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

## Review of 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 of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants, most of which has been completed, and young children. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

2. This discussion paper provides estimated nickel exposures for infants and young children in the UK aged 0 to 12 months and 1 to 5 years, respectively. There are currently no Government dietary recommendations for infants and young children which relate to nickel.

### 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, the divalent form of nickel (Ni(II)) generally occurs in food and water as this is its most stable oxidation state (EFSA, 2015).

4. The general population is primarily exposed to nickel 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).

5. Following oral exposure in humans, nickel is bioavailable at levels from 1% up to 40%. Bioavailability appears to be lower when exposure to nickel 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. 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) 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).

8. Oral ingestion of nickel salts in experimental animals has resulted in a wide range of adverse effects including nephrotoxicity, hepatotoxicity and metabolic effects. Nickel is able to cross the placental barrier and exerts its primary toxic effects in experimental animals by affecting 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).

9. 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*

10. 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 International Agency for Research on Cancer (IARC) has published an evaluation of the carcinogenicity of nickel and nickel compounds (IARC, 2012).

*EFSA*

11. In their 2015 scientific opinion (Annex A), the EFSA CONTAM Panel stated that across Europe, mean chronic dietary exposures to nickel in 'infants' ranged from 3.3 to 6.3 µg/kg body weight (bw)/day, while 95$^{th}$ percentile chronic dietary exposures ranged from 8.0 to 12.3 µg/kg bw/day[1]. The mean and 95$^{th}$ percentile chronic dietary exposures to nickel in 'toddlers' ranged from 5.3 to 13.1 µg/kg bw/day and from 8.7 to 20.1 µg/kg bw/day, respectively. The Panel reported that amongst the different age groups, alongside 'other children', the 'toddlers' group showed the highest chronic dietary exposure to nickel (EFSA, 2015).

12. The CONTAM Panel also detailed the acute dietary exposures to nickel in 'infants' and 'toddlers' across Europe. The mean acute exposures for 'infants' ranged from 5.6 to 6.4 µg/kg bw/day, while the 95$^{th}$ percentile acute exposure was 15.1 µg/kg bw/day. The mean and 95$^{th}$ percentile acute exposures for 'toddlers' ranged from 7.5 to 14.3 µg/kg bw/day and 16.6 to 35.0 µg/kg bw/day, respectively. Once again, the Panel reported that the highest acute exposures to nickel were observed in the 'toddlers' and 'other children' age groups (EFSA, 2015).

13. As part of their assessment, the CONTAM Panel established a new tolerable daily intake (TDI) for nickel. The Panel identified the increased incidence of litters with post-implantation fetal loss observed in different reproductive toxicity studies in rats as the critical effect. A lower 95% confidence limit for a benchmark dose at 10% extra risk ($BMDL_{10}$) of 0.28 mg/kg bw/day was calculated for this effect from the dose-response analysis of the combined data from a 1-generation dose range finding study and a 2-generation study in rats given nickel sulphate hexahydrate via oral gavage (Siglin 2000a and 2000b). The Panel applied a default uncertainty factor of 100 to this $BMDL_{10}$ to account for inter-species differences and inter-individual variability, and derived a TDI of 2.8 µg/kg bw/day (EFSA, 2015).

14. As the Panel considered that the new TDI may not be sufficiently protective of nickel-sensitised individuals, they also assessed acute dietary exposures to nickel. The critical effect was identified as eczematous flare-up reactions in the skin of nickel-sensitised individuals; three studies addressed this issue and were suitable for dose-response analysis (Gawkrodger *et al*., 1986; Hindsén *et al*., 2001; Jensen *et al*., 2003). The Panel calculated a range of $BMDL_{10}$s, 1.1 to 2.6 µg/kg bw/day, and selected the lowest as a reference point for assessing acute oral exposure to nickel (1.1 µg/kg bw/day from Jensen *et al*., 2003). Although there is some evidence that there are dose-dependent relationships between the amounts of nickel ingested and the probability or severity of a flare-up, the Panel decided not to define an acute reference dose as thresholds had not been formally established for sensitisation to most contact allergens. A margin of exposure (MOE) approach was adopted instead, with the Panel deciding that an MOE of 10 or higher would be indicative of a low health concern as the selected reference point was based on a highly sensitive study group of fasted individuals given nickel in capsules[2]. In making this decision, the

[1] Estimates were only available from one dietary survey.
[2] Under such conditions, absorption of nickel is assumed to be considerably higher than it would be from food or in a non-fasted state.

Panel took into account the fact that the critical effect is relatively less severe than other toxic effects in humans, but that there is large inter-individual variability in immune responses and that the studies involved a limited number of participants (EFSA, 2015).

15. Acute exposures have not been estimated or assessed in the current risk assessment as the Committee previously concluded that pre-school children are less likely to be sensitised to nickel than adults, and would therefore not be considered a sensitive sub-group with regard to the elicitation of eczematous flare-up reactions following acute exposures to nickel (paragraph 9).

16. Overall, the CONTAM Panel concluded that current chronic dietary exposure to nickel raises concern when considering the mean and 95$^{th}$ percentile exposures for all age groups. The Panel also concluded that, at the current levels of acute dietary exposure to nickel, there is a concern that nickel-sensitised individuals may develop eczematous flare-up skin reactions (EFSA, 2015).

*EVM*

17. When the EVM reviewed nickel, they noted that dietary intakes of nickel in the UK were 190 µg/day for 1 to 4 year olds. Average dietary nickel intakes for infants aged 0 to 12 months were 0.005 mg/kg bw (EVM, 2002).

18. The EVM stated that the key toxicological endpoint for nickel in humans is the aggravation of nickel sensitisation, and reported that oral intakes of nickel as low as 0.49 to 0.72 mg may be able to trigger flare-ups of dermatitis, particularly if taken on an empty stomach. They also reported that the prevalence of nickel sensitivity is high, and proposed that many individuals may not be aware that they are sensitised. Furthermore, the absorption of nickel is greater when taken on an empty stomach and in the absence of food, as may occur with dietary supplements. Overall, the EVM concluded that it was not possible to set a safe upper level or guidance value for supplemental intake of nickel, but stated that they did not expect UK dietary intake of nickel in food to result in harmful effects (EVM, 2003).

