the highest 97.5th percentile) were up to 93 and 140% of the UL in the average and high level consumers respectively, (Table 19).

75. Using the EVM SUL, intakes from ready-to-feed infant formula ranged from 24 to 32 and 36 to 48% of the SUL in the average and high level consumers. Mean and high-level exposure to copper from infant formula reconstituted with water containing copper up to 280 µg/L (the highest 97.5th percentile) were up to 58 and 88% of the UL in the average and high level consumers respectively, (Table 20).

Table 19. Estimated average and high level dietary intakes of copper from exclusive feeding on infant formulae for 0 to 6 month olds as a percentage of the SCF UL.

Infant Formula	**Copper Intake as percentage of SCF UL (100 µg/kg bw/day)**			
	0 to <4 months		**4 to <6 months**	
	Average consumer (800 mL/day)	**High level consumer (1200 mL/day)**	**Average consumer (800 mL/day)**	**High level consumer (1200 mL/day)**

Ready-to-Feed [a]	51	76	39	58
Dry Powder [b, c]	61	92	46	69
Dry Powder [c] + TDS water of 20 µg/L [d]	63	95	48	72
Dry Powder [c] + median water of 10 µg/L [d]	62	94	47	70
Dry Powder [c] + 97.5th percentile water of 280 µg/L [d]	93	140	70	110

Values rounded to 2 SF

Table 20. Estimated average and high level dietary intakes of copper from exclusive feeding on infant formulae for 0 to 6 month olds as a percentage of the EVM SUL..

Infant Formula	**Copper Intake as percentage of EVM SUL (160 µg/kg bw/day)**			
	0 to <4 months		**4 to <6 months**	
	Average consumer (800 mL/day)	**High level consumer (1200 mL/day)**	**Average consumer (800 mL/day)**	**High level consumer (1200 mL/day)**
Ready-to-Feed [a]	32	48	24	36
Dry Powder [b, c]	38	58	29	43
Dry Powder [c] + TDS water of 20 µg/L [d]	39	59	30	45
Dry Powder [c] + median water of 10 µg/L [d]	39	59	29	44
Dry Powder [c] + 97.5th percentile water of 280 µg/L [d]	58	88	44	69

Values rounded to 2 SF

76. Total mean intakes (excluding water) of copper from infant formulae, commercial infant foods, and other foods, for 4 to 12 month olds were 37 to 40% of the SCF UL and the 97.5th percentile intakes were 62 to 72% of the UL (Table 21).

77. Total mean intakes (excluding water) of copper from infant formulae, commercial infant foods, and other foods, for 4 to 12 month olds were 23 and 25 % of the EVM SUL and the 97.5th percentile intakes were 39 to 45% of the SUL (Table 22).

Table 21. Estimated dietary intake of copper from infant formulae, commercial infant foods and other foods for 4 to 12 month olds as a percentage of the SCF UL..

	Copper Intake as percentage of SCF UL (100 µg/kg bw/day)					
Food	**4 to <6 Months (n=116)**		**6 to <9 Months (n=606)**		**9 to <12 Months (n=686)**	
	Mean	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**
Infant formula	24	53	19	41	14	30
Commercial infant foods	5.7	21	8.3	29	7.7	31
Other foods	5.1	24	11	34	16	40
UB Total (excl. water)	37	72*	40	68*	38	62*
Total, inc. tap water+ at highest Median conc. 10 µg/L	37	72	40	68	38	62
Total, inc. tap water+ At highest 97.5th percentile conc. 280 µg/L	38	73	43	71	41	65

Values rounded to 2 SF

Table 22. Estimated dietary intake of copper from infant formulae, commercial infant foods and other foods for 4 to 12 month olds as a percentage of the EVM SUL...

