TOX/2020/35

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

Discussion paper for the EFSA Public Consultation on the draft "Update of the risk assessment of nickel in food and drinking water"

Introduction

1. The European Food Safety Authority (EFSA) have recently opened a public consultation on the Contaminants in the Food Chain (CONTAM) Panel's "Update of the risk assessment of nickel in food and drinking water".

2. In this update the CONTAM Panel has established a tolerable daily intake (TDI) of 13 µg/kg bw for nickel. Due to the possibility of eczematous flare-up reactions elicited in the skin in nickel-sensitised individuals, an approach for acute assessment was also considered. A lowest observed adverse effect level (LOAEL) of 4.3 µg Ni/kg bw was selected as the reference point and a margin of exposure (MOE) of 30 or higher was considered to be indicative of low concern to human health.

Background

Previous evaluations

3. "In 2015 the CONTAM Panel assessed the acute and chronic effects of nickel. For the assessment of chronic effects of nickel, developmental toxicity in experimental animals was considered the critical effect. A TDI of 2.8 µg/kg bw was derived from a BMDL lower confidence limit for an extra risk of 10 % ($BMDL_{10}$) of 0.28 mg/kg bw for post-implantation loss in rats based on the data from a dose-range-finding (DRF) reproductive toxicity study (SLI, 2000a) and a two-generation reproductive toxicity study (SLI, 2000b). The default uncertainty factor of 1000 was applied. The dietary exposures to nickel raised a concern when considering the mean and chronic exposure levels for all age classes." (EFSA, 2020)

4. "The critical assessment for the acute effects of nickel, the Panel selected the systemic contact dermatitis (SCD) elicited in nickel-sensitised humans after oral exposure to nickel. BMD analyses were performed on data from three studies on human volunteers (Gawkrodger *et al.*, 1986; Hindsén *et al.*, 2001; Jensen *et al.*, 2003). The lowest BMDL10 of 0.08 mg Ni per person corresponding to 1.1 µg Ni/kg bw, calculated from the data by Jensen *et al.* (2003) was selected as the reference point for SCD elicited in nickel-sensitive humans after acute oral exposure to nickel. The CONTAM Panel applied a margin of exposure (MOE) approach and considered an MOE of 10 to be indicative of a low health concern." (EFSA, 2020).

5. EFSA considered evaluations on Nickel that had been carried out since their Opinion from 2015.

6. Risk assessments have also been carried out by:

i. the Danish Environmental Protection Agency established a TDI of 5.5 µg/kg bw (Nielsen and Larsen, 2013). A health-based quality criterion in drinking water for repeated exposure to soluble inorganic nickel salts of 17 µg Ni/L was then calculated. Then a health-based quality criterion in drinking water for acute exposure of 37 µg Ni/L was calculated.

ii. In the WHO Drinking water quality guidelines (WHO, 2017) the guideline value for nickel is 70 µg/L.

7. Although not considered by EFSA, the COT has also previously reviewed nickel[1], when looking at the diet of infants aged 0-12 months and young children aged 1-5 years. The COT had assessed chronic risk against a toddler toxicity reference value of 20 µg/kg bw per day established by Haber *et al.* (2017). Acute risks were assessed against an acute reference value of 4 µg Ni/kg bw (Haber *et al.*, 2017) and a reference point of 1.1 µg Ni/kg bw with an MOE value of 10 or higher being considered as indicative of low health concern (EFSA, 2015).

8. In its 2018 statement, the COT had not compared chronic risks against the EFSA 2015 TDI for nickel as the Committee had concluded that it was not applicable to these age groups because it was based on embryo/fetal toxicity, an effect that is possible only when exposure occurs prior to birth.

Summary of 2020 EFSA evaluation

Toxicokinetics and Toxicity

9. This draft EFSA Update of the risk assessment of nickel in food and drinking water reviewed a number of toxicokinetic and toxicity (including animal and observations in human) studies that had been published since the 2015 Opinion. These are summarised in the EFSA Opinion.

