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

Statement 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.

Background

2. Copper is 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.

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

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

Toxicokinetics

Absorption

5. Copper in the lumen of the gut is largely bound to amino acids. Copper is taken up by enterocytes by the action of the copper transporting protein Ctr1, for which the Cu^{+} form is the substrate. (Nose *et al* 2006). Ctr1 expression appears to be regulated by hypoxia-inducible factor 2α (HIF 2α). (Pourvali *et al*,2012)

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

7. Copper absorption appears to have an inverse relationship with the amount present in the gut at physiological concentrations. Turnlund *et* al, (1989) studied the effects of three levels of dietary copper on copper absorption and retention in a group of young men. Cu absorption was dependent on its dietary intake but the percentage absorbed decreased as intake increased. Moreover, absorption percentage increased more rapidly when intake decreased than it decreased when intake increased. The authors suggested that absorption was the first point of Cu metabolic regulation and is particularly important when dietary levels are relatively low. Changes in endogenous loss appear to compensate for incomplete regulation at the level of absorption and eliminate excess Cu when dietary levels increase.

Distribution

8. When copper is released from Ctr1 into the cytoplasm, its fate is tightly regulated by the presence of a number of chaperone proteins that direct it towards its functional sites, storage or excretion (Prohaska 2012)

9. 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 system. In the portal circulation, copper is bound to histidine, albumin or 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. Copper not incorporated into ceruloplasmin is stored bound to metallothionein or incorporated in Cu-dependent enzymes. (EFSA 2015)

10. 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 (EFSA 2015). If ATP7B is deficient then copper accumulates in the liver, brain and eyes, leading to the signs and symptoms of Wilson's disease (Coffey *et al*, 2013).

Metabolism

11. 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 ability of copper to alternate between +1 and +2 oxidation states is also how it functions in redox enzymes such as amine oxidases, lysyl oxidases, dopamine β hydroxylase and superoxide dismutase (EFSA 2015)

12. 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

13. 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).

Toxicology

Acute toxicity

14. High acute levels of oral copper can cause 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).

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 result from malabsorption, for example, from a high intake of zinc, or as a consequence of gastric surgery (Myint et al, 2018). Copper malabsorption as a result of lack of ATP7A is a sign of Menkes disease (Tümer & Møller, 2010).

16. In excess, first, changes in uptake and transport are seen, along with changes in the activities of copper-dependent enzymes. Blood cholesterol and triglyceride levels increase, along with the liver copper burden. As levels increase further, intestinal metallothionein levels rise, systolic blood pressure increases and at higher levels of copper, the metabolism of other nutrients is grossly disturbed, although these are initially reversible changes. At high excess there are irreversible metabolic changes and death. (Chambers *et al* (2010)

Oxidative stress

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

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

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

The hydroxyl radical then initiates the oxidative damage.

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

Carcinogenicity

19. The IARC evaluation (1987) on copper (II) 8-hydroxyquinoline allocated it to Group 3: “Not classifiable as to its carcinogenicity to humans”, based on inadequate evidence in experimental animals and the absence of adequate data on humans. 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 showed carcinogenicity.

Expert opinions

20. 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 EC 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 exposure to copper via drinking water as part of the development of their ‘Guidelines for Drinking Water Quality’ (WHO, 1982).

The EC Scientific Committee on Food (SCF)

21. The *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 (the highest dose tested) 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 (EFSA, 2006).

WHO

22. 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 was established.

EVM

23. The Expert Group on Vitamins and Minerals stated in their statement of 2003 (EVM, 2003):

"*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".*

24. The tolerable Upper Level (UL) of 100 μg/kg bw/day derived by the SCF and the Safe Upper Level (SUL) of 0.16 mg/kg bw/day or 160 μg/kg bw/day, derived by the EVM, are not substantially different from one another but, based on the relative robustness of the studies used to derive them, the EVM value has been used in the Risk Characterisation section below.

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

<u>Sources of copper exposure</u>

Human breast milk

25. Dorea (2000) reported concentrations of copper in breast milk ranging from about 200 to 1000 μg/L over the course of lactation, with most values in the order of 300–400 μg/L. (cited by EFSA, 2015).