Food	Copper Intake as percentage of EVM SUL (160 µg/kg bw/day)					
	4 to <6 Months (n=116)		6 to <9 Months (n=606)		9 to <12 Months (n=686)	
	Mean	97.5th	Mean	97.5th	Mean	97.5th
Infant formula	15	33	12	26	9.0	19
Commercial infant foods	3.6	13	5.2	18	4.8	19
Other foods	3.2	15	6.9	21	10	25
UB Total (excl. water)	23	45*	25	43	24	39*
Total, inc. tap water+ at highest Median conc. 10 µg/L	23	45	45	43	24	39
Total, inc. tap water+ At highest 97.5th percentile conc. 280 µg/L	24	46	27	44	26	41

Values rounded to 2 SF

Children aged 12 to 18 months

Intake estimates based on the Infant Metals Survey

78. The ranges of total mean and 97.5th percentile intakes (excluding water) of copper from infant formula, commercial infant foods and other foods were 26 to 29 and 48 to 55% of the SCF UL respectively.(Table 23)

79. The ranges of total mean and 97.5th percentile intakes (excluding water) of copper from infant formula, commercial infant foods and other foods were 16 to 18 and 31 to 34% of the EVM SUL, respectively. (Table 24)

Table 23. Estimated dietary intake of copper from infant formulae, commercial infant foods and other foods in children aged 12 to 18 months as a percentage of the SCF UL.

Food	Copper Intake as percentage of SCF UL (100 µg/kg bw/day)			
	12 to <15 Months (n=670)		15 to <18 Months (n=605)	
	Mean	97.5th	Mean	97.5th

Infant formula	5.3	24	2.9	17
Commercial infant foods	4.4	21	2.4	13
Other Foods	19	39	21	40
Total (excl. water)	29	55	26	49*
Total, inc. tap water+ at highest Median conc. 10 µg/L	29	55	26	49
Total, inc. tap water+ At highest 97.5th percentile conc. 280 µg/L	33	59	30	53

Values rounded to 2 SF

Table 24. Estimated dietary intake of copper from infant formulae, commercial infant foods and other foods in children aged 12 to 18 months as a percentage of the EVM SUL...

Food	**Copper Intake as percentage of EVM SUL (160 µg/kg bw/day)**			
	12 to <15 Months (n=670)		**15 to <18 Months (n=605)**	
	Mean	**97.5th**	**Mean**	**97.5th**
Infant formula	3.3	15	1.8	11
Commercial infant foods	2.8	13	1.5	8.1
Other Foods	12	24	13	25
Total (excl. water)	18	34	16	31*
Total, inc. tap water+ at highest Median conc. 10 µg/L	18	34	16	31
Total, inc. tap water+ At highest 97.5th percentile conc. 280 µg/L	21	37	19	33

Values rounded to 2 SF

Intake estimates based on the TDS

80. Tables 25 and 26 show that the estimated copper intakes derived from TDS data for children aged 12 to 18 months are affected by up to approximately 10%.by water in the diet where the water contains the highest 97.5th percentile of the concentrations of copper measured in the UK and Northern Ireland. Even this high level, however, dietary intake does not exceed either the SFC UL (Table 25) or the EVM SUL (Table 26).

Table 25 Estimated dietary intake of copper based on the TDS data in children aged 12 to 18 months as a percentage of the SCF UL.

Copper concentration in the water µg/L	Copper Intake as percentage of SCF UL (100 µg/kg bw/day)			
	12 to <15 Months (n=670)		15 to <18 Months (n=605)	
	Mean	97.5th	Mean	97.5th
20 (TDS)	32-33	60-61	36-37	63-64
10(highest median)	32-33	60-61	36-37	63-64
280 (highest 97.5th percentile)	35-36	66-67	39-40	69-70

Values rounded to 2 SF

Table 26. Estimated dietary intake of copper based on the TDS data in children aged 12 to 18 months as a percentage of the EVM SUL...