19. During their review, the EVM also considered data from animal studies. They noted that, in animals, nickel has fairly non-specific toxic effects, but appears to be associated with increased perinatal mortality in multi-generation studies. A lowest observed adverse effect level (LOAEL) of 1.3 mg/kg bw/day was selected from a study by Smith *et al*. (1993) in which female rats were given nickel chloride in drinking water for 11 weeks prior to breeding and throughout gestation and lactation. No overt toxicity was reported but there was a dose-related increase in pups born dead, or dying shortly after birth. The EVM applied a total uncertainty factor of 300 (3 for LOAEL to no observed adverse effect level (NOAEL) extrapolation, 10 for inter-species variation and 10 for intra-individual variation), and concluded that a total nickel intake of 0.0043 mg/kg bw/day would not be expected to have adverse effects in non-sensitised individuals (EVM, 2003).

*WHO*

20. The WHO established a provisional guidance value of 70 µg/L for nickel in drinking water in 2005, but has stated that a concentration of 20 µg/L should be achievable by conventional water treatment (WHO, 2005 and 2011).

21. When reviewing nickel in drinking water, the WHO established a general toxicity value of 130 µg/L. This value was determined using a TDI of 22 µg/kg bw, by assuming a 60 kg adult human drinking 2 litres of water per day, and by allocating a conservative 20% of the TDI to drinking water. The TDI was based on a NOAEL of 2.2 mg/kg bw/day taken from a two-generation study on rats; the NOAEL was identified for all end-points studied including post-implantation/perinatal lethality. The WHO applied an uncertainty factor of 100 to the NOAEL (10 to account for interspecies variation and 10 to account for intra-species variation) to derive the TDI (WHO, 2005).

22. The WHO considered that this general toxicity value may not be sufficiently protective of individuals sensitised to nickel, for whom a sufficiently high oral challenge could elicit an eczematous reaction. The WHO therefore derived the aforementioned guideline value for nickel in drinking water (70 µg/L) using a TDI of 12 µg/kg bw. The TDI was based on a LOAEL of 12 µg/kg bw that had been identified by Nielsen *et al*. (1999) following administration of fasted patients with a single dose of nickel that was much higher than would normally be possible through drinking water and/or with the presence of food in the stomach, which would significantly reduce the absorption. No uncertainty factors were applied to the LOAEL when deriving the TDI, as it was based on a highly sensitive human population. When deriving the guideline value, the WHO once again assumed a 60 kg adult human drinking 2 litres of water per day and allocated 20% of the TDI to drinking water. The WHO stated that "*Although this value is close to the acute LOAEL, the LOAEL is based on the total exposure to nickel, in this study, being from drinking-water, and the absorption of nickel from drinking water on an empty stomach is 10- to 40-fold higher than the absorption from food. Basing the total acceptable intake for oral challenge from studies using drinking-water on an empty stomach in fasted patients can, therefore, be considered a worst-case scenario.*" (WHO, 2005).

*IARC*

23. The IARC has reviewed nickel and nickel compounds multiple times, most recently in 2011, and has classified them as human carcinogens that cause cancers of the lung, nasal cavity and paranasal sinuses after inhalation (IARC, 2012). There is currently no consistency in the epidemiological data to suggest that nickel compounds cause cancer at additional sites or by additional routes, and no tumours have been observed in oral carcinogenicity studies in experimental animals. The EFSA CONTAM Panel therefore considered it unlikely that dietary exposure to nickel results in cancer in humans (EFSA, 2015).

*Notes on the health-based guidance values*

24. Whilst reviewing the results of a 2014 survey of metals and other elements in infant foods (FSA, 2016a), the Committee concluded that it would not be appropriate to use the EFSA's TDI to assess exposures to nickel in those aged 0 to 5 years. This

was because the TDI is based on an adverse reproductive effect which is not relevant for this age group; the Committee suggested that an alternative health-based guidance value (HGBV) be sought (TOX/2016/29[3] and TOX/MIN/2016/04[4]).

25. Table 1 lists the currently available HBGVs for nickel which are not based on adverse reproductive effects (adapted from EFSA, 2015), the HBGV derived by the EVM was not reported by the EFSA and has not been included in this table as it is based on adverse reproductive effects. The critical studies used to derive the HBGVs in table 1 have been described below.

Table 1. Currently available health-based guidance values for nickel which are not based on adverse reproductive effects (adapted from EFSA, 2015).

| **Group** | **Limit type** | **HBGV (µg/kg bw/day)** | **Species** | **Reference point (mg/kg bw/day)** | **Critical effect** | **Critical study reference** | **UF** |
|---|---|---|---|---|---|---|---|
| FSCJ (2012) | TDI | 4 | Human (fasted) | LOAEL – 0.012 | Eczematous reaction | Nielsen *et al*. (1999) | 3 |
| WHO (2005) | TDI | 12 | Human (fasted) | LOAEL – 0.012 | Eczematous reaction | Nielsen *et al*. (1999) | 1 |
| RIVM (2001) | TDI | 50 | Rat | NOAEL – 5 | Decreased organ and body weight | Ambrose *et al*. (1976) | 100 |
| TERA (1999) | RfD | 8 | Rat | LOAEL – 8 | Increased kidney weight | Vyskočil *et al*. (1994) | 1000 |
| Health Canada (1994) | TI (nickel sulphate) | 50 | Rat | NOAEL – 5 | Decreased organ and body weight | Ambrose *et al*. (1976) | 100 |
| USA EPA (1996) | RfD | 20 (soluble nickel salts) | Rat | NOAEL – 5 | Decreased organ and body weight | Ambrose *et al*. (1976) | 300 |

HBGV = health-based guidance value, bw = body weight, UF = uncertainty factor, TDI = tolerable daily intake, RfD = reference dose, TI = tolerable intake, LOAEL = lowest observed adverse effect level, NOAEL = no observed adverse effect level

26. Nielsen *et al*. performed two studies to examine the influence of fasting and food intake on the absorption and retention of nickel that had been added to drinking water, and to determine if nickel sensitisation had any impact on these factors. In the first study, 8 non-allergic male volunteers were given nickel in drinking water, followed by meals at different time intervals. No adverse reactions were recorded in any of the volunteers. Overall, serum nickel levels peaked sooner and higher when nickel was ingested before food than when it was ingested with food (Nielsen *et al*., 1999).

