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

Statement on potential risks from nickel 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 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 statement gives an overview of the potential risks from nickel in the diets of infants and young children in the UK aged 0 to 12 months and 1 to 5 years, respectively.

Background

3. Nickel is a metal that exists in various mineral forms and is present throughout the environment. It is used in a wide variety of processes including electroplating and alloy production, and is present in a wide range of consumer products. Nickel concentrations in the environment reflect both natural and anthropogenic contributions. Although it can exist in various oxidation states, nickel in food and water generally occurs in the divalent form of nickel (Ni(II)), as this is its most stable oxidation state (EFSA, 2015).

4. The general population is exposed to nickel primarily via food and drinking water, with inhalation from ambient air and percutaneous exposure acting as generally minor sources of exposure. Food is generally considered to be a more important source of oral exposure to nickel than drinking water (EFSA, 2015; EVM, 2003; WHO, 2005). High mean levels of nickel have been reported for 'legumes, nuts and oilseeds' and 'cocoa beans and cocoa products' (EFSA, 2015).

5. Following oral exposure in humans, nickel is bioavailable at levels from 1% up to 40%. Bioavailability appears to be lower when exposure occurs in the presence of food or under non-fasted conditions, than when nickel is dosed in drinking water alone (EFSA, 2015). It has been reported that typically <10% of nickel ingested with food is absorbed, while nickel from drinking water alone is more highly absorbed at ~20-25% (EVM, 2002 and 2003). In rats, nickel is rapidly but poorly absorbed following ingestion; absorption has been reported to range from 0.01 to 33.3% depending on the solubility of the nickel compound that had been ingested. Absorbed nickel can bind to serum proteins and is widely distributed in the organism. Absorbed nickel is mainly excreted via urine; it is excreted to a lower extent in breast milk. An estimated elimination half-life of 28 ± 9 hours was calculated in human volunteers (EFSA, 2015).

6. Although nickel is an essential micronutrient for higher plants and some animal species, there are currently no data proving that it is essential for humans (EFSA, 2015).

7. Nickel has been evaluated by the International Agency for Research on Cancer (IARC) (2012) and nickel compounds are considered carcinogenic to humans (Group 1). However, this was based on inhalation data and is not relevant for exposure via the oral route.

8. In humans, the non-carcinogenic effects of oral exposure to nickel include effects on the gastrointestinal, haematological, neurological, and immune systems. Gastrointestinal (i.e. vomiting, abdominal cramps, and diarrhoea) and neurological (i.e. giddiness, headache, and weariness) signs and symptoms are the most reported effects after acute exposure. Exposure to nickel through skin or by inhalation may lead to nickel sensitisation; although oral exposure is not known to lead to sensitisation, it may be able to elicit eczematous flare-up reactions in the skin of nickel-sensitised individuals (EFSA, 2015).

9. Oral ingestion of nickel salts in experimental animals can result in a wide range of adverse effects including nephrotoxicity, hepatotoxicity and metabolic effects. Nickel is able to cross the placental barrier and exert toxic effects in the developing embryo or fetus. Increases in pre- and perinatal mortality have been reported in the offspring of female rats ingesting nickel salts. The currently available epidemiological data do not support an association between dietary nickel exposure and reproductive and developmental effects in humans (EFSA, 2015).

10. The COT has commented on nickel in food a number of times in the past; the general conclusion has been that dietary exposures to nickel were unlikely to be of toxicological concern. The Committee has also concluded that although nickel may exacerbate contact dermatitis/eczema in sensitised individuals, pre-school children are less likely than adults to be sensitised and would therefore not be considered to be a sensitive sub-group (COT, 2008).

Expert opinions

11. An expert opinion on exposure to nickel 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 Expert Group on Vitamins and Minerals (EVM) reviewed nickel in their report on the 'Safe Upper Levels of Vitamins and Minerals' (EVM, 2003). The World Health Organization (WHO) has reviewed exposures to nickel via drinking water as part of the development of their 'Guidelines for Drinking Water Quality' (WHO, 2005 and 2011). The IARC has published an evaluation of the carcinogenicity of nickel and nickel compounds (IARC, 2012).

Derivation of health-based guidance values/margin of exposure (MOE)

Chronic effects

12. Haber *et al.* (2017) established a toddler toxicity reference value (TRV) to fulfil a need for toddler-specific TRVs to risk assess soil remediation, as toddlers have the highest soil intake of all population groups, on a per kg bodyweight (bw) basis.

13. Haber *et al.* identified four 2-generation studies of toxicity in rats with effects in the F1 generation that would reflect the pre-pubescent population (Ambrose *et al.*, 1976; RTI, 1988; Smith *et al.*, 1993; and SLI, 2000). Decreased body weight in the F1 generation appeared to be the most sensitive systemic endpoint and the SLI, 2000 study provided the most reliable data.

14. F1b generation rats in the SLI (2000) study were exposed to 0, 0.2, 0.6, 1.1 and 2.2 mg Ni/kg bw/day (as nickel sulphate hexahydrate). The exposures were *in utero,* through lactation and then through gavage from weaning until adulthood and through the mating period. Bodyweight measurements were taken at postnatal days 1, 4, 7 and 21 and then weekly from when they were weaned until they mated, for males and females. There were no adverse effects on pup body weights at any of the time points or exposure levels. Therefore, the NOAEL for this study was 2.2 mg Ni/kg bw/day, the highest dose tested.

15. Haber *et al* selected 2.2 mg Ni/kg bw/day from this study as the point of departure for deriving a TRV. This value was supported by effects on body weight from the other 3 reproductive studies (Ambrose *et al.,* 1976; Smith *et al.,* 1993*;* RTI, 1988), but was markedly lower (it was the highest dose tested). The authors also noted that the value of 2.2 mg Ni/kg bw/day was the same as the NOAEL in a chronic study by Heim *et al.* (2007).

16. Default uncertainty factors of 10 each for interspecies and intraspecies differences were selected and applied to the NOAEL of 2.2 mg/kg bw/day to derive a TRV of 22, rounded to 20 µg/kg bw/day. Based on this, a tolerable

daily intake (TDI) of 20 µg/kg bw will be used to assess dietary exposures in this report.

Hypersensitivity reactions

17. There is no evidence that ingested nickel causes nickel sensitisation. However, it has been shown that ingestion of nickel by sensitised individuals may cause a dermal reaction. There is a concern that establishment of a TDI or TRV, whilst protective of the general population, would not necessarily be protective of the nickel sensitised population. Haber *et al.* (2017) established an acute reference dose (ARfD) and EFSA (2015) derived a reference point for an MOE approach for sensitised individuals.

Haber et al. (2017)

18. Jensen *et al.* (2006) reviewed 17 clinical studies published between 1966 and 2004 and performed a meta-analysis to determine an oral nickel exposure threshold for elicitation of systemic contact dermatitis. Of the 17 studies reviewed by Jensen *et al.* (2006), Gawkrodger *et al.* (1986), Hindsén *et al.* (2001) and Jensen *et al.* (2003) were the 3 studies modelled by Haber *et al*. None of these studies measured body weight so doses were estimated based on default values. Background dietary nickel was also not considered in any of these studies, so it is not known what impact this may have had on exposure.

19. The benchmark dose (BMD) modelling was carried out using 10% extra risk and 95% lower bounds on the BMDs (BMDLs) and profile likelihood methods. A 2-step process was used to determine the model with the best fit. Initially, acceptable models were selected based on the goodness-of-fit P-value (accepted models had P>0.1). From the accepted models, the best-fitting models were evaluated by taking the following points into consideration:

a. Akaike Information Criterion (AIC)
b. The scaled residuals, evaluated at the dose with a response closest to the BMR. Models with a scaled residual of less than 2 were rejected
c. Visual fit was evaluated only subjectively, with a focus on how well the model fit the underlying data, taking special consideration of data at the lower-dose end of the data.