Copper concentration in the water µg/L	Copper Intake as percentage of EVM SUL (160 µg/kg bw/day)			
	12 to <15 Months (n=670)		15 to <18 Months (n=605)	
	Mean	97.5th	Mean	97.5th
20 (TDS)	20-21	38	23	39-40
10(highest median)	20-21	38	23	39-40
280 (highest 97.5th percentile)	22-23	41-42	24-25	43-44

Values rounded to 2 SF

Children aged 18 months to 5 years

Intake estimates based on the TDS

81. Tables 27 and 28 show that the estimated copper intakes derived from TDS data for children aged 12 to 18 months are affected by up to approximately 10%.by water in the diet where the water contains the highest 97.5th percentile of the

concentrations of copper measured in the UK and Northern Ireland. Even this high level, however dietary intake does not exceed either the SFC UL (Table 27) or the EVM SUL (Table 28).

Table 27 Estimated dietary intake of copper in children aged 18 months to 5 years as a percentage of the SCF UL.

Copper concentration in water µg/L	Copper Intake as percentage of SCF UL (100 µg/kg bw/day)			
	18 to <24 Months (n=70)		24 to <60 Months (n=429)	
	Mean	97.5th	Mean	97.5th
20 (TDS)	40-41	60-61	35-36	57-58
10(highest median)	40-41	60-61	35-36	57-58
280(highest 97.5th percentile)	43-44	65	38	61-62

Values rounded to 2 SF

Table 28. Estimated dietary intake of copper in children aged 18 months to 5 years as a percentage of the EVM SUL...

Copper concentration in water µg/L	Copper Intake as percentage of EVM SUL (160 µg/kg bw/day)			
	18 to <24 Months (n=70)		24 to <60 Months (n=429)	
	Mean	97.5th	Mean	97.5th
20 (TDS)	25-26	38	22-23	36
10(highest median)	25-26	38	22-23	36
280(highest 97.5th percentile)	27-28	41	24	38-39

Values rounded to 2 SF

Environment

Dust

82. Potential intakes of UK infants aged 6 to 12 months and young children aged 1 to 5 years to copper in dust were 0.65 to 30% of the SCF UL respectively (Table 29).

83. Potential intakes of UK infants aged 6 to 12 months and young children aged 1 to 5 years to copper in dust were 0.41 to 19% of the EVM SUL respectively (Table 30).

Table 29. Possible copper intake from dust in infants and young children aged 6 months to 5 years as a percentage of the SCF UL..

Copper concentration (mg/kg)	Copper Intake as percentage of SCF UL (100 µg/kg bw/day)					
	Age (months)					
	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
208 (Mean)	0.72	0.65	1.2	1.1	1.0	0.78
5300 (Maximum)	18	17	30	28	27	20

Values rounded to 2 SF

Table 30. Possible copper intake from dust in infants and young children aged 6 months to 5 years as a percentage of the EVM SUL....

Copper concentration (mg/kg)	Copper Intake as percentage of EVM SUL (160 µg/kg bw/day)					
	Age (months)					
	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
11.8 (Mean)	0.45	0.41	0.75	0.69	0.63	0.49
5300 (Maximum)	11	11	19	18	17	13

Values rounded to 2 SF

Soil

84. Potential intakes of UK infants aged 6 to 12 months and young children aged 1 to 5 years to copper in soil were 0.10 to 0.49% of the SCF UL respectively.

85. Potential intakes of UK infants aged 6 to 12 months and young children aged 1 to 5 years to copper in soil were 0.063 to 0.31% of the EVM SUL respectively.

Table 31. Possible copper intake from soil in infants and young children aged 6 months to 5 years as a percentage of the SCF UL.

Copper concentration (mg/kg)	Copper Intake as percentage of SCF SUL (100 µg/kg bw/day)					
	Age (months)					
	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
32 (Median)	0.11	0.10	0.15	0.14	0.13	0.099
105 (95^{th} percentile)	0.36	0.33	0.49	0.47	0.44	0.33

Values rounded to 2 SF

Table 32. Possible copper intake from soil in infants and young children aged 6 months to 5 years as a percentage of the EVM SUL...