[3] https://cot.food.gov.uk/sites/default/files/tox2016-29.pdf
[4] https://cot.food.gov.uk/sites/default/files/draftminutesjuly16.pdf

27. In the second study, 20 nickel-sensitised women and 20 age-matched controls were given a stable nickel isotope in drinking water at a dose of 12 µg/kg bw. The nickel was ingested on an empty stomach, and fasting was maintained for a further 4 hours following nickel administration. Both groups had vesicular hand eczema of the pompholyx type, all patients were examined by the same dermatologist who was blinded regarding nickel allergy. Following nickel intake, 9 out of 20 of the nickel-sensitised women developed a flare-up of symptoms and reported increased use of topical steroids, all exacerbations started within 12 hours after nickel administration. The authors reported that the clinical symptoms were unrelated to the magnitude of nickel concentrations found in serum and urine. They also reported that the course of nickel absorption and excretion in the allergic groups in the second study did not differ and was similar to the pattern seen in the volunteers in the first study (Nielsen *et al*., 1999).

28. The results from Nielsen *et al*. (1999) were used by the Food Safety Commission of Japan (FSCJ, 2012) and the WHO (WHO, 2005) to derive their TDIs. While the WHO did not apply any uncertainty factors to the LOAEL (12 µg/kg bw) (paragraph 22), the FSCJ applied an uncertainty factor of 3 to account for the use of a LOAEL rather than a NOAEL when deriving their TDI.

29. Ambrose *et al*. (1976) performed a two-year feeding study with 4 groups of albino Wistar rats (25 of each sex). The groups were placed on diets consisting of 0, 100, 1000, and 2500 ppm nickel. Overall, growth was significantly depressed in rats on the 1000 and 2500 ppm diets, and organ-to-body weight data indicated increased heart and decreased liver ratios for females on the same diets. Haematological and urinary findings were normal, histopathological studies revealed no lesions, and assessment of tissue storage of nickel in various organs indicated no important storage sites. The authors also reported the results of a two-year feeding study in dogs and a three-generation study in rats in the same article (Ambrose *et al*., 1976).

30. A NOAEL of 5 mg/kg bw/day was derived from the study by Ambrose *et al.* based on the absence of effects in the diet containing 100 ppm nickel. This NOAEL was used by the Dutch National Institute for Public Health and the Environment (RIVM, 2001), Health Canada (Health Canada, 1994), and the United States Environmental Protection Agency (US EPA, 1996), to derive their HBGVs. Both the RIVM and Health Canada applied a total uncertainty factor of 100 (based on the default factors of 10 each for intra- and inter-species extrapolation) to the NOAEL. The US EPA applied an uncertainty factor of 300; they used the same default factors as the RIVM and Health Canada but added a further factor of 3 to account for inadequacies in the study (i.e. a small sample size).

31. Vyskočil *et al*. (1994) performed a sub-chronic study in groups of male and female Wistar rats (40 of each in total). The rats received either demineralised water (control) or water containing nickel (as nickel sulphate) at a concentration of 100 mg/L. After 3 and 6 months of exposure, 10 control and 10 exposed rats of each sex were placed in individual metabolic cages for 24 hours to collect urine, and were then sacrificed, with the kidneys being quickly dissected and weighed. Nickel intakes were 7.56±2.13 and 6.25±0.76 mg/kg bw/day for the male rats exposed for 3 and 6 months, respectively, and 8.40±1.39 and 6.76±2.39 mg/kg bw/day for the female rats exposed for 3 and 6 months, respectively. After 6 months, kidney weights were

significantly increased in both male and female exposed groups, and urinary excretion of albumin was significantly increased female exposed rats. No significant changes were observed in other parameters (Vyskočil *et al*., 1994).

32. The study by Vyskočil *et al*. was used by the Toxicology Excellence for Risk Assessment Center in the USA (TERA, 1999) to derive their reference dose. The TERA derived a LOAEL of 8 mg/kg bw/day from the study and applied an uncertainty factor of 1000: 10 each for intra- and inter-species extrapolation, and a further 10 for sub-chronic-to-chronic extrapolation, an insufficient database, and use of a minimal LOAEL.

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

### *Sources of nickel exposure*

*Human breast milk*

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

34. As part of the 2004 SUREmilk study, levels of nickel were measured in breast milk from women in the UK. The highest concentration in an individual sample was 39 µg/kg; approximately 14% of the 104 samples had concentrations that were equal to or below a limit of detection (LOD) of 0.3 µg/kg, while ~40% of them were equal to or below a limit of quantification (LOQ) of 1.0 µg/kg (Woolridge *et al*., 2004).

35. The COT[5] noted that the SUREmilk samples were collected primarily to explore the viability of breast milk collection methods (COT, 2004), and not as part of a rigorous survey. On this basis, and due to the lack of more complete summary statistics (i.e. a median or mean), literature searches were performed to search for more applicable UK data. These literature searches did not identify any further data for nickel concentrations in breast milk in the UK, so were expanded to include non-UK data. The searches identified a number of studies, some of which had been take account of in the EFSA's scientific opinion (EFSA, 2015); the studies are summarised in Table 2 and are detailed below.

Table 2. Concentrations of nickel breast milk available from the published literature

| Country | Number of samples | Average concentration (µg/L)[a] | Minimum concentration (µg/L) | Maximum concentration (µg/L) | Reference |
|---|---|---|---|---|---|
| UK | 104 | - | <0.3 | 39 | Woolridge *et al*., 2004 |
| USA | 46 | 1.2±0.4 | - | - | Casey and Neville, 1987 |

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

| | | | | | |
|---|---|---|---|---|---|
| Guatemala | 74 | 12.9±1.38* | - | - | Parr *et al*., 1991 |
| Hungary | 70 | 14.4±0.7* | - | - | |
| Nigeria | 14 | 12.2±3.6* | - | - | |
| Philippines | 62 | 16.1±1.2* | - | - | |
| Sweden | 31 | 11.0±1.1* | - | - | |
| Zaire | 59 | 4.9±1.7* | - | - | |
| Austria | 27 | 0.79* | <0.13 | 6.35 | Krachler *et al*., 2000 |
| Turkey | 30 | 27.8 | - | - | Turan *et al*., 2001 |
| United Arab Emirates | 205 | 2.58 (2.64*) | 0.15 | 12.4 | Abdulrazzaq *et al*., 2008 |
| Iraq | 30 | 6.56 | - | - | Hassan, 2009 |
| Portugal | 34 (colostrum) | 7.6±7.9 (4.6*) | 1.0 | 35.8 | Almeida *et al*., 2008 |
| | 19 (mature) | 5.8±1.8 (5.3*) | 3.7 | 10.7 | |
| Sweden | 60 | 0.96±6.5 (<0*) | - | 47 | Björklund *et al*., 2012 |
| Turkey | 60 | 43.9±33.8 (30.3*) | 8.3 | 148.6 | Gürbay *et al*., 2012 |
| Brazil | 58 | 1.19* | 0.22 | 3.23 | Cardoso *et al*., 2014 |
| Iran | 150 | 51.0±7.6 | - | - | Salmani *et al*., 2016 |

[a] Average concentration is the mean or median, where it is the median this has been indicated with *. Where it has been available, the standard deviation has also been provided (as ±…).