20. When there was no clear best-fitting model, and more than 1 model had a similar fit, an arithmetic average from all models with a similarly good fit was calculated.

21. Haber *et al.* identified the Jensen *et al.* (2003) study as the most sensitive for the identification of oral nickel exposures associated with systemic contact dermatitis. The authors noted that the response was

identical at the 2 lower doses, but that the confidence limits on each data point were wide due to the small sample size. Therefore, none of the models went through or close to all of the data points. However, the models all had acceptable goodness of fit P-values and scaled residuals. Therefore, an arithmetic average was taken of the results from all of the models to determine a $BMDL_{10}$. The range of values was 0.08 to 0.45 mg nickel. The average $BMDL_{10}$ was 0.30 mg nickel.

22. This $BMDL_{10}$ value was used to develop an ARfD. A body weight of 70 kg and an uncertainty factor of 1 resulted in an ARfD of 4.3 µg Ni/kg, rounded to 4 µg Ni/kg bw.

EFSA

23. EFSA concluded that the meta-analysis by Jensen *et al.* (2006) was unsuitable for derivation of a health based guidance value. EFSA assessed the studies by Gawkrodger *et al.*, 1986; Hindsén *et al.*, 2001; and Jensen *et al.*, 2003 by BMD analysis.

24. The analysis was performed according to guidance developed by EFSA (2009; 2011). The quality of the data was checked according to the 3 criteria listed below. The dose-response data were considered poor when at least one of the criteria below was not met:

i. Different accepted models resulted in widely different BMDL values;

ii. The confidence interval around the BMD was wide;

iii. The BMD was estimated by extrapolation considerably outside the range of observation, such that the BMD/L would depend heavily on the model used.

25. EFSA used all of the models available for dichotomous data in the BMDS software, with a benchmark response (BMR) of 10% extra risk. EFSA selected the minimum BMDL obtained from all accepted models as the BMDL for that dataset, as long as the above criteria were met.

26. EFSA identified Jensen *et al.* (2003) as the most sensitive study. A $BMDL_{10}$ of 0.08 mg Ni per person (1.1 µg Ni/kg bw) was derived, using BMD analysis, as a reference point for systemic contact dermatitis elicited in nickel-sensitive individuals after acute oral exposure to nickel.

27. EFSA decided not to establish an acute reference dose, but to adopt a margin of exposure approach for risk characterisation of this critical effect. The selected reference point was based on a highly sensitive study group of sensitised, fasted individuals given nickel sulphate in lactose capsules (Jensen et al., 2003). Under fasted conditions, absorption is considered to be higher than when food is present. The selected reference point could be conservative for the characterisation of acute risks. However, the large inter-

individual variability in the immune response may not be captured by the limited number of individuals in the studies. Therefore, EFSA concluded that an MOE of 10 or higher would be indicative of low health concern.

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

Sources of nickel exposure

Human breast milk

28. In general, the levels of nickel found in breast milk are low (EFSA, 2015).

29. Two concentrations of nickel in breast milk were selected from the literature and used to represent the low and high levels of nickel measured in samples of breast milk. A minimum value of 0.13 µg/L was determined in a study by Krachler *et al.* (2000). As part of their study, they measured the concentration of nickel in 27 transitory and mature breast milk samples collected from 27 healthy mothers at a hospital in Austria. There were too few samples to consider splitting them into subgroups with regard to different lactation stages. The median concentration of nickel was 0.79 µg/L, while the observed range was <0.13 to 6.35 µg/L (Krachler et al., 2000).

30. A maximum value of 47 µg/L was determined by Bjorklund *et al.* (2012). This study reported a mean concentration of 0.96 µg/L for 60 samples of breast milk collected in 2002-2009 from Swedish first-time mothers at 2-3 weeks postpartum. The authors reported that 75% of the samples fell below the LOD for nickel (0.085 µg/L) and that the minimum and maximum concentrations were "*not determined*" and 47 µg/L, respectively. The overall aim of the study was to provide updated information on the concentrations of a range of toxic and essential elements in breast milk (Björklund *et al*., 2012).

31. These values are taken from studies in European countries but the minimum (0.3 µg/kg) and maximum (39 µg/kg) nickel concentrations, from the UK data from the SUREmilk study (Woolridge *et al.*, 2004), are within this range of values.

Infant formulae and food

32. Concentrations of nickel 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), and in the composite food samples of the 2014 Total Diet Study (TDS).

Food contact materials

33. The migration of nickel from food contact materials could represent an additional source of nickel in food and drinking water. In general, nickel-

containing food contact materials are made of highly corrosion resistant stainless steel so that the metal should not migrate into food in quantities that would endanger human health. Stainless steel products are used in food transportation, for food processing equipment and containers, for cooking utensils and tableware, and for electric kettles and other kitchen appliances. Nickel may also be released from nickel-plated kitchenware; however nickel-plating is less resistant to corrosion than stainless steel so nickel-plated articles are not normally used for materials that are meant to come into contact with food (EFSA, 2015).

34. At present, as recommended by the Council of Europe, manufacturers of food preparation and handling tools and equipment made of stainless steel should respect the migration of nickel compliant with a specific release limit (SRL) of 0.14 mg/kg food (EDQM, 2013; EFSA, 2015).

35. The EFSA CONTAM Panel concluded that the extent of nickel migration due to the use of good quality stainless steel in food contact materials has likely little or no relevance compared to dietary exposure from the intrinsic presence of nickel in the diet. However, leaching of nickel may not be negligible for food contact materials made of poor quality stainless steel, or of other nickel-containing metal alloys (EFSA, 2015).

36. The EVM reported that the quantity of nickel released from food cooked in “already used” stainless steel pans was low to negligible (< 0.07 µg/g), and although release from pans on their first use was higher (up to 0.27 µg/g), the amounts released were still considered relatively small (EVM, 2002).

37. The EFSA stated that the potential leaching of nickel into food from food contact materials was not covered by the occurrence dataset that was used to estimate dietary exposure (EFSA, 2015). The 2014 TDS food samples were prepared ‘as consumed’ prior to analysis and thus any potential levels of nickel leached into food from food contact materials will be reflected in the overall concentrations. However, this is not the case for the samples in the Infant Metals Survey.

Drinking water

38. The primary source of nickel in drinking water is leaching from metals in contact with the water, such as pipes and taps. Although the nickel concentration in drinking water is normally less than 20 µg/L, release from such metal fittings could contribute up to 1 mg/L. Nickel may also be present in some groundwater as a consequence of dissolution from nickel ore-bearing rocks (WHO, 2005 and 2011).

39. EU legislation sets a value of 20 µg/L for nickel in water intended for human consumption (Directive 98/83/EC), and a maximum level of 20 µg/L in natural mineral waters (Directive 2003/40/EC). The WHO has established a guidance level of 70 µg/L for nickel in drinking water, but has stated that a

concentration of 20 µg/L should be achievable by conventional water treatment (WHO, 2011).

40. Levels of nickel in drinking water in 2014/2015 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 1. These values have been used to calculate exposures to nickel from drinking water in combination with exposures from food.

Table 1. Median and 97.5th percentile concentrations (µg/L) of nickel in water across the UK for 2014/2015.

Country	Number of samples	Limit of Detection (µg/L)	Median concentration (µg/L)	97.5th Percentile concentration (µg/L)
England and Wales	14708	0.8-2.0*	1.36	4.63
Northern Ireland	392	0.4	1.14	4.47
Scotland	1500	0.2	0.30	1.95

* 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 (20 µg/L for nickel)

Environmental

Dust

41. The Agency for Toxic Substances and Disease Registry (ATSDR) of the US Department of Health and Human Services advises that nickel concentrations in household dust can be high and therefore pose an increased risk to young children who have greater contact with floors (ATSDR, 2005).