Copper concentration (mg/kg)	Copper Intake as percentage of EVM SUL (160 µg/kg bw/day)					
	Age (months)					
	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
68 (Median)	0.069	0.063	0.094	0.088	0.081	0.062
97 (95th percentile)	0.23	0.21	0.31	0.29	0.28	0.21

Values rounded to 2 SF

Air

86. Potential exposures of UK infants aged 0 to 12 months and young children aged 1 to 5 years to copper in air, relative to the SCF UL are shown in Table 33. Exposures ranged from 0.00023 to 0.12% of the UL.

87. Potential exposures of UK infants aged 0 to 12 months and young children aged 1 to 5 years to copper in air, relative to the EVM SUL are shown in Table 34. Exposures ranged from 0.00014 to 0.075% of the SUL.

Table 33. Possible copper intake in infants and young children from air as a percentage of the SCF UL.

Copper concentration (ng/m^3)	Copper Intake as percentage of SCF UL (100 µg/kg bw/day)							
	Ages (months)							
	0 to <4	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60
0.43 (lowest median value)	0.00026	0.00023	0.00027	0.00024	0.00032	0.00031	0.00029	0.00027
54 (highest median)	0.032	0.028	0.034	0.030	0.041	0.039	0.036	0.034
0.77(lowest 99th percentile value)	0.00046	0.00040	0.00048	0.00043	0.00058	0.00055	0.00051	0.00048
160(highest 99th percentile value)	0.095	0.084	0.099	0.090	0.12	0.11	0.11	0.10

Values rounded to 2 SF

Table 34. Possible copper intake in infants and young children from air as a percentage of the EVM SUL.

Copper concentration (ng/m^3)	Copper Intake as percentage of EVM SUL (160 µg/kg bw/day)							
	Ages (months)							
	0 to <4	4 to <6	6 to <9	9 to <12	12 to <15	15 to <18	18 to <24	24 to <60

0.8 (lowest median value)	0.00016	0.00014	0.00017	0.00015	0.00020	0.00019	0.00018	0.00017
8.65 (highest median)	0.020	0.018	0.021	0.019	0.026	0.024	0.023	0.021
1.4(lowest 99th percentile value)	0.00029	0.00025	0.00030	0.00027	0.00036	0.00034	0.00032	0.00030
167(highest 99th percentile value)	0.059	0.053	0.062	0.056	0.075	0.071	0.066	0.063

Values rounded to 2 SF

88. Estimated copper intake values by all routes for all age groups were all lower than the EVM SUL of 160 µg/kg bw. Only the high level consumers of infant formula, reconstituted with drinking water containing the 97.5th percentile concentration of copper, exceeded the SCF UL of 100 µg/kg bw. These exceedances were low: only 40% in the 0 – <4 month age group and 10% in the 4 – <6 month age group (Table 19)

Questions for the Committee

1. Which HBGV does the Committee consider more appropriate for the risk assessment of copper in the infant diet: the value of 100 µg/kg bw/day from SCF or the value of 160 µg/kg bw/day from the EVM?
2. Does the Committee consider that presenting aggregate exposures is necessary in the case of copper?
3. Does the Committee have any other comments on this paper?

Secretariat

August 2017

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Search terms

Copper AND Breast milk
Toxicology
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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Review of potential risks from Copper in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Possible Copper exposure from dietary sources in children aged 4 to 18 months

Two surveys were conducted during 2014 which measured the concentrations of elements in food consumed by infants (4 to 18 months) and young children (18 months to 5 years). The first survey was a survey on types of foods eaten by infants (referred to as the Infant Metals Survey), the other was a total diet study (TDS) which focused on sampling foods eaten by young children. Both studies measured the concentrations of Copper.