36. Casey and Neville (1987) measured nickel concentrations in 46 samples of breast milk collected between delivery and 38 days post-partum from 13 women in the USA. The overall mean nickel concentration was 1.2±0.4 µg/L. The nickel concentrations did not change over time (Casey and Neville, 1987 – *abstract only*).

37. Nickel concentrations were determined in human whole milk samples from Guatemala, Hungary, Nigeria, Philippines, Sweden, and Zaire as part of a WHO/International Atomic Energy Agency (IAEA) joint project to assess infant exposures to minor and trace elements in breast milk. It is not clear when the samples were taken but the study was initiated in 1973. The samples were collected at roughly 3 months post-partum. The median concentrations ranged from 4.9 (Zaire) to 16.1 µg/L (Philippines), the number of samples from each country ranged from 14 (Nigeria) to 74 (Guatemala) (Parr *et al*., 1991).

38. Krachler *et al*. (2000) conducted a study to elucidate the potential of magnetic sector field inductively coupled plasma-mass spectrometry (ICP-MS) for reliable determination of essential and non-essential trace elements, and toxic elements in human milk. 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 reported to be 0.79 μg/L, while the observed range was <0.13 to 6.35 μg/L (Krachler *et al*., 2000).

39. Turan *et al*. (2001) determined the nickel concentrations in 30 samples of colostrum collected from middle-class mothers in Turkey; the mean concentration of nickel was reported to be 27.8 μg/L (Turan *et al*., 2001 – *abstract only*).

40. Abdulrazzaq *et al*. (2008) undertook a study to determine the trace metal and nutrient content of breast milk and plasma in lactating women during or after the first month post-partum. A total of 205 samples of breast milk were analysed, samples were collected from mothers visiting a maternal and child health unit in the United Arab Emirates. A mean nickel concentration of 2.58±1.51 μg/L (median = 2.64 μg/L) was reported, along with minimum and maximum concentrations of 0.15 and 12.4 μg/L, respectively. There was no correlation between the concentration of nickel in the breast milk and that in the plasma (Abdulrazzaq *et al*., 2008).

41. Hassan (2009) aimed to compare the availability of trace elements in human and animal (cow and goat) milk. A total of 30 breast milk samples were collected from 10 women on days 1 to 3 post-partum at a hospital in Iraq. Hassan reported a mean nickel concentration of 6.56 μg/L (Hassan, 2009).

42. Almeida *et al*. (2008) analysed the nickel concentration of samples of colostrum and mature breast milk collected from 44 women who were enrolled into their study at a hospital in Portugal while still pregnant in November 2003. The aims were to study the relationship between the levels of certain trace elements in maternal milk and their corresponding levels in blood, to evaluate the changes in their concentrations in milk during the first month of lactation, and to detect potential inter-element correlation within each type of sample. Overall, 34 samples of colostrum (taken 2 days post-partum), and 19 samples of mature breast milk (taken 1 month post-partum), were collected. The mean concentration of nickel in the colostrum samples was 7.6±7.9 μ/L (median = 4.6 μg/L), while the minimum and maximum concentrations were 1.0 and 35.8 μg/L, respectively. The mean concentration of nickel in the mature milk samples was 5.8±1.8 μ/L (median = 5.3 μg/L), while the minimum and maximum concentrations were 3.7 and 10.7 μg/L, respectively. The detection limit was 0.12 μg/L. The decrease in nickel concentration from colostrum to mature milk was not statistically significant, and no correlations were observed between the levels of nickel in blood and colostrum samples. There were significant correlations between the concentrations of nickel and lead, and nickel and manganese, in the mature milk samples (Almeida *et al*., 2008).

43. Björklund *et al*. (2012) reported a mean concentration of 0.96 μg/L (median < 0 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). This study was not mentioned in the EFSA's scientific opinion.

44. Gürbay *et al*. (2012) determined the nickel concentration of breast milk samples from women in Turkey in order to assess the level of contamination. A total of 64 samples were collected at 2 to 5 days post-partum between October 2007 and March 2008. The mean nickel concentration of 60 samples was reported to be 43.9±33.8 µg/L (median = 30.3 µg/L), while the minimum and maximum concentrations were 8.3 and 148.6 µg/L, respectively. Overall, the authors reported that 8 of the samples were none detects, 25 had concentrations ≤ 30 µg/L, 16 had concentrations of 31 to ≤ 60 µg/L, 11 had concentrations of 61 to ≤ 100 µg/L, and 4 samples had concentrations of 101 to 150 µg/L (Gürbay *et al*., 2012).

45. Cardoso *et al*. (2014) undertook a study to determine the relationship between the concentrations of a number of metals in breast milk, drinking water, and soil, in a specific municipality of Brazil. A total of 58 samples of breast milk were collected during the first month of lactation. The median concentration of nickel in breast milk was 1.19 µg/L, while the minimum and maximum concentrations were 0.22 and 3.23 µg/L, respectively. The LOQ for was reported to be 0.1 µg/L. Similar concentration profiles were observed when comparing the concentrations of nickel in breast milk with those in drinking water, but not those in soil (Cardoso *et al*., 2014).

46. Salmani *et al*. (2016) conducted a study to assess whether the nickel concentration in the breast milk of lactating mothers was associated with certain demographic parameters (education level, age and employment status). Breast milk samples were collected from 150 mothers visiting health centres in Iran in the first month post-partum. The mean concentration of nickel overall was reported to be 51.0±7.6 µg/L; when the samples were split according to the different demographics parameters, the mean concentrations ranged between 46.0±6.69 µg/L and 56.7±3.85 µg/L. There were no significant associations between the concentrations of nickel in breast milk and the different demographic parameters of the mothers (Salmani *et al*., 2016).