42. The median and maximum nickel concentrations of 53.3 and 97.1 mg/kg respectively, reported by Turner and Simmonds (2006), have been used in the present assessment to estimate exposures to nickel via dust for UK infants and young children.

Soil

43. Nickel is present at about 20 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, disposal of sewage sludge, and emissions from motor vehicles and electric power utilities, and from natural activities such as weathering and erosion of geological materials. The EFSA have estimated that soil ingestion by children would make a low contribution to their overall nickel exposure (EFSA, 2015).

44. In 2012 and 2013, Defra published normal background concentrations (NBCs) for nickel 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 topsoils (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.

45. 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 nickel. 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 23 mg/kg and a 95th percentile of 42 mg/kg (n = 41,768 samples). The statistics reported for the same domain in Wales were a median of 22 mg/kg and a 95th percentile of 38 mg/kg (n = 1,327 samples).

46. The highest median and 95th percentile concentrations for nickel in soil from the Defra-commissioned BGS project on NBCs (23 and 42 mg/kg respectively) have been used to estimate exposures to soil in the present assessment. These data have been used as they are recent, and represent a relevant domain for estimating exposure for the general population.

Air

47. In the atmosphere, nickel occurs mainly as fine respirable particles (<2 µm) and is eventually suspended onto particulate matter. Anthropogenic sources account for more than 80% of the atmospheric nickel burden, with the remainder accounted for by natural sources such as soil dust, volcanoes and forest fires (EFSA, 2015).

48. EU legislation sets a target value[1] of 20 ng/m^3 for nickel in air (Directive 2004/107/EC). Annual mean ambient particulate phase concentrations of nickel in the urban environment are typically of the order of 1 ng/m^3, with the exception of a few industrial areas, where higher annual means may occur, in some locations exceeding the target value of 20 ng/m^3 (Defra, 2015).

[1] A value set by the Air Quality Directive and Fourth Daughter Directive, but which is not legally mandatory. Member States must take all necessary measures but not entailing disproportionate costs to meet the target value. (Defra, 2015)

49. Nickel in atmospheric particulate matter less than 10 µm (PM_{10}) was measured at 23 sites and as metal deposition was measured at 5 sites across the UK in 2014/2015. Median values from these sites ranged from 0.27 to 6.80 ng/m^3 and 99th percentile values ranged from 2.23 to 56.23 ng/m^3. One site in Wales was excluded from the analysis as it regularly measured much higher values than any other site (Defra, 2015).

Exposure assessment

Chronic

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 nickel exposures are shown in Table 2 below.

51. Thorough exposure assessments have been performed for the dietary sources of exposure to nickel. 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 2. Average bodyweights used in the estimation of nickel exposures, where individual bodyweight data 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]
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)

Breast milk

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 nickel from breast milk. These estimates were based on low and high nickel concentrations of 0.13 and 47 µg/L, respectively (Paragraphs 14 and 15). The ranges of exposure to nickel in exclusively breastfed 0 to 6 month olds were 0.01 to 0.02 and 0.02 to 0.03 µg/kg bw/day in average and high level consumers respectively with a nickel concentration of 0.13 µg/L. For breast milk with a nickel concentration of 47 µg/L the ranges of exposures to nickel were 4.8 to 6.4 and 7.2 to 9.6 µg/kg bw/day in average and high level consumers respectively (Table 3).

Table 3. Estimated nickel exposure from exclusive breastfeeding in 0 to 6 month old infants.

Nickel 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**
0.13	0.02	0.01	0.03	0.02
47	6.4	4.8	9.6	7.2

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 6), based on low and high nickel concentrations of 0.13 and 47 µg/L. There were too few records of breast milk consumption for children older than 18 months in the NDNS to allow a reliable exposure assessment, but breast milk is expected to contribute minimally in this age group.

54. Mean exposures to nickel for 4 to 18-month olds with a breast milk nickel concentration of 0.13 µg/L were 0.003 to 0.01 µg/kg bw/day, and 97.5th percentile exposures were 0.01 to 0.02 µg/kg bw/day. A nickel concentration in breast milk of 47 µg/L could lead to mean nickel exposures of 1.2 to 4.3 µg/kg bw/day and 97.5th percentile exposures of 2.4 to 7.5 µg/kg bw/day (Table 4).

Table 4. Estimated chronic nickel exposure in 4 to 18 months old infants from breast milk

Nickel concentration in breast milk (µg/L)	4 to <6 months (n=116)		6 to <9 months (n=606)		9 to <12 months (n=686)		12 to <15 months (n=670)		15 to <18 months (n=605)	
	Mean	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**
0.13	0.01	0.02	0.01	0.02	0.005	0.02	0.004	0.01	0.003	0.01
47	4.3	7.3	3.1	7.5	1.8	5.4	1.4	3.5	`1.2	2.4

Values rounded to 2 SF

Infant formulae and complementary foods

55. Nickel exposure estimates for this category were derived using occurrence data from the Infant Metals Survey (FSA, 2016a), based on both lower bound (LB) and upper bound (UB) concentrations. 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 7). Consumption data from the DNSIYC were used to estimate exposures for 4 to 12 month olds (DH, 2013) (Table 8).

56. In 0 to 6 month olds, exposures to nickel from ready-to-feed formula were 0 to 1.2 µg/kg bw/day in average consumers, and 0 to 1.8 µg/kg bw/day in high level consumers. Exposures to nickel calculated for reconstituted formula incorporating the water concentration from the TDS, and the highest median and 97.5th percentile concentrations for nickel in water reported in Table 3 were 0.40 to 2.0 µg/kg bw/day in average consumers, and of 0.60 to 3.0 µg/kg bw/day in high level consumers (Table 5).

Table 5. Estimated average and high level exposures to nickel from exclusive feeding on infant formulae for 0 to 6 months old infants.

Infant Formula	Nickel exposure (LB-UB Range) (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]	0 - 1.2	0 - 1.8	0 - 0.92	0 - 1.4
Dry Powder [b, c]	0.37 - 1.1	0.55 - 1.6	0.28 - 0.83	0.42 - 1.2
Dry Powder [c] + TDS water of <8	1.3 - 2.0	1.9 - 3.0	0.98 - 1.5	1.5 - 2.2

µg/L [d]				
Dry Powder [c] + median water of 1.36 µg/L [d]	0.53 - 1.3	0.79 - 1.8	0.40 - 0.94	0.60 - 1.4
Dry Powder [c] + 97.5th percentile water of 4.63 µg/L [d]	0.90 - 1.6	1.4 - 2.4	0.68 - 1.2	1.0 - 1.8

Values rounded to 2 SF
[a] Exposure based on first milk infant formula using LB to UB nickel concentrations of 0-9 µg/L
[b] Exposure does not include the contribution from water
[c] Exposure based on first milk infant formula using LB to UB nickel concentrations of 18-54 µg/kg
[d] Calculated assuming reconstituted formula comprises 85% water

57. Total mean exposures (excluding water) to nickel from infant formulae, commercial infant foods, and other foods for 4 to 12 month olds were 1.2 to 2.9 µg/kg bw/day. Nickel exposures for the 97.5th percentile were 3.9 to 5.9 µg/kg bw/day (Table 6). Total mean and 97.5th percentile exposures were also calculated using the highest median and 97.5th percentile concentrations for nickel in water reported in Table 1. The resulting total mean and 97.5th percentile exposures indicated that levels of nickel in water made a negligible contribution to total exposure.