The Infant Metals Survey measured the concentrations of metals and other elements in food 'as sold', in the following categories: infant formula (Table B1) commercial infant foods (Table B2), and groups of food comprising the top 50 most commonly consumed varieties of foods not specifically marketed for infants (Table B3). The results from this survey were used together with food consumption data from the Diet and Nutrition Survey for Infants and Young Children (DNSIYC) (DH, 2013) to estimate dietary exposures for children aged 4 to 18 months.

The TDS consisted of: (i) selecting foods based on food consumption data, to represent as best as possible a typical diet; (ii) their preparation to food as consumed and (iii) the subsequent pooling of related foods before analysing the composite samples for elements. The concentrations of 26 elements, including Copper, were measured in the 2014 TDS. The composite samples for 27 food groups (Table B4) were collected from 24 UK towns and analysed for their levels of Copper and other elements. Where appropriate, tap water was used in the preparation and cooking of food samples. The results from this survey were also used together with food consumption data from the DNSIYC (DH, 2013) to estimate dietary exposures for children aged 12 to 18 months.

Table B1. Infant formula

Infant Formula	
Dry Powder	**Made Up Formula**
First and Hungrier Milk	First Milk and Hungrier Milk
Follow On Milk	Follow On milk
Growing Up Milk	Growing up Milk
Soy Milk	
Goat Milk	
Organic Milk	

Comfort Milk	

Table B2. Commercial infant foods

Commercial Infant Foods
Cereal Based Foods and Dishes
Dairy Based Foods and Dishes
Fruit Based Foods and Dishes
Meat and Fish Based Foods and Dishes
Snacks (Sweet and Savoury)
Other Savoury Based Foods and Dishes (excluding Meat)
Drinks

Table B3. Other foods commonly eaten by infants.

Other Foods	
Beverages	Fruit Products
Bread	Green Vegetables
Canned Vegetables	Meat Products
Cereals	Milk
Dairy Products	Other Vegetables
Eggs	Potatoes
Fish	Poultry/Chicken
Fresh Fruit	

Table B4. The 27 food groups used for analysis of Copper and other elements in the 2014 TDS

TDS Food Groups*	
Bread	Fresh Fruit
Miscellaneous Cereals	Fruit Products
Carcase Meat	Non-alcoholic Beverages
Offal	Milk
Meat Products	Dairy Products
Poultry	Nuts
Fish	Alcoholic Drinks
Fats and Oils	Meat Substitutes
Eggs	Snacks
Sugars	Desserts
Green Vegetables	Condiments
Potatoes	Tap Water
Other Vegetables	Bottled Water
Canned Vegetables	

*Food samples representative of the UK diet are purchased throughout the year in 24 towns covering the UK and 137 categories of foods are combined into 27 groups of similar foods for analysis

Exposure Assessments

Infant Metals Survey

Tables B5, B6 and B7 summarise lower- (LB) and upper-bound (UB) total dietary exposures to Copper calculated using results from the infants Metal Survey for ages 4 to 18 months.

Table B5. Estimated copper exposure from infant formula in children aged 4 to 18 months using data from the Infant Metals Survey

Food Groups	Exposure- LB-UB (ug/kg bw/day)									
	4 to <6		6 to <9		9 to <12		12 to <15		15 to <18	
	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile
Comfort	0	0	0.061	0	0.215	0	0	0	0	0
First Milk: From Birth (Powder)	0.166	3.41	0.241	0	0.067	0	0.00014	0	0	0
Follow On Milk: 6 Months (Powder)	0	0	0.136	0	0.237	1.64	0.012	0	0.031	0
Growing Up Milk: 12 Months (Powder)	0	0	0	0	0	0	0.091	0	0.033	0
Goat Milk Formula	0	0	0.128	0	0	0	0	0	0	0
Hipp Organic	0	0	0.020	0	0.011	0	0.003	0	0	0
Soy	0.049-0.33	0	0.024-0.162	0	0.025-0.166	0	0.007-0.048	0	0.004-0.029	0
First Milk: From Birth (Ready to Feed)	21.4	52.8	8.8	39.4	3.8	24.7	0.561	10.5	0.129	0
Follow on: 6 Months (Ready to Feed)	2.5	26.2	9.2	31.8	8.9	28.8	2.2	18.6	1.1	12.1
Growing up Milk: 12 Months (Ready to Feed)	0	0	0.017	0	0.27	0	2.4	19.1	1.5	14.8
Upper-BoundTotal	24	53	19	41	14	30	5.3	24	2.9	17