47. To assess nickel exposures via breast milk, the EFSA used the highest published mean nickel concentration of 43.9 µg/L reported by Gürbay *et al*. (2012), and considered mean and maximum breast milk consumption levels of 800 and 1200 mL/day, respectively, for an exclusively breast-fed infant aged 3 months and weighing 6.1 kg. These assumptions generated mean and high level exposure estimates of 5.8 and 8.6 µg/kg bw/day, respectively. Based on these exposures, the EFSA considered that nickel exposures in breastfeeding infants to be similar to or lower than non-breastfeeding infants (EFSA, 2015).

48. The mean nickel concentration of 43.9 µg/L reported by Gürbay *et al*. (2012) has also been used to assess exposures to nickel via breast milk in the current assessment.

*Infant formulae and food*

49. 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*

50. The migration of nickel from food contact materials could represent an additional source for the presence 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; although 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).

51. 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).

52. 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 the dietary exposure determined by 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).

53. 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).

54. 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 concentration. However, this is not the case for the samples of the infant metals survey.

*Drinking water*

55. The primary source of nickel in drinking water is leaching from metals in contact with drinking 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).

56. In water, nickel is most likely to be present as Ni(II) (paragraph 3). In their assessment, the EFSA found the contribution of drinking water to the total exposure to nickel to be very small across all age groups (EFSA, 2015).

57. 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).

58. 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 97.5$^{th}$ percentile values calculated from this data are shown in Table 3. These values have been used to calculate exposures to nickel from drinking water in combination with exposures from food.

Table 3. Median and 97.5$^{th}$ 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) | 97.5$^{th}$ 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

59. 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).

60. Literature searches have identified two studies that have assessed the concentration of nickel in dust in the UK. The first study, Harrison (1979), measured total nickel in 4 samples of household dust. The mean concentration was reported to be 43±8 mg/kg, while the range was 36 to 52 mg/kg (Harrison, 1979).

61. The second study, Turner and Simmonds (2006), determined nickel concentrations in samples of dust collected from 32 randomly selected private households within 4 different regions of the UK. The mean concentration of nickel in the samples was 56.5±20.0 mg/kg (median = 53.3 mg/kg), the range was 27.2 to 97.1 mg/kg (Turner and Simmonds, 2006).

62. The concentrations of nickel in household dust reported in these studies are fairly comparable with those reported by a research group in Canada who have recently undertaken a number of studies to assess the concentrations of several elements in dust in the home. Overall they have reported mean nickel concentrations of 62.9 mg/kg in 48 samples (median = 51.5, range = 16.0 to 243.3 mg/kg, 95$^{th}$ percentile = 116.4 mg/kg), and of 102±188 mg/kg in 1025 samples (median = 62.3 mg/kg, range = 17.3 to 2300 mg/kg, 95$^{th}$ percentile = 322 mg/kg) (Rasmussen *et al*., 2001; Rasmussen *et al*., 2013).

63. 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 this assessment to estimate exposures to nickel via dust for UK infants and young children.

Soil

64. 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 nickel exposure (EFSA, 2015).

65. Concentrations of nickel were measured in 5,670 topsoil (from a depth of 0 to 15 cm) samples collected between 1978 and 1982 in England and Wales, avoiding large urban areas. Samples were analysed 30 years later (Rawlins *et al.*, 2012). The median and 90$^{th}$ percentile concentrations were reported as 21 and 39 mg/kg, respectively.

66. In 2012 and 2013, the Defra published normal background concentrations (NBCs) for nickel in soil in England and Wales (Defra, 2012 and 2013). An NBC is the 95$^{th}$ 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 BGS project to define the typical background concentrations for soil contaminants.

67. 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 95$^{th}$ 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 95$^{th}$ percentile of 38 mg/kg (n = 1,327 samples).

68. 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 limit of detection used was 1.4 mg/kg (Smyth and Johnston, 2013). The median and 95$^{th}$ percentile concentrations derived from the data[6] are 29 and 155 mg/kg, respectively.

69. The highest median and 95$^{th}$ 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 this assessment. These data have been used as they are recent, and represent a relevant domain for estimating exposure for the general population.

Air

70. 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).

71. EU legislation sets a target value 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).

72. Nickel in 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 99$^{th}$ 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***

73. 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 4 below.

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[6] Data available for download from https://www.opendatani.gov.uk/dataset/rural-soil-survey/resource/1c35fb41-1c4e-4c33-956e-3b2e7850ee93

74. 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 thorough as the focus of this statement is the diet of infants and young children.

Table 4. Average bodyweights used in the estimation of nickel exposures

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

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

*Infants (0 to 12 months)*

Breast milk

75. 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 breastmilk. These estimates were based on a mean nickel concentration of 43.9 µg/L. The ranges of exposure to nickel in exclusively breastfed 0 to 6 month olds were 4.5 to 6.0 and 6.8 to 8.9 µg/kg bw/day in average and high level consumers respectively (Table 5).

Table 5. Estimated nickel exposure from exclusive breastfeeding in 0 to 6 month old infants, with breast milk containing nickel at 43.9 µg/L.

| 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 |
| 43.9 | 6.0 | 4.5 | 8.9 | 6.8 |

Values rounded to 2 significant figures (SF)

76. 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 a mean nickel concentration of 43.9 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, and breast milk is expected to contribute minimally in this age group.

77. Mean exposures to nickel for 4 to 18 month olds were 1.1 to 4.0 µg/kg bw/day, and 97.5$^{th}$ percentile exposures were 2.3 to 7.0 µg/kg bw/day (Table 6).

Table 6. Estimated nickel exposure in 4 to 18 month old infants from breast milk, containing nickel at 43.9 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 | 4.0 | 2.9 | 1.7 | 1.3 | 1.1 |
| 97.5$^{th}$ percentile | 6.8 | 7.0 | 5.1 | 3.3 | 2.3 |

Values rounded to 2 SF

Infant formulae and complementary foods

78. 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).

79. 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 97.5$^{th}$ 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 7).