Table 6. Estimated chronic exposures to nickel from infant formulae, commercial infant foods and other foods for 4 to 12 months old infants

	Nickel Exposure (LB-UB Range) (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	0.0044 - 0.59	0.030 - 1.3	0.0031 - 0.43	0 - 0.98	0.0021 - 0.31	0 - 0.68
Commercial infant foods	0.64 - 0.84	2.3 - 3.0	0.89 - 1.2	3.0 - 4.0	0.80 - 1.1	3.0 - 4.2
Other foods	0.46 - 0.57	2.8 - 3.0	0.82 - 1.1	2.9 - 3.6	0.96 - 1.5	3.0 - 4.0
Total (excl. water)	1.2 - 2.1	4.1 - 5.7*	1.8 - 2.8	3.9 - 5.7*	1.8 - 2.9	4.4 - 5.9*

Values rounded to 2 SF
* 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 nickel 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 nickel 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. Exposure estimates based on both LB and UB concentrations are provided.

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 chronic total mean and 97.5th percentile exposures (excluding water) to nickel from infant formula, commercial infant foods and other foods were 1.3 to 2.5 and 2.8 to 5.2 µg/kg bw/day, respectively. As for infants, the total mean and 97.5th percentile exposures including water (calculated using the highest median and 97.5th percentile values in Table 3) were the same as those estimated for the total mean exposures excluding water (Table 7).

Table 7. Estimated chronic exposures to nickel from infant formulae, commercial infant foods and other foods for children aged 12 to 18 months

Food	Nickel Exposure (LB-UB Range) (µg/kg bw/d)			
	12 to <15 Months (n=670)		15 to <18 Months (n=605)	
	Mean	97.5th	Mean	97.5th
Infant formula	0.00050 - 0.13	0 - 0.57	0.00030 - 0.070	0 - 0.42
Commercial infant foods	0.45 - 0.60	2.0 - 2.8	0.24 - 0.32	1.2 - 1.7
Other Foods	0.96 - 1.7	2.6 - 3.8	1.0 - 1.8	2.5 - 3.5
Total (excl. water)	1.4 - 2.5	3.6 - 5.2*	1.3 - 2.2	2.8 - 4.3*

Values rounded to 2 SF

* 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 8 shows the estimated nickel exposures calculated using the TDS data for children aged 12 to 18 months. The nickel concentration for the tap water group in the TDS was reported to be below the limit of detection (LOD) of 8 µg/L. This LOD is higher than that reported for nickel in tap water by the water authorities across the UK (Table 1). The calculation was therefore also performed using the highest median (1.36 µg/L) and 97.5th percentile (4.63 µg/L) nickel concentration in tap water reported in Table 1.

62. Total mean and 97.5th percentile exposures to nickel from a combination of all food groups are in the region of 3.7 to 5.0 and 7.7 to 8.8 µg/kg bw/day, respectively (Table 8). 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 8 demonstrate that the nickel content of water has a negligible impact on total dietary exposure to nickel of young children in the UK.

Table 8. Estimated chronic dietary exposure to nickel based on the TDS data in children aged 12 to 18 months.

Nickel concentration in the water	**Nickel 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**
1.36 µg/L	3.7 - 4.5	7.7 - 8.6	4.0 - 4.9	7.8 - 8.7
4.63 µg/L	3.7 - 4.5	7.7 - 8.6	4.0 - 4.9	7.9 - 8.7

Values rounded to 2 SF

63. In general, the food groups making the highest contribution to nickel exposure were miscellaneous cereals (includes pasta and rice products), poultry and potatoes groups (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 9 shows the nickel exposures that were calculated using the TDS data for children aged 18 months to 5 years. Detailed exposure assessments are presented in Annex C. As described in paragraph 61, the exposures have been estimated using the TDS water concentration (8 µg/L, the LOD), and the highest median (1.36 µg/L) and 97.5th percentile (4.63 µg/L) nickel concentrations in water reported in Table 1. This results in total mean and 97.5th percentile exposures to nickel from a combination of all food

groups of 4.3 to 5.6 and 7.1 to 8.7 µg/kg bw/day, respectively (Table 9). Overall the figures in Table 9 demonstrate that the nickel content of water has a negligible impact on total dietary exposure to nickel of young children in the UK.

Table 9. Estimated chronic dietary exposure to nickel in children aged 18 months to 5 years.

Nickel concentration in water	Nickel 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
1.36 µg/L	4.7 - 5.6	7.5 - 8.7	4.3 - 5.0	7.1 - 8.0
4.63 µg/L	4.8 - 5.6	7.5 - 8.7	4.4 - 5.0	7.1 - 8.0

Values rounded to 2 SF

66. As with the younger children, the food groups making the highest contribution to nickel exposure in the TDS were miscellaneous cereals (includes pasta and rice products), poultry and potatoes groups (FSA, 2016b).

Acute

67. It is possible for infants and young children to be sensitised to nickel through an increased exposure to nickel in the environment. Possible flare-up reactions may be caused by exposure to high levels of nickel in food. Therefore, acute exposures have been calculated. Consumption data on a bodyweight basis used in calculating acute exposures to nickel were derived from a distribution of the highest amount of foods eaten on a given survey day by DNSIYC and NDNS survey respondents.

Infants (4 to 12 months)

Breast milk

68. Data on acute exposure to nickel from breast milk in 4 to 12 months old infants are shown in Table 10. Mean and high-level acute exposures from breast milk were between 1.1 and 1.6-fold higher than corresponding chronic exposures from this source (Table 4).

Table 10. Estimated acute nickel exposure (µg/kg bw/day)µ in 4 to 18 months old infants from breast milk

Nickel concentration in breast milk (µg/L)	**4 to <6 months (n=116)**		**6 to <9 months (n=606)**		**9 to <12 months (n=686)**		**12 to <15 months (n=670)**		**15 to <18 months (n=605)**	
	Mean	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**	**Mean**	**97.5th**
0.13	0.01	0.02	0.01	0.02	0.01	0.02	0.005	0.01	0.004	0.01
47	4.9	8.3	3.7	8.5	2.2	6.0	1.7	4.1	1.6	3.8

Infants aged 0 to 12 months

Exposure estimates based on the Infant Metals Survey

69. Nickel exposure estimates for this category were derived using occurrence data from the Infant Metals Survey (FSA, 2016a), based on both lower bound (LB) and upper bound (UB) concentrations. Acute consumption data from the DNSIYC were used to estimate exposures for 4 to 12 month olds (DH, 2013) (Table 11).

70. The ranges of acute total mean and 97.5th percentile exposures to nickel from infant formula, commercial infant foods and other foods (Table 11) are slightly higher than corresponding chronic exposures and are in the region of 1.8 to 4.0 and 5.4 to 8.3 µg/kg bw/day, respectively.

Table 11. Estimated total acute exposures to nickel from infant formulae, commercial infant foods and other foods for infants aged 4 to 12 months.

Nickel exposure (LB - UB range) (µg/kg bw/day)					
4 to <6 months		6 to <9 months		9 to <12 months	
mean	97.5th	Mean	97.5th	Mean	97.5th
1.8 – 2.7	5.4 – 7.0	2.6 – 3.7	5.9 – 7.5	2.7 – 4.0	6.6 – 8.3

Values rounded to 2 SF

Children aged 12 to 18 months

71. Acute nickel exposures were calculated for children aged 12 to 18 months using data from the Infant Metals Survey and the TDS. Mean and 97.5th percentile acute nickel exposures based on data from the Infant Metals Survey range from 2.3 to 3.5 and 4.9 to 7.1 µg/kg bw/day, respectively. Acute mean and 97.5th percentile exposures for this age group based on data from the TDS were slightly higher than corresponding chronic exposures and range from 5.2 to 6.5 µg/kg bw/day and 11 to 12 µg/kg bw/day, respectively (Table 12).