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

27. 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 in breast milk vary between approximately 130 and 450 μg/l; reported maximum values range from 209 to 895 μg/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 samples	Average concentration (μg/L)	Minimum concentration (μg/L)	Maximum concentration (μg/L)	Reference
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)

28. 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

29. 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.

[1] https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2004/cotstatebreastmilk

Food contact materials

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

31. 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$\pm$50 ml). 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).

32. 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

33. The primary source of copper in drinking water is leaching from copper plumbing. The UK Drinking Water Inspectorate 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, a layer of copper oxide forms on the inner surface of the pipes (red cuprous oxide in cold water pipes, black cupric oxide in hot water pipes), which is overlaid by a layer of green copper hydroxycarbonate. These layers reduce the release of copper into the water[2].

34. In houses with new pipes that have not developed a passivating layer of copper oxide on their surface, levels after a period of inactivity, such as overnight or over a weekend, may exceed the guidance level. Where such an effect might 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[3].

35. Copper oxides are very sparingly soluble in water across temperature ranges covered by the water in domestic hot supplies (Palmer and Bénézeth, 2004) but corrosion of copper pipes is greatest at about 50^{o}C, leading to higher amounts of suspended copper in the hot water supply than the cold (Kristiansen, 1977)

36. EU legislation sets a maximum 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) https://www.lenntech.com/applications/drinking/standards/eu-s-drinking-water-standards.htm

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[2] http://www.fwr.org/copper.pdf
[3] http://dwi.defra.gov.uk/consumers/advice-leaflets/copper.pdf

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

37. Water companies should abide by the methodology of the Standing Committee of Analysts, 'The Microbiology of Drinking Water (2010) – Part 2 – Practices and procedures of sampling' Samples for copper, lead and nickel are taken pre-flushing, others would be following a suitable length of time required to flush the length of pipework concerned (but normally a minimum of 2 minutes).

38. 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 drinking 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

39. Copper has an estimated upper continental crustal abundance of about 15 mg/kg, though it is much more abundant in basalts (90 mg/kg) and shales (45 mg/kg) relative to other rock types. Copper also has strong affinities with sulphur in mineralisation centres and with humified organic matter in some lowland peats (Rawlins et al., 2012). There are upper limit values for soil Cu concentrations and

Statutory Instrument (SI 1263, 1989) gives a maximum Cu concentration for agricultural soils receiving sewage sludge of 135 mg/kg dry weight. Most soils away from mining areas are well below this value, almost 90% being less than 30 mg/kg.

40. 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 19 and 38 mg/kg, respectively.

41. 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 British Geological Survey (BGS) project to define the typical background concentrations for soil contaminants.

42. 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 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 for the same domain in Wales were a median of 22 mg/kg and a 95th percentile of 43 mg/kg (n = 966 samples).

43. 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 were 32 and 105 mg/kg, respectively.

44. 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 from soil in this assessment, as these are the most conservative values among the three countries.

Air

45. Data from 25 air sampling sites across the UK have been collected by

Defra[4]. The data for 2016 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

46. 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 mg/kg (Mean ± SD, n = 4, range 94 – 253mg/kg).

47. 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).

48. Data from the London boroughs are used in this paper, as these are the most representative values for the general population.

Exposure assessment

49. 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.

50. 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 extensive 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, where individual bodyweights were not available.

Age group (months)	Bodyweight (kg)
0 to <4	5.9[a]
4 to <6	7.8[b]
6 to <9	8.7[b]

[4] https://uk-air.defra.gov.uk/data/non-auto-data?uka_id=UKA00168&view=data&network=metals&year=2016&pollutant=262#view

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)

51. 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 breast milk. 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 34 - 91 and 50 - 140 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)

52. 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 copper concentration of 327 and 640 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.

53. Mean exposures to copper for 4 to 18-month olds were 8.3 to 59 µg/kg bw/day, and 97.5th percentile exposures were 17 to 100 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 640 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

54. 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)

55. 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 highlevel 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 14.3 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

56. 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.. 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.