Table 7. Estimated average and high level exposures to nickel from exclusive feeding on infant formulae for 0 to 6 month olds.

| 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 µg/L [d] | 1.3-2.0 | 1.9-3.0 | 0.98-1.5 | 1.5-2.2 |
| 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] + 97.5$^{th}$ 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

80. 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, and 97.5$^{th}$ percentile exposures were 3.9 to 5.9 µg/kg bw/day. Detailed exposure assessments for 4 to 18 month old infants and young children are provided in Annex B. Total mean and 97.5$^{th}$ percentile exposures were also calculated using the highest median and 97.5$^{th}$ percentile concentrations for nickel in water reported in Table 3. The resulting total mean and 97.5$^{th}$ percentile exposures indicated that levels of nickel in water made a negligible contribution to total exposure (Table 8).

Table 8. Estimated exposures to nickel from infant formulae, commercial infant foods and other foods for 4 to 12 month olds.

| **Food** | **Nickel Exposure (LB-UB Range) (µg/kg bw/d)** | | | | | |
|---|---|---|---|---|---|---|
| | **4 to <6 Months (n=116)** | | **6 to <9 Months (n=606)** | | **9 to <12 Months (n=686)** | |
| | **Mean** | **97.5$^{th}$** | **Mean** | **97.5$^{th}$** | **Mean** | **97.5$^{th}$** |
| 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 97.5$^{th}$ percentile consumption value for each of the three food categories

*Children aged 12 to 18 months*

81. 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.

82. 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

83. The ranges of total mean and 97.5$^{th}$ 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 97.5$^{th}$ percentile exposures including water (calculated using the highest median and 97.5$^{th}$ percentile values in Table 3) were equal to those estimated for the total mean exposures excluding water (Table 9).

Table 9. Estimated exposures to nickel from infant formulae, commercial infant foods and other foods in 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 | 97.5$^{th}$ | Mean | 97.5$^{th}$ |
| 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

84. Table 10 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 3). 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 3.

85. 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 10). 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 nickel content of water has a negligible impact on total dietary exposure to nickel of young children in the UK.

Table 10. Estimated 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

86. 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*

87. 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).

88. Table 11 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 80, 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 3. This results in total mean and 97.5th percentile exposures to

nickel from a combination of all food groups of 4.3 to 5.7 and 7.1 to 8.7 µg/kg bw/day, respectively (Table 11). Overall the figures in Table 11 demonstrate that the nickel content of water has a negligible impact on total dietary exposure to nickel of young children in the UK.

Table 11. Estimated 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

89. 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).

Dust

90. 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 63) (Table 12).

Table 12. 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

91. 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 69) (Table 13).

Table 13. 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

92. 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 4, and by assuming the mean ventilation rates presented in Table 14; these rates have been derived from the US EPA exposure factors handbook (US EPA, 2011b). The resulting exposures are presented in Table 15.

Table 14. 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 |

93. 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 72).

Table 15. 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 99$^{th}$ percentile value) | 0.0013 | 0.0012 | 0.0014 | 0.0013 | 0.0017 | 0.0016 | 0.0015 | 0.0014 |
| 56.23 (highest 99$^{th}$ percentile value) | 0.033 | 0.030 | 0.035 | 0.032 | 0.042 | 0.040 | 0.037 | 0.035 |

Values rounded to 2 SF

**Questions on which the views of the Committee are sought**

94. Members are invited to comment on the exposure calculations and to answer the following questions.

i. How should the bioavailability of nickel from food and drinking water be taken into account in this assessment?

ii. Which HBGV should be used to assess chronic exposures of infants and young children to nickel?

iii. Should acute exposures to nickel be considered as part of this risk assessment? If so, would the reference point ($BMDL_{10}$ of 1.1 µg/kg bw) established by the EFSA be suitable for assessing acute exposures in this age group?

iv. Do Members agree with the concentration of nickel used to assess exposures from breast milk?

v. Do Members require any further information to come to a conclusion?

vi. Do Members have any further comments?

**Secretariat**
**November 2016**

## 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

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

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

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

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

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

The EFSA CONTAM Panel's '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 is available from the EFSA website at
http://www.efsa.europa.eu/en/efsajournal/pub/4002

**Secretariat**
**November 2016**

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

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

### *Possible nickel exposure from dietary sources in children aged 4 to 18 months*

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

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

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

Table B1. Infant formula

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

Table B2. Commercial infant foods

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

Table B3. Other foods commonly eaten by infants.

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

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

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

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

## ***Exposure Assessments***

*Infant Metals Survey*

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

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

| Food Groups | Exposure- LB-UB (ug/kg bw/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 4 to <6 | | 6 to <9 | | 9 to <12 | | 12 to <15 | | 15 to <18 | |
| | Mean | 97.5th Percentile | Mean | 97.5th Percentile | Mean | 97.5th Percentile | Mean | 97.5th Percentile | Mean | 97.5th Percentile |
| Comfort | 0 | 0 | 0-0.00080 | 0 | 0-0.0029 | 0 | 0 | 0 | 0 | 0 |
| First Milk: From Birth (Powder) | 0.0010-0.0030 | 0.021-0.062 | 0.0015-0.0044 | 0 | 0.00040-0.0012 | 0 | 0 | 0 | 0 | 0 |
| Follow On Milk: 6 Months (Powder) | 0 | 0 | 0-0.0019 | 0 | 0-0.0033 | 0-0.023 | 0-0.00020 | 0 | 0-0.00040 | 0 |
| Growing Up Milk: 12 Months (Powder) | 0 | 0 | 0 | 0 | 0 | 0 | 0-0.0011 | 0 | 0-0.00040 | 0 |
| Goat Milk Formula | 0 | 0 | 0-0.0014 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hipp Organic | 0 | 0 | 0-0.00020 | 0 | 0-0.00010 | 0 | 0 | 0 | 0 | 0 |
| Soy | 0.0034-0.022 | 0 | 0.0017-0.011 | 0 | 0.0017-0.012 | 0 | 0.00050-0.0033 | 0 | 0.00030-0.0020 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| First Milk: From Birth (Ready to Feed) | 0-0.51 | 0-1.3 | 0-0.21 | 0-0.95 | 0-0.091 | 0-0.59 | 0-0.013 | 0-0.25 | 0-0.0031 | 0 |
| Follow on: 6 Months (Ready to Feed) | 0-0.054 | 0-0.56 | 0-0.20 | 0-0.68 | 0-0.19 | 0-0.61 | 0-0.047 | 0-0.40 | 0-0.024 | 0-0.26 |
| Growing up Milk: 12 Months (Ready to Feed) | 0 | 0 | 0-0.00040 | 0 | 0-0.0070 | 0 | 0-0.062 | 0-0.50 | 0-0.040 | 0-0.38 |
| Total | 0.0044-0.59 | 0.030-1.3 | 0.0031-0.43 | 0-0.98 | 0.0021-0.31 | 0-0.68 | 0.00050-0.13 | 0-0.57 | 0.00030-0.070 | 0-0.42 |