Table 12. Estimated total acute exposures to nickel from Infant Metals Survey and TDS for children age 12 to 18 months.

Exposures based on data from	Nickel exposure (LB - UB range) (µg/kg bw/day)			
	12 to <15 months		15 to <18 months	
	Mean	97.5th	Mean	97.5th
Infant Metals Survey	2.3 – 3.5	5.2 – 7.1	2.1 – 3.3	4.9 – 6.6
TDS	5.2 – 6.0	11	5.6 – 6.5	11 – 12

Values rounded to 2 SF

Children aged 18 months to 5 years

72. Acute total mean and 97.5th percentile exposures for children aged 18 months to 5 years were calculated from TDS data (Table 13) and ranged from 5.8 to 7.4 and 11 to 12 µg/kg bw/day, respectively.

Table 13. Estimated total acute exposures to nickel from TDS for children aged 18 to 60 months.

Nickel exposure (LB - UB range) (µg/kg bw/day)			
18 to <24 months		24 to <60 months	
Mean	97.5th	Mean	97.5th
6.5 – 7.4	11	5.8 – 6.5	12

Values rounded to 2 SF

Dust

73. Potential exposures of UK infants aged 6 to 12 months and young children aged 1 to 5 years to nickel 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. Median and maximum nickel concentrations in dust of 53.3 and 97.1 mg/kg, respectively, were used to estimate average and high level exposures (paragraph 27) (Table 14).

Table 14. Possible nickel exposures from dust in infants and young children aged 6 months to 5 years.

Nickel 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**
53.3 (Median)	0.18	0.17	0.30	0.29	0.27	0.20
97.1 (Maximum)	0.34	0.30	0.55	0.52	0.49	0.36

Values rounded to 2 SF

Soil

74. Potential exposures of UK infants aged 6 to 12 months and young children aged 1 to 5 years to nickel 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 nickel concentrations of 23 and 42 mg/kg respectively were used in these exposure estimations (paragraph 31) (Table 15).

Table 15. Possible nickel exposures from soil in infants and young children aged 6 months to 5 years.

Nickel 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**
23 (Median)	0.079	0.072	0.11	0.10	0.096	0.071
42 (95th percentile)	0.14	0.13	0.20	0.19	0.18	0.13

Values rounded to 2 SF

Air

75. Potential exposures of UK infants aged 0 to 12 months and young children aged 1 to 5 years to nickel in air were estimated using the body weights shown in Table 2, and by assuming the mean ventilation rates presented in Table 16; these rates have been derived from the US EPA exposure factors handbook (US EPA, 2011b). The resulting exposures are presented in Table 17.

Table 16. Mean ventilation rates used in the estimation of nickel 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

76. The nickel concentrations used in the exposure calculations were the lowest and highest median values and lowest and highest 99th percentile

values of 0.27, 6.80, 2.23 and 56.23 ng/m^3, respectively, from monitoring sites in the UK (paragraph 34).

Table 17. Possible exposures to nickel in infants and young children from air

Nickel 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
0.27 (lowest median value)	0.00016	0.00014	0.00017	0.00015	0.00020	0.00019	0.00018	0.00017
6.80 (highest median value)	0.0040	0.0036	0.0042	0.0038	0.0051	0.0049	0.0045	0.0043
2.23 (lowest 99th percentile value)	0.0013	0.0012	0.0014	0.0013	0.0017	0.0016	0.0015	0.0014
56.23 (highest 99th percentile value)	0.033	0.030	0.035	0.032	0.042	0.040	0.037	0.035

Values rounded to 2 SF

Risk Characterisation

Chronic

77. All nickel exposures for infants and young children aged 1 to 5 years were below the TDI of 20 µg/kg bw (Tables 4 to 9).

Acute

Assuming an MOE reference point of 1.1 µg/kg bw

78. Potential risks from the acute exposure of infants and young children to nickel were characterised by margins of exposure (MOEs), calculated as the ratio of the $BMDL_{10}$ value of 1.1 µg/kg bw, to estimated exposures from dietary sources.

79. Mean acute breast milk exposures in children aged 4 to <18 months (Table 10) with a nickel concentration of 0.13 µg/L ranged from 0.004 to 0.01 µg/kg bw/day. This corresponded to MOEs of 275 to 110, respectively. 97.5th percentile acute breast milk exposures with nickel concentration of 0.13 µg/L ranged from 0.01 to 0.02 µg/kg bw/day, corresponding to MOEs of 110 to 55, respectively. These exposures with a breast milk nickel concentration of 0.13 µg/L all result in MOEs of greater than 10 and it is unlikely that there would be a risk, but in sensitive individuals could lead to exacerbation of nickel sensitisation.

80. Mean acute nickel exposures from breast milk with a nickel concentration of 47 µg/L ranged from 1.6 to 4.9 µg/kg bw/day which corresponds to MOE values ranging from 0.7 to 0.2, respectively. 97.5th percentile breast milk nickel exposures with this nickel concentration ranged from 3.8 to 8.5. This corresponds to MOE values of 0.3 to 0.1, respectively. These mean and 97.5th percentile MOE values are all considerably less than 10.

81. Mean acute nickel exposures in children aged 4 to <12 months (Table 11) from infant formulae, commercial infant foods and other foods range from 1.8 to 4.0 µg/kg bw/day. This corresponds to MOE values from 0.6 to 0.3. 97.5th percentile acute exposures from these sources range from 5.4 to 8.3 µg/kg bw/day, corresponding to MOE values from 0.2 to 0.1. These MOE values are all considerably less than 10.

82. The mean acute nickel exposures based on data from the Infant Metals Survey in children aged 12 to <18 months (Table 12) range from 2.1 to 3.5 µg/kg bw/day and 97.5th percentile exposures range from 4.9 to 7.1 µg/kg bw/day. These correspond to MOE values of 0.5 to 0.3, and 0.2 to 0.2, which are much lower than 10.

83. Mean and 97.5th percentile nickel exposures based on data from the TDS in children aged 12 to <18 months (Table 12) range from 5.2 to 6.5 and 11 – 12 µg/kg bw/day, respectively. From this MOEs were calculated to range from 0.2 to 0.2 and from 0.1 to 0.09. These MOEs are all considerably lower than 10.

84. Mean and 97.5th percentile acute nickel exposures based on data from the TDS in children aged 18 months to 5 years (Table 13) range from 5.8 to 7.4 and 11 to 12 µg/kg bw/day, respectively. Calculated MOEs for these ranges were 0.2 to 0.1 and 0.1 to 0.09, respectively. These MOEs are all much lower than 10.

Assuming an ARfD of 4.0 µg/kg bw

85. Mean acute breast milk exposures in children aged 4 to <18 months (Table 10) with a nickel concentration of 0.13 µg/L ranged from 0.004 to 0.01 µg/kg bw/day. 97.5th percentile acute breast milk exposures with nickel concentration of 0.13 µg/L ranged from 0.01 to 0.02 µg/kg bw/day. These exposures with a breast milk nickel concentration of 0.13 µg/L are all below the ARfD.

86. Mean nickel exposures from breast milk with a nickel concentration of 47 µg/L (Table 10) ranged from 1.6 to 4.9 µg/kg bw/day. 97.5th percentile breast milk nickel exposures with this nickel concentration ranged from 3.8 to 8.5. The mean exposures from nickel at a concentration of 47 µg/L range from 36 to 120% of the ARfD and 97.5th percentile exposures ranged from 95 to 210% of the ARfD.