Table B6. Estimated Copper exposure from commercial infant foods in children aged 4 to 18 months using data from the Infant Metals Survey

Food Groups	Commercial Infant Foods Copper LB to UB									
	4 to <6		6 to <9		9 to <12		12 to <15		15 to <18	
	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile	Mean	97.5th Percentile
Cereal Based Dishes	0.606618	2.9346	0.702164	3.56785	0.500463	3.20465	0.209154	2.06685	0.08249	0.932159
Dairy Based Dishes	0.415422	4.05712	0.415549	3.7667	0.258795	2.69396	0.135443	1.85472	0.0471648	0.739307
Fruit Based Dishes	1.51858	11.6655	2.23668	12.6118	2.11569	11.4505	1.3285	9.72564	0.815697	7.06976
Meat Based Dishes	1.60196	10.3083	2.59615	13.1476	2.45559	12.3305	1.44104	9.9687	0.737472	5.89463
Drinks	0.0332287	0.327613	0.0434247	0.435703	0.0373411	0.333899	0.0186624	0.278921	0.016871	0.200599
Other savoury based dishes	0.949344	6.23707	1.37579	7.86937	1.46924	10.1961	0.576951	5.65425	0.286097	4.30121
Snacks - sweet and savoury	0.604908	3.75983	0.902083	4.67719	0.882361	4.70209	0.648737	4.26349	0.397005	2.49923
Total	5.7	21	8.3	29	7.7	31	4.4	21	2.4	13

Table B7. Estimated Copper exposure from other foods commonly eaten by children aged 4 to 18 months using data from the Infant Metals Survey

Food Groups	**Other Food Copper LB to UB**									
	4 to <6		**6 to <9**		**9 to <12**		**12 to <15**		**15 to <18**	
	Mean	**97.5th Percentile**	**Mean**	**97.5th Percentile**	**Mean**	**97.5th Percentile**	**Mean**	**97.5th Percentile**	**Mean**	**97.5th Percentile**
Beverages	0-0.00159283	0-0.0242862	0-0.00445276	0-0.0352027	0-0.00336014	0-0.0440386	0-0.00287353	0-0.0338905	0-0.0041553	0-0.0697848
Bread	0.0851993	1.21821	0.786012	5.14122	2.20185	8.8206	3.33654	11.1194	3.72399	12.2596
Canned Vegetables	0.104814	1.35363	0.476964	5.09503	1.12809	8.17176	1.70902	9.60536	1.49673	6.97712
Cereal	0.121856	1.45021	2.02596	11.156	3.04909	13.5985	3.77348	15.3757	4.66281	16.2422
Dairy Products	0.2101	1.23888	0.441399	1.86184	0.542298	2.04146	0.549089	1.97063	0.50193	1.73404
Egg	0.00890086	0.00970931	0.0907166	0.928361	0.186152	1.42726	0.294817	1.80779	0.308908	1.86939
Fish	0.0128449-0.012845	0.0750233-0.0750237	0.0976166-0.0976171	0.922507-0.922512	0.208246-0.208248	1.37713-1.37714	0.271341-0.271343	1.29965-1.29966	0.240133-0.240134	1.27079
Fresh fruit	0.704413	4.81896	1.37308	6.39388	2.06402	8.4543	2.83194	10.0001	3.45647	10.063
Fruit products	0.0757656-0.0757641	1.22401-1.22399	0.11667-0.116667	1.2328-1.23278	0.116632-0.11663	1.19848-1.19845	0.19208-0.192076	1.80186-1.80182	0.276107-0.276101	2.08426-2.08422
Green vegetables	0.318097	2.72673	0.680171	3.21607	0.758896	5.0776	0.734954	3.59477	0.761024	3.72435
Meat products	0	0	0.056922	1.01417	0.142944	1.34794	0.284763	1.93173	0.381553	3.13002
Milk	0.0160481	0.178639	0.0882409	0.488923	0.225222	1.84582	0.928881	2.65586	0.928094	2.26152
Other vegetables	2.77154	20.2545	3.65004	17.1153	3.34998	14.2473	2.27758	9.91489	2.21864	8.64924
Potato	0.616533	4.22228	1.35059	6.31668	1.8605	7.4419	2.01113	8.92006	1.81381	7.23084
Poultry	0.0241607	0.158721	0.0727352	0.583242	0.0952248	0.679086	0.098654	0.571275	0.091826	0.6143
Upper-bound Total	5.1	24	11	34	16	40	19	39	21	40