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

| Food Groups | Exposure LB-UB (ug/kg bw/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 4 to <6 | | 6 to <9 | | 9 to <12 | | 12 to <15 | | 15 to <18 | |
| | Mean | 97.5th Percentile | Mean | 97.5th Percentile | Mean | 97.5th Percentile | Mean | 97.5th Percentile | Mean | 97.5th Percentile |
| Cereal Based Dishes | 0.17-0.18 | 0.83-0.85 | 0.2 | 1 | 0.14 | 0.90-0.93 | 0.059-0.061 | 0.58-0.60 | 0.023-0.024 | 0.26-0.27 |
| Dairy Based Dishes | 0.028-0.053 | 0.27-0.51 | 0.028-0.053 | 0.25-0.48 | 0.017-0.033 | 0.19-0.34 | 0.0090-0.017 | 0.12-0.24 | 0.0031-0.0060 | 0.049-0.094 |
| Fruit Based Dishes | 0.16-0.21 | 1.2-1.6 | 0.24-0.30 | 1.3-1.7 | 0.23-0.29 | 1.2-1.6 | 0.14-0.18 | 1.0-1.3 | 0.087-0.11 | 0.75-0.96 |
| Meat Based Dishes | 0.12-0.19 | 0.75-1.2 | 0.19-0.31 | 0.95-1.6 | 0.18-0.30 | 0.89-1.5 | 0.10-0.17 | 0.72-1.2 | 0.053-0.089 | 0.43-0.71 |
| Drinks | 0-0.013 | 0-0.12 | 0-0.016 | 0-0.16 | 0-0.014 | 0-0.13 | 0-0.0070 | 0-0.10 | 0-0.0063 | 0-0.075 |
| Other savoury based dishes | 0.081-0.12 | 0.53-0.78 | 0.12-0.17 | 0.67-0.99 | 0.13-0.18 | 0.87-1.3 | 0.049-0.072 | 0.48-0.71 | 0.024-0.036 | 0.37-0.54 |
| Snacks - sweet and savoury | 0.08 | 0.5 | 0.12 | 0.62 | 0.12 | 0.62 | 0.086 | 0.57 | 0.053 | 0.33 |
| Total | 0.64-0.84 | 2.3-3.0 | 0.89-1.2 | 3.0-4.0 | 0.80-1.1 | 3.0-4.2 | 0.45-0.60 | 2.0-2.8 | 0.24-0.32 | 1.2-1.7 |

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

| Food Groups | Exposure LB-UB (ug/kg bw/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 4 to <6 | | 6 to <9 | | 9 to <12 | | 12 to <15 | | 15 to <18 | |
| | Mean | 97.5th Percentile | Mean | 97.5th Percentile | Mean | 97.5th Percentile | Mean | 97.5th Percentile | Mean | 97.5th Percentile |
| Beverages | 0-0.0028 | 0-0.043 | 0-0.0078 | 0-0.062 | 0-0.0059 | 0-0.077 | 0-0.0050 | 0-0.059 | 0-0.0073 | 0-0.12 |
| Bread | 0-0.0038 | 0-0.054 | 0-0.035 | 0-0.23 | 0-0.098 | 0-0.39 | 0-0.15 | 0-0.50 | 0-0.17 | 0-0.55 |
| Canned Vegetables | 0.014-0.017 | 0.18-0.22 | 0.062-0.076 | 0.66-0.81 | 0.15-0.18 | 1.1-1.3 | 0.22-0.27 | 1.2-1.5 | 0.19-0.24 | 0.90-1.1 |
| Cereal | 0.0065-0.0092 | 0.078-0.11 | 0.11-0.15 | 0.60-0.84 | 0.16-0.23 | 0.73-1.0 | 0.20-0.28 | 0.82-1.2 | 0.25-0.35 | 0.87-1.2 |
| Dairy Products | 0-0.031 | 0-0.18 | 0-0.064 | 0-0.27 | 0-0.079 | 0-0.30 | 0-0.080 | 0-0.29 | 0-0.073 | 0-0.25 |
| Egg | 0-0.00030 | 0-0.00030 | 0-0.0032 | 0-0.033 | 0-0.0066 | 0-0.051 | 0-0.011 | 0-0.065 | 0-0.011 | 0-0.067 |
| Fish | 0-0.00060 | 0-0.0037 | 0-0.0049 | 0-0.046 | 0-0.010 | 0-0.068 | 0-0.014 | 0-0.065 | 0-0.012 | 0-0.063 |
| Fresh fruit | 0.027-0.039 | 0.18-0.27 | 0.052-0.076 | 0.24-0.35 | 0.079-0.11 | 0.32-0.47 | 0.11-0.16 | 0.38-0.55 | 0.13-0.19 | 0.38-0.56 |
| Fruit products | 0-0.0047 | 0-0.077 | 0-0.0073 | 0-0.077 | 0-0.0073 | 0-0.075 | 0-0.012 | 0-0.11 | 0-0.017 | 0-0.13 |
| Green vegetables | 0.062 | 0.53 | 0.13 | 0.62 | 0.15 | 0.98 | 0.14 | 0.70 | 0.15 | 0.72 |
| Meat products | 0 | 0 | 0-0.0041 | 0-0.074 | 0-0.010 | 0-0.098 | 0-0.021 | 0-0.14 | 0-0.028 | 0-0.23 |
| Milk | 0-0.0032 | 0-0.035 | 0-0.017 | 0-0.096 | 0-0.044 | 0-0.36 | 0-0.18 | 0-0.52 | 0-0.18 | 0-0.45 |
| Other vegetables | 0.35-0.37 | 2.6-2.7 | 0.46-0.48 | 2.2-2.3 | 0.42-0.44 | 1.8-1.9 | 0.29-0.30 | 1.3 | 0.28-0.29 | 1.1 |
| Potato | 0-0.024 | 0-0.16 | 0-0.053 | 0-0.25 | 0-0.073 | 0-0.29 | 0-0.079 | 0-0.35 | 0-0.071 | 0-0.28 |
| Poultry | 0-0.0018 | 0-0.012 | 0-0.0054 | 0-0.043 | 0-0.0071 | 0-0.050 | 0-0.0073 | 0-0.042 | 0-0.0068 | 0-0.046 |
| Total | 0.46-0.57 | 2.8-3.0 | 0.82-1.1 | 2.9-3.6 | 0.96-1.5 | 3.0-4.0 | 0.96-1.7 | 2.6-3.8 | 1.0-1.8 | 2.5-3.5 |