87. Mean acute nickel exposures in children aged 4 to <12 months (Table 11) from infant formulae, commercial infant foods and other foods range from 1.8 to 4.0 µg/kg bw/day. These exposures are all below the ARfD. 97.5^{th} percentile acute exposures from these sources range from 5.4 to 8.3 µg/kg bw/day, corresponding to 140 to 210% of the ARfD.

88. The mean acute nickel exposures based on data from the Infant Metals Survey in children aged 12 to <18 months (Table 12) range from 2.1 to 3.5, which are below the ARfD and 97.5^{th} percentile exposures range from 4.9 to 7.1. These are 120 to 180% of the ARfD.

89. Mean and 97.5^{th} percentile nickel exposures based on data from the TDS in children aged 12 to <18 months (Table 12) range from 5.2 to 6.5 and 11 – 12 µg/kg bw/day, respectively. These exposures range from 130 to 160 and from 280 to 300% of the ARfD, respectively.

90. Mean and 97.5^{th} percentile acute nickel exposures based on data from the TDS in children aged 18 months to 5 years (Table 13) range from 5.8 to 7.4 and 11 to 12 µg/kg bw/day, respectively. These exposures range from 150 to 190 and 280 to 300% of the ARfD, respectively.

Uncertainties

91. The number of infants and young children that are sensitised to nickel is likely to be a small percentage of the population in this age range (0.9 to 12.9 % (Barros *et al.*, 1999; Bruckner, Weston and Morelli, 2000). It is possible that sensitised individuals will be following a diet that is low in nickel by avoiding foods associated with nickel contamination.

92. Infants and young children may become tolerised to nickel through ingestion via the oral route.

Conclusions

93. Nickel is a metal that exists in various mineral forms and is present throughout the environment. It is used in a wide variety of processes including electroplating and alloy production, and is present in a wide range of consumer products. Nickel concentrations in the environment reflect both natural and anthropogenic contributions.

94. The general population is exposed to nickel primarily via food and drinking water, with inhalation from ambient air and percutaneous exposure acting as generally minor sources of exposure. Following oral exposure in humans, nickel is bioavailable at levels from 1% up to 40% and has lower bioavailability when in the presence of food than in the presence of drinking water alone.

95. In humans, the effects of oral exposure to nickel include effects on the gastrointestinal, haematological, neurological, and immune systems.

Exposure to nickel through skin or by inhalation may lead to nickel sensitisation; although oral exposure is not known to lead to sensitisation, it may be able to elicit eczematous flare-up reactions in the skin of nickel-sensitised individuals.

96. Haber *et al.*, (2017) established a TDI of 20 µg/kg bw for the toddler population and an ARfD of 4.0 µg/kg bw for sensitised individuals. A reference point of 1.1 µg/kg bw for an MOE approach, was established by EFSA for assessing exposures of sensitised individuals to nickel.

97. Nickel exposures from dust, soil and air were considerably lower than from dietary exposures for infants aged 0 to 12 months and young children aged 1 to 5 years.

Chronic

98. Nickel exposures for all age groups and food categories were below the TDI of 20 µg/kg bw. The Committee concluded that there was no toxicological concern to the long term health of infants aged 0 to 12 months and young children aged 1 to 5 years (Table 18).

Acute

99. Assuming an MOE reference point of 1.1 µg/kg bw: EFSA concluded that an MOE of 10 or greater would be indicative of low health concern. Table 19 shows the MOEs calculated from the exposures. Apart from average and high level consumption of breast milk with a low concentration of nickel, all other exposures result in an MOE value of less than 10. Hence, there is the possibility of a dermal response to an oral exposure of nickel at the concentrations currently found in food.

100. Assuming an ARfD of 4.0 µg/kg bw: Nickel exposures show exceedance of the ARfD of up to about 2-fold for high level food and formulae consumers aged 4 to 60 months. Average consumers in this age group may slightly exceed the ARfD. There may be some risk to consumers from nickel exposure aged 4 to 60 months (Table 19). However, there are uncertainties associated with the exposure assessment due to the significant degree of compositing of food items into groups in a TDS. In particular, it is not possible to reliably estimate the contribution of specific food items to total exposure for refining the assessment to reduce these uncertainties.

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

Table 18. Summary of estimated chronic dietary nickel exposures compared to the TDI of 20 µg/kg bw

		Exclusive breast milk		Breast milk		Infant formulae (nickel concentration of the water)					Total (infant formulae+ commercial infant foods +other foods) (excl. water)		Nickel exposure from foods in the TDS		Nickel exposure from foods in the TDS	
		0.13 µg/L	47 µg/L	0.13 µg/L	47 µg/L	Ready-to-Feed	Dry powder	Dry powder (<8 µg/L)	Dry powder (1.36 µg/L)	Dry powder (4.63 µg/L)			(1.36 µg/L)	4.63 µg/L)	(1.36 µg/L)	4.63 µg/L)
Survey/Consumption data		N/A	N/A	IMS	IMS	N/A	N/A	N/A	N/A	N/A	IMS/ DNSIYC	IMS/ DNSIYC	TDS/ DNSIYC	TDS/ DNSIYC	TDS/ NDNS	TDS/ NDNS
Age (months)		0 to 6	0 to 6	4 to <18	4 to <18	0 to 6	0 to 6	0 to 6	0 to 6	0 to 6	4 to 12	12 to 18	12 to 18	12 to 18	18 to 60	18 to 60
Estimated dietary exposures (µg/kg bw/day)[a]	Average consumer	0.01 – 0.02	4.8 – 6.4	0.003 – 0.01	1.2 – 4.3	0 – 1.2	0.28 – 1.1	0.98 - 2.0	0.40 – 1.3	0.68 – 1.6	1.2 – 2.9	1.3 – 2.5	3.7 – 4.9	3.7 – 4.9	4.3 – 5.6	4.4 – 5.6
	High level consumer	0.02 – 0.03	7.2 – 9.6	0.01 – 0.02	2.4 – 7.5	0 – 1.8	0.42 – 1.6	1.5 – 3.0	0.60 – 1.8	1.0 – 2.4	3.9 – 5.9	2.8 – 5.2	7.7 – 8.7	7.7 – 8.7	7.1 – 8.7	7.1 – 8.7
% TDI (20 µg/kg bw)	Average consumer	0.050 – 0.10	24 – 32	0.015 – 0.050	6.0 - 22	0 – 6.0	1.4 – 5.5	4.9 - 10	2.0 – 6.5	3.4 – 8.0	6.0 – 15	6.5 - 13	19 - 25	19 - 25	22 - 28	22 - 28
	High level consumer	0.10 – 0.15	36 - 48	0.050 – 0.10	12 - 36	0 – 9.0	2.1 – 8.0	7.5 - 15	3.0 – 9.0	5.0 - 12	20 - 30	14 - 26	39 - 44	39 - 44	36 - 44	36 - 44

[a] Values are rounded to 2SF and are the lowest lower bound and highest upper bound estimates for the age range

[b] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 µg/kg bw/day by the respective dietary exposure and rounding to 1 SF. The range relates to the upper bound to lower bound estimates of exposure, only one MOE is shown when the estimated dietary exposures generated the same value.

[c] Based on the assumption that reconstituted infant formula comprises 85% water

Table 19. Summary of estimated acute dietary nickel exposures compared to the reference point (RP) for an MOE approach of using a reference point of 1.1 µg/kg bw and the ADI of 4.0 µg/kg bw for sensitised individuals.