	Copper Exposure (µg/kg bw/d)					
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+	37	72	40	68	38	62

at highest Median conc.14.3 µg/L						
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

57. 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.

58. 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

59. 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.

60. The resulting total mean and 97.5th percentile exposures indicated that levels of copper in water made a contribution of up to approximately 15% to total exposure.

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. 14.3 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 (14.3 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.

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

Copper concentration in the water	Copper Exposure (LB-UB Range) (µg/kg bw/day)	
	12 to <15 Months	

µg/L	(n=670)		15 to <18 Months (n=605)	
	Mean	97.5th	Mean	97.5th
20 (TDS)	32-33	60-61	36-37	63-64
14.3(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 As described in paragraph 61, the exposures have been estimated using the TDS water concentration (20 µg/L), and the highest median (14.3 µg/L) and 97.5th percentile (280 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
14.3 (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 48) (Table 11). Average exposure to copper from dust in infants and young children was at least an order of magnitude less than that from the diet. Maximum exposure to copper from dust could make a modest contribution to overall exposure in these sub-groups.

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) 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).

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 45). The resulting exposures are presented in Table 14. Exposure of infants and young children to copper in air is negligible compared with exposure from the diet.

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 EVM Safe Upper Level, as shown in the following tables.

72. Intakes ranged from 21 to 57 and 31 to 88% of the SUL in the average and high-level consumers respectively (Table 15).

Table 15. 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. The intakes of copper in 4 to 18-month old infants from breast milk ranged from 5.2 to 37 and 11 to 63% of the SUL in the average and high level consumers respectively (Table 16).

Table 16. 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

74. Intakes from ready-to-feed infant formula ranged from 24 to 32 and 36 to 48% of the EVM 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 SUL in the average and high-level consumers respectively, (Table 17).

Table 17. 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	32	48	24	36
Dry Powder	38	58	29	43
Dry Powder + TDS water of 20 µg/L	39	59	30	45
Dry Powder + median	39	59	29	44

water of 10 μg/L				
Dry Powder + 97.5th percentile water of 280 μg/L	58	88	44	69

Values rounded to 2 SF

75. Total mean intakes (excluding water) of copper from infant formulae, commercial infant foods, and other foods, for 4 to 12 month olds were 23 to 25 % of the EVM SUL and the 97.5th percentile intakes were 39 to 45% of the SUL (Table 18).

Table 18. 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.

	Copper Intake as percentage of EVM SUL (160 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	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

76. 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 19)

Table 19. 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

77. Tables 20 shows that the estimated copper intakes derived from TDS data for children aged 12 to 18 months are increased by up to approximately 19% 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 dietary intake, however, does not exceed the EVM SUL

Table 20. 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

78. Tables 21 shows that the estimated copper intakes derived from TDS data for children aged 12 to 18 months are increased 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 dietary intake, however, does not exceed the EVM SUL.

Table 21. 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

79. 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 22).

Table 22 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

80. 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 23. 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

81. 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 24. Exposures ranged from 0.00014 to 0.075% of the SUL.

Table 24. 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

82. Estimated copper intake values by all routes for all age groups were lower than the EVM SUL of 160 µg/kg bw.

Conclusions

83. The intake of copper by infants from 0 to 12 months and children aged 1 to 5 years through consumption of breast milk, infant formula, food and drinking water is below the Safe Upper Level derived by the EVM and thus there is no toxicological concern to the health of infants and young children with normal copper homeostasis.

84. The contribution of environmental sources (soil, dust and air) is minor to very minor compared with dietary exposure and is not of toxicological concern.

85. The Committee noted that the current advice from NHS Choices on making up infant formula did not explicitly reflect DWI advice that water from the mains tap was preferable to tank-stored water when preparing food and drink unless the tank was intended, set up and maintained adequately to store water in potable condition. DWI also advise running the tap for several seconds before use. Following this

advice would help reduce the ingestion by infants of copper and other contaminants from drinking water.

COT Statement 2018/11

October 2018

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