*Total Diet Study*

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

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

| Food Groups | Exposure-LB-UB (ug/kg bw/day) | | | |
|---|---|---|---|---|
| | 12 to <15 | | 15<18 | |
| | Mean | 97.5th Percentile | Mean | 97.5th Percentile |
| Bread | 0.18 | 0.48 | 0.20 | 0.53 |
| Miscellaneous Cereals | 0.96 | 3.0 | 1.2 | 3.4 |
| Carcase meat | 0.048 | 0.25 | 0.060 | 0.30 |
| Offal | 0-0.00010 | 0 | 0-0.0010 | 0 |
| Meat products | 0.16 | 0.86 | 0.20 | 0.92 |
| Poultry | 0.30 | 1.3 | 0.34 | 1.4 |
| Fish | 0.093 | 0.43 | 0.087 | 0.44 |
| Fats and oils | 0-0.0053 | 0-0.021 | 0-0.0063 | 0-0.023 |
| Eggs | 0-0.014 | 0-0.071 | 0-0.014 | 0-0.073 |
| Sugars | 0.091 | 0.56 | 0.14 | 0.68 |
| Green vegetables | 0.061 | 0.27 | 0.067 | 0.25 |
| Potatoes | 0.35 | 1.3 | 0.33 | 1.1 |
| Other vegetables | 0.16 | 0.60 | 0.17 | 0.55 |
| Canned vegetables | 0.24 | 1.2 | 0.23 | 1.1 |
| Fresh fruit | 0-0.23 | 0-0.78 | 0-0.28 | 0-0.80 |
| Fruit products | 0.11 | 0.80 | 0.13 | 0.84 |
| Non-alcoholic beverages | 0.36 | 1.7 | 0.44 | 2.1 |
| Milk | 0-0.52 | 0-1.5 | 0-0.53 | 0-1.3 |
| Dairy products | 0.30 | 1.6 | 0.25 | 1.1 |
| Nuts | 0.16 | 0.70 | 0.075 | 0.69 |
| Alcoholic drinks | 0-0.00020 | 0-0.0011 | 0-0.00010 | 0 |
| Meat substitutes | 0.0026 | 0 | 0.0074 | 0.090 |
| Snacks | 0.019 | 0.13 | 0.030 | 0.21 |
| Desserts | 0.080 | 0.69 | 0.11 | 0.80 |
| Condiments | 0.032 | 0.19 | 0.036 | 0.19 |
| Tap water | 0-0.079 | 0-0.30 | 0-0.090 | 0-0.36 |
| Bottled water | 0-0.0041 | 0-0.036 | 0-0.0054 | 0-0.083 |
| Total | 3.7-4.5 | 7.7-8.6 | 4.0-5.0 | 7.8-8.8 |

**Secretariat**
**November 2016**

## References

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/

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

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

### *Possible nickel exposure from dietary sources in young children aged 18 to 60 months*

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

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

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

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

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

***Exposure Assessment***

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

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

| **Food Groups** | **Exposure-LB to UB** | | | |
|---|---|---|---|---|
| | **18 to <24** | | **24 to <60** | |
| | **Mean** | **97.5th Percentile** | **Mean** | **97.5th Percentile** |
| Bread | 0.21 | 0.47 | 0.24 | 0.56 |
| Miscellaneous Cereals | 1.2 | 2.6 | 1.0 | 2.6 |
| Carcase meat | 0.066 | 0.34 | 0.040 | 0.21 |
| Offal | 0-0.00020 | 0 | 0-0.00030 | 0 |
| Meat products | 0.24 | 1.1 | 0.29 | 0.97 |
| Poultry | 0.39 | 1.1 | 0.33 | 1.4 |
| Fish | 0.12 | 0.46 | 0.088 | 0.34 |
| Fats and oils | 0-0.0085 | 0-0.027 | 0-0.0076 | 0-0.025 |
| Eggs | 0-0.011 | 0-0.059 | 0-0.011 | 0-0.061 |
| Sugars | 0.16 | 0.77 | 0.23 | 0.98 |
| Green vegetables | 0.057 | 0.34 | 0.059 | 0.24 |
| Potatoes | 0.33 | 0.70 | 0.30 | 0.89 |
| Other vegetables | 0.10 | 0.34 | 0.11 | 0.38 |
| Canned vegetables | 0.40 | 1.5 | 0.25 | 0.95 |
| Fresh fruit | 0-0.34 | 0-0.89 | 0-0.25 | 0-0.65 |
| Fruit products | 0.28 | 1.1 | 0.26 | 1.2 |
| Non-alcoholic beverages | 0.60 | 2.5 | 0.57 | 1.7 |
| Milk | 0-0.49 | 0-1.5 | 0-0.35 | 0-1.0 |
| Dairy products | 0.27 | 1.3 | 0.15 | 0.61 |
| Nuts | 0.040 | 0.057 | 0.12 | 1.7 |
| Alcoholic drinks | 0-0.00020 | 0 | 0-0.00020 | 0 |
| Meat substitutes | 0.0019 | 0.032 | 0.0083 | 0.13 |
| Snacks | 0.035 | 0.21 | 0.041 | 0.22 |
| Desserts | 0.17 | 0.91 | 0.19 | 0.89 |
| Condiments | 0.026 | 0.13 | 0.040 | 0.21 |
| Tap water | 0-0.089 | 0-0.47 | 0-0.081 | 0-0.30 |
| Bottled water | 0-0.0027 | 0-0.028 | 0-0.0071 | 0-0.076 |
| Total | 4.7-5.7 | 7.5-8.7 | 4.3-5.0 | 7.1-8.0 |

## References

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