Total Diet Study

Table B8 summarise lower- and upper-bound total dietary exposures to Copper calculated using the 2014 TDS for ages 12 to 18 months. The data for each food category is reported separately so that the contribution to exposure from each class could be assessed more transparently for the most relevant infant age group. In addition the total exposure from the diet has also been provided.

Table B8. Estimated Copper exposure from food eaten by young children aged 12 months to 18 months using data from the TDS Groups.

Food Groups	Exposure-LB-UB (ug/kg bw/day)			
	12 to <15		15<18	
	Mean	97.5th Percentile	Mean	97.5th Percentile
Bread	3.49578	9.53507	3.92337	10.5406
Miscellaneous Cereals	8.53981	26.8166	10.3297	30.4373
Carcase meat	0.691168	3.55476	0.861982	4.28736
Offal	0.0768679	0	0.566031	0
Meat products	0.736011	3.88574	0.905591	4.16982
Poultry	0.516504	2.26749	0.58107	2.49622
Fish	0.621306	2.88335	0.582583	2.95326
Fats and oils	0-0.00530298	0-0.0213408	0-0.00630398	0-0.0232921
Eggs	0.345151	1.81178	0.354453	1.86726
Sugars	0.352701	2.15117	0.531905	2.65385
Green vegetables	0.397798	1.76305	0.435232	1.63616
Potatoes	3.22949	11.8574	2.99183	9.78527
Other vegetables	2.26727	8.26029	2.30294	7.54486
Canned vegetables	1.80081	9.2145	1.75545	8.13397
Fresh fruit	3.79391	13.0276	4.67014	13.4027
Fruit products	0.832731	5.98034	0.952499	6.30737
Non-alcoholic beverages	0.486354	2.29335	0.588271	2.76264
Milk	0-0.52428	0-1.49644	0-0.525962	0-1.2741
Dairy products	2.38801	12.7468	2.0215	8.87423
Nuts	0.776838	3.30974	0.35329	3.23774
Alcoholic drinks	0.000366252	0.00223024	0.000175261	0
Meat substitutes	0.0474644	0	0.132127	1.60907
Snacks	0.270618	1.8553	0.42093	2.91582
Desserts	0.324275	2.79344	0.443358	3.24794
Condiments	0.235054	1.39551	0.264419	1.36196
Tap water	0.197406	0.752166	0.224318	0.899296
Bottled water	0-0.00412729	0-0.0358304	0-0.00542066	0-0.0828532
Total	32-33	60-61	36-37	63-64

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

Review of potential risks from Copper in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Possible Copper exposure from dietary sources in young children aged 18 to 60 months

A Total Diet Study (TDS) was conducted during 2014 which measured the concentrations of Copper by young children (18 months and older).