		Breast milk		Total (infant formulae+ commercial infant foods +other foods) (excl. water)		Nickel exposure from foods in the TDS	Nickel exposure from foods in the TDS
		0.13 µg/L	47 µg/L				
Survey/Consumption data		IMS	IMS	IMS/ DNSIYC	IMS/ DNSIYC	TDS/ DNSIYC	TDS/ NDNS
Age (months)		4 to <18	4 to <18	4 to 12	12 to 18	12 to 18	18 to 60
Estimated dietary exposures (µg/kg bw/day)[a]	Average consumer	0.004 – 0.01	1.6 – 4.9	1.8 – 4.0	2.1 – 3.5	5.2 – 6.5	5.8 – 7.4
	High level consumer	0.01 – 0.02	3.8 – 8.3	5.4 – 8.3	4.9 – 7.1	11 - 12	11 - 12
MOE (reference point of 1.1 µg/kg bw	Average consumer	275 - 110	0.69 – 0.22	0.61 -0.28	0.52 – 0.31	0.21 – 0.17	0.19 – 0.15
	High level consumer	110 - 55	0.29 – 0.13	0.20 – 0.13	0.22 – 0.15	0.10 – 0.092	0.10 – 0.092
% ADI (4.0 µg/kg bw)	Average consumer	0.10 – 0.25	40 – 120	45 - 100	53 - 88	130 - 160	150 - 190
	High level consumer	0.25 – 0.5	95 - 210	140 - 210	120 - 180	280 - 300	280 - 300

[a] Values are rounded to 2SF and are the lowest lower bound and highest upper bound estimates for the age range
[b] The MOE is calculated by dividing the $BMDL_{0.5}$ of 3.0 µg/kg bw/day by the respective dietary exposure and rounding to 1 SF. The range relates to the upper bound to lower bound estimates of exposure, only one MOE is shown when the estimated dietary exposures generated the same value.
[c] Based on the assumption that reconstituted infant formula comprises 85% water

COT Statement 2018/02

February 2018

References

Almeida, AA.; Lopes, CMPV.; Silva, AMS. and Barrado, E. (2008) 'Trace elements in human milk: Correlation with blood levels, inter-element correlations and changes in concentration during the first month of lactation' *Journal of Trace Elements in Medicine and Biology* 22 pp.196-205

Ambrose, AM.; Larson, PS.; Borzelleca, JF. and Hennigar, GR Jr. (1976) 'Long term toxicological assessment of nickel in rats and dogs' *Journal of Food Science and Technology* 13 pp.181-187

Ander, EL.; Cave, MR.; Johnson, CC. and Palumbo-Roe, B. (2012) 'Normal background concentrations of contaminants in the soils of England. Results of the data exploration for Cd, Cu, Hg and Ni' *British Geological Survey Commissioned Report*, CR/12/041. 88pp. Available at: http://randd.defra.gov.uk/Default.aspx?Menu=Menu&Module=More&Location=None&Completed=0&ProjectID=17768

Ander, EL.; Cave, MR. and Johnson, CC. (2013) 'Normal background concentrations of contaminants in the soils of Wales. Exploratory data analysis and statistical methods.' *British Geological Survey Commissioned Report*, CR/12/107. 128pp. Available at: http://randd.defra.gov.uk/Default.aspx?Menu=Menu&Module=More&Location=None&Completed=0&ProjectID=17768

ATSDR (2005) *Toxicological Profile for Nickel* 'Chapter 2: Relevance to Public Health' Available at: http://www.atsdr.cdc.gov/toxprofiles/tp15.pdf

Barros MA, Baptista A, Correia TM and Azevedo F. (1991). Patch testing in children: a study of 562 schoolchildren. *Contact Dermatitis*. **25:** 156-159

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

Björklund, KL.; Vahter, M.; Palm, B.; Grandér, M.; Lignell, S. and Berglund M. (2012) 'Metals and trace element concentrations in breast milk of first time healthy mothers: a biological monitoring study' *Environmental Health* 11 pp.92

Bruckner AL, Weston WL and Morelli JG. (2000). Does sensitization to contact allergens begin in infancy? *Pediatrics*. **105(1):** e3

Cardoso, OO.; Julião, FC.; Alves, RIS.; Baena, AR.; Díez, IG.; Suzuki, MN.; Celere, BS.; Nadal, M.; Domingo, JL. and Segura-Muñoz, SI. (2014) 'Concentration profiles of metals in breast milk, drinking water, and soil: relationship between matrices' *Biological Trace Element Research* 160 pp.116-122

Casey, CE. and Neville, MC. (1987) 'Studies in human lactation 3: molybdenum and nickel in human milk during the first month of lactation' *American Journal of Clinical Nutrition* 45(5) pp.921-926 – *Abstract only*

COT (2004) 'Statement on a toxicological evaluation of chemical analyses carried out as part of a pilot study for a breast milk archive' Available at: http://cot.food.gov.uk/sites/default/files/cot/cotsuremilk.pdf

COT (2008) 'COT Statement on the 2006 UK Total Diet Study of Metals and Other Elements' Available at: http://cot.food.gov.uk/sites/default/files/cot/cotstatementtds200808.pdf

Defra (Department for Environment, Food and rural affairs) (2012) 'Technical Guidance on normal levels of contaminants in English soil: Nickel.' Available at: http://randd.defra.gov.uk/Default.aspx?Menu=Menu&Module=More&Location=None&Completed=0&ProjectID=17768

Defra (2013) 'Technical Guidance on normal levels of contaminants in Welsh soil: Nickel.' Available at: http://randd.defra.gov.uk/Default.aspx?Menu=Menu&Module=More&Location=None&Completed=0&ProjectID=17768

Defra (2015) 'Air pollution in the UK 2014' Available at: http://uk-air.defra.gov.uk/assets/documents/annualreport/air_pollution_uk_2014_issue_1.pdf

DH (2013). Diet and Nutrition Survey of Infants and Young Children (DNSIYC), 2011. Available at: http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/

EDQM (European Directorate for the Quality of Medicines & Healthcare) (2013) ''Metals and Alloys Used in Food Contact Materials and Articles - A Practical Guide for Manufacturers and Regulators 1st edition' Committee of Experts on Packaging Materials for Food and Pharmaceutical Products, EDQM, Council of Europe: Strasbourg Available at: https://www.edqm.eu/medias/fichiers/list_of_contents_metals_and_alloys_1st_edition.pdf

EFSA (2015) 'Scientific opinion on the risks to public health related to the presence of nickel in food and drinking water' *EFSA Journal* 13 (2) pp.4002 Available at: http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1351.pdf

European Parliament and Council of the European Union (1998) '*Directive 98/83/EC of the European Parliament and of the Council of 3 November 1998 on the quality of water intended for human consumption'* Available at:

http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31998L0083&from=EN

European Parliament and Council of the European Union (2003) '*Directive 2003/40/EC of the European Parliament and of the Council of 16 May 2003 establishing the list, concentration limits and labelling requirements for the constituents of natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters'* Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003L0040&from=EN

European Parliament and Council of the European Union (2004) '*Directive 2004/107/EC of the European Parliament and of the Council of 15 December 2004 relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air'* Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0107&from=EN

EVM (2002) 'Review of Nickel' prepared for the report on the 'Safe Upper Levels of Vitamins and Minerals' Available at: http://tna.europarchive.org/20110911090542/http:/www.food.gov.uk/multimedia/webpage/vitandmin/evmpapers

EVM (2003) 'Safe Upper Levels of Vitamins and Minerals: Nickel' Available at: http://tna.europarchive.org/20110911090542/http://cot.food.gov.uk/pdfs/vitmin2003.pdf

FSA (2016a) 'Survey of metals and other elements in infant foods' (to be published)

FSA (2016b) 'Metals and other elements in the 2014 Total Diet Study' (to be published)

FSCJ (2012) 'Risk Assessment Report: Nickel (beverages)' Available at: https://www.fsc.go.jp/english/evaluationreports/chemicals/nickel_fs683_2012.pdf (*English translation of an excerpt from the original full report*)