The TDS consisted of: (i) selecting foods based on food consumption data, to represent as best as possible a typical diet; (ii) their preparation to food as consumed and (iii) the subsequent pooling of related foods before analysing the composite samples for elements. The concentrations of 26 elements, including Copper, were measured in the 2014 TDS. The composite samples for 27 food groups (Table C1) were collected from 24 UK towns and analysed for their levels of Copper and other elements. Where appropriate, tap water was used in the preparation and cooking of food samples. The results from this survey were also used together with food consumption data from years 1 to 4 of the National Diet and Nutrition Survey Rolling Programme (NDNS) (Bates *et al.,* 2014) to estimate dietary exposures for young children aged 18 months to 5 years.

Table C1. Food groups used for analysis of Copper and other elements in the 2014 TDS.

TDS Food Groups*	
Bread	Fresh Fruit
Miscellaneous Cereals	Fruit Products
Carcase Meat	Non Alcoholic Beverages
Offal	Milk
Meat Products	Dairy Products
Poultry	Nuts
Fish	Alcoholic Drinks
Fats and Oils	Meat Substitutes
Eggs	Snacks
Sugars	Desserts
Green Vegetables	Condiments
Potatoes	Tap Water
Other Vegetables	Bottled Water
Canned Vegetables	

*Food samples representative of the UK diet are purchased throughout the year in 24 towns covering the UK and 137 categories of foods are combined into 27 groups of similar foods for analysis

Exposure Assessment

Table C2 summarises lower- and upper-bound total dietary exposures to Copper calculated using the 2014 TDS for young children aged 18 months to 5 years. The data for each food category is reported separately so that the contribution to exposure from each class could be assessed more transparently for the most relevant infant age group. In addition the total exposure from the diet has also been provided.

Table C2. Estimated Copper exposure from food eaten by young children aged 18 months to 5 years using data from the TDS Groups.

Food Groups	Exposure-LB to UB			
	18 to <24		24 to <60	
	Mean	97.5th Percentile	Mean	97.5th Percentile
Bread	4.14281	9.315	4.71666	10.9691
Miscellaneous Cereals	11.038	23.1248	9.01896	22.8159
Carcase meat	0.951272	4.88878	0.575267	3.07768
Offal	0.131294	0	0.188101	0
Meat products	1.07866	4.99223	1.31375	4.37121
Poultry	0.672821	1.9084	0.566754	2.45147
Fish	0.77044	3.07699	0.590177	2.26514
Fats and oils	0-0.00851049	0-0.0271711	0-0.00761752	0-0.0252491
Eggs	0.267099	1.49622	0.274435	1.55366
Sugars	0.627	2.9676	0.90204	3.79642
Green vegetables	0.37298	2.23125	0.384072	1.55816
Potatoes	3.06662	6.46511	2.78712	8.15512
Other vegetables	1.39125	4.6502	1.45249	5.1819
Canned vegetables	2.99797	11.4964	1.846	7.1339
Fresh fruit	5.69344	14.9263	4.11256	10.8401
Fruit products	2.13191	8.23661	1.94247	9.36026

Non-alcoholic beverages	0.793847	3.28034	0.765168	2.21937
Milk	0-0.491712	0-1.54717	0-0.347416	0-1.00258
Dairy products	2.18298	10.3906	1.21967	4.87706
Nuts	0.1882	0.267803	0.573156	8.03132
Alcoholic drinks	0.000444121	0	0.000306106	0
Meat substitutes	0.0342487	0.581209	0.148169	2.25672
Snacks	0.493461	2.9863	0.571504	3.0189
Desserts	0.672994	3.68963	0.750061	3.59368
Condiments	0.185594	0.916791	0.287752	1.51638
Tap water	0.22315	1.17066	0.201161	0.759167
Bottled water	0-0.00274799	0-0.0281818	0-0.00710707	0-0.0763774
Total	40-41	60-61	35-36	57-58

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Bates, B.; Lennox, A.; Prentice, A.; Bates, C.; Page, P.; Nicholson, S.; Swan, G. (2014) National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/2012) Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310995/NDNS_Y1_to_4_UK_report.pdf