Gawkrodger, DJ.; Cook, SW.; Fell, GS. and Hunter, JA. (1986) 'Nickel dermatitis: the reaction to oral nickel challenge' *British Journal of Dermatology* 115 pp.33-38

Gürbay, A.; Charehsaz, M.; Eken, A.; Sayal, A.; Girgin, G.; Yurdakök, M.; Yiğit, Ş.; Erol, DD.; Şahin, G. and Aydin, A. (2012) 'Toxic metals in breast milk samples from Ankara, Turkey: Assessment of lead, cadmium, nickel and arsenic levels' *Biological Trace Element Research* 149 pp.117-122

Haber LT, Bates HK, Allen BC, Vincent MJ, Oller AR. (2017). Derivation of an oral toxicity reference value for nickel. *Regul Toxicol Pharmacol*. 87 Suppl 1:S1-S18. doi: 10.1016/j.yrtph.2017.03.011. Epub 2017 Mar 12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28300623

Harrison, RM. (1979) 'Toxic metals in street and household dusts' *Science of the Total Environment* 11 pp.89-97

Hassan, SH. (2009) 'A comparative study of trace elements in human, animal and commercial milk samples in Erbil, Iraq' *National Journal of Chemistry* 35 pp.543-552

Health Canada (1994) 'Priority Substances List Assessment Report: Nickel and its compounds' *Canadian Environmental Protection Act* Available at: http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl1-lsp1/compounds_nickel_composes/nickel-eng.pdf

Hindsén, M.; Bruze, M. and Christensen, OB. (2001) 'Flare-up reactions after oral challenge with nickel in relation to challenge dose and intensity and time of previous patch test reactions' *Journal of the American Academy of Dermatology* 44 pp.616-623

IARC (2012) 'Monograph 100C – Nickel and nickel compounds' pp.169 Available at: http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C.pdf

Jensen, CS.; Menne, T.; Lisby, S.; Kristiansen, J. and Veien, NK (2003) 'Experimental systemic contact dermatitis from nickel: a dose-response study' *Contact Dermatitis* 49 pp.124-132

Krachler, M.; Prohaska, T.; Koellensperger, G.; Rossipal, E. and Stingeder, G. (2000) 'Concentrations of selected trace elements in human milk and in infant formulas determined by magnetic sector field inductively coupled plasma-mass spectrometry' *Biological Trace Element Research* 76 pp.97-112

Nielsen, GD.; Søderberg, U.; Jørgensen, PJ.; Templeton, DM.; Rasmussen, SN.; Andersen, KE. and Grandjean, P. (1999) 'Absorption and retention of nickel from drinking water in relation to food intake and nickel sensitivity' *Toxicology and Applied Pharmacology* 154 pp.67-75

Parr, RM.; DeMaeyer, EM.; Iyengar, VG.; Byrne, AR.; Kirkbright, GF.; Schöch, G.; Niinistö, L.; Pineda, O.; Vis, HL.; Hofvander, Y. and Omololu, A. (1991) 'Minor and trace elements in human milk from Guatemala, Hungary, Nigeria, Philippines, Sweden, and Zaire' *Biological Trace Element Research* 29 pp.51-75

Rasmussen, PE.; Subramanian, KS. and Jessiman, BJ. (2001) 'A multi-element profile of housedust in relation to exterior dust and soils in the city of Ottawa, Canada' *Science of the Total Environment* 267 pp.125-140

Rasmussen, PE.; Levesque, C.; Chénier, M.; Gardner, HD.; Jones-Otazo, H. and Petrovic, S. (2013) 'Canadian House Dust Study: Population-based concentrations, loads and loading rates of arsenic, cadmium, copper, nickel, lead, and zinc inside urban homes' *Science of the Total Environment* 443 pp.520-529

Rawlins, BG.; McGrath, SP.; Scheib, AJ.; Breward, N.; Cave, M.; Lister, TR.; Ingham, M.; Gowing, C. and Carter, S. (2012) 'The Advanced Soil Geochemical Atlas of England and Wales' Available at: http://resources.bgs.ac.uk/ebooks/AdvancedSoilGeochemicalAtlasEbook/index.html#/1/

RIVM (2001) 'Re-evaluation of human-toxicological maximum permissible risk levels' Appendix 1.11 Nickel Available at: http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf

Salmani, MH.; Mozaffari-Khosravi, H. and Rezaei, Z. (2016) 'The nickel concentration in breast milk during the first month of lactation in Yazd, Center of Iran' *Biological Trace Element Research* 174 pp.65-70

Siglin, JC (2000a) An Oral (Gavage) One-Generation Reproduction Study of Nickel Sulfate Hexahydrate in Rats, Study No. 3472.1. Final Report to NiPERA, November 16 2000, Charles River Laboratories-Ohio

Siglin, JC (2000b) An Oral (Gavage) Two-Generation Reproduction Toxicity Study in Sprague Dawley Rats with Nickel Sulfate Hexahydrate in Rats, Study No. 3472.2. Final Report to NiPERA, November 16 2000, Charles River Laboratories-Ohio

Smyth, D. and Johnston, C. (2013) 'Geochemistry: Methodology' in: Young, M. and Donald, A. (eds.) *A Guide to the Tellus Data* Belfast, UK: Geological Survey of Northern Ireland pp.33-44 Available at: http://nora.nerc.ac.uk/509171/

TERA (1999) 'Toxicological review of soluble nickel salts' Prepared for the Metal Finishing Association of Southern California, Inc., the US EPA, and Health Canada Available at: http://www.tera.org/ART/Nickel/Ni%20main%20text.PDF

Turan, S.; Sayqi, S.; Kiliç, Z. and Acar, O. (2001) 'Determination of heavy metal contents in human colostrum samples by electrothermal atomic absorption spectrophotometry' *Journal of Tropical Pediatrics* 47(2) pp.81-85 – *Abstract only*

Turner, A. and Simmonds, L. (2006) 'Elemental concentrations and metal bioaccessibility in UK household dust' *Science of the Total Environment* 371 pp.74-81

US EPA (1996) 'Chemical Assessment Summary: Nickel, soluble salts; CASRN various' Available at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=271

US EPA (2011a) 'Exposure Factors Handbook Chapter 5: Soil and Dust Ingestion' Available at:
https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252&CFID=69447188&CFTOKEN=21916199

US EPA (2011b) 'Exposure Factors Handbook Chapter 6: Inhalation Rates' Available at:
https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252&CFID=69447188&CFTOKEN=21916199

Vyskočil, A.; Viau, C. and Čížková, M. (1994) 'Chronic nephrotoxicity of soluble nickel in rats' *Human & Experimental Toxicology* 13 pp.689-693

WHO (2005) 'Nickel in Drinking-water: Background document for development of the WHO Guidelines for Drinking-water Quality' Available at:
http://www.who.int/water_sanitation_health/gdwqrevision/nickel2005.pdf

WHO (2011) 'Guidelines for Drinking Water Quality 4th Edition: 12 Nickel' pp.396 Available at:
http://apps.who.int/iris/bitstream/10665/44584/1/9789241548151_eng.pdf

Woolridge, M.; Hay, A.; Renfrew, R.; Cade, J.; Doughty, J.; Law, G.; Madden, S.; McCormick, F.; Newell, S.; Roman, E.; Shelton, N.; Sutcliffe, A. and Wallis, S. (2004) 'SUREmilk study - Surveillance of residues in human milk: Pilot studies to explore alternative methods for the recruitment, collection, storage and management of an archive of breast milk samples.' Final Report to FSA Available at:
http://tna.europarchive.org/20110116113217/http://www.food.gov.uk/multimedia/pdfs/suremilkmain.pdf