10. EFSA noted that the short-term toxicity studies published since the 2015 Opinion have reported similar effects to those published previously. It was also noted that none of the animal or human studies were adequate for the derivation of a reference point for the risk characterisation of chronic oral exposure to nickel.

[1] COT statement on potential risks of nickel in the diet of children aged 1 to 5 years (2018)

Critical effects, dose-response assessment and derivation of health-based guidance values

Critical effects

11. The CONTAM Panel decided to base its chronic assessment on rat studies and the acute assessment on epidemiological data.

Chronic

12. In their 2015 Opinion, the CONTAM Panel had identified reproductive and developmental toxicity as the critical effect for the risk characterisation of chronic oral exposure to nickel. The most reliable dose-response information for reproductive and developmental toxicity came from a one-generation DRF study performed with nickel sulfate hexahydrate in rats (SLI, 2000a) and the subsequent two-generation study (SLI, 2000b).

13. Based on the available data (including studies published since the 2015 Opinion), the CONTAM Panel still considered the incidence of post-implantation loss in rats the critical effect. They also considered the one- and two-generation studies by SLI (2000a and b) are still the most suitable studies for dose-response modelling.

Acute

14. Unlike nickel exposure through the skin or inhalation, oral exposure is not known to cause nickel sensitisation. However, nickel absorption via the oral route may elicit eczematous flare-up reactions in the skin in nickel-sensitised individuals.

15. The CONTAM Panel concluded that the critical effect for the acute risk characterisation is the skin contact dermatitis elicited after oral exposure to nickel in previously sensitised individuals. No new studies had been identified as being suitable for the dose-response analysis therefore the CONTAM Panel used the same 3 studies as in 2015 (Jensen *et al*., 2003; Hindsén *et al*., 2001; Gawkrodger *et al*., 1986).

Dose-response assessment

16. The CONTAM Panel carried out BMD analysis according to the updated EFSA guidance (EFSA Scientific Committee, 2017) using PROAST 61.3. A detailed description of the BMD analysis can be found in Appendix III and Annex A of the EFSA draft opinion.

Chronic effects

17. The CONTAM Panel considered the incidence of post-implantation loss in rats was the critical effect and the studies by SLI (2000 a and b) were the most suitable for dose-response modelling. The studies consisted of nine

doses (0, 0.2, 0.6, 1.1, 2.2, 4.4, 6.6, 11 and 17 mg Ni/kg bw per day). The dataset from these studies consists of three subsets: the one-generation DRF study, the F0/F1 generation of the two-generation study (2GEN F0F1) and the F1/F2 generation of the two-generation study (2GEN F1F2).

18. When the CONTAM Panel calculated the dose-response in 2015 they used the incidence of post-implantation losses per treatment group and the incidence of litters with three or more post-implantation losses per treatment group for benchmark dose (BMD) analysis. In that instance the individual data were not used to derive a reference point due to the BMD guidance (EFSA, 2009a). However, due to updated BMD guidance (EFSA, 2017) the analysis for the current characterisation used the individual data.

19. A benchmark response (BMR) of 10% was applied, model averaging was applied, and the study used as the covariate. The resulting $BMDL_{10}$ values for post-implantation loss were 1.40 and 1.34 mg Ni/kg bw per day for the DRF and 2GEN F0F1 studies, respectively. The CONTAM Panel selected the $BMDL_{10}$ value of 1.3 mg Ni/kg bw per day for the increase of post-implantation loss in rats as a reference point for chronic effects caused by nickel.

Acute effects

20. After consideration of the three studies and some initial analysis the CONTAM Panel decided to use a no observed adverse effect level (NOAEL)/LOAEL approach based on the Jensen *et al.* (2003) study. A LOAEL of 0.3 mg Ni/person, the lowest dose tested, was identified. Assuming a bodyweight of 70 kg, this corresponds to 4.3 µg Ni/kg bw.

Derivation of Health Based Guidance Values

Chronic

21. Using the $BMDL_{10}$ of 1.3 mg Ni/kg bw, calculated for the incidence of post-implantation loss in rats, as the reference point and applying the default uncertainty factor of 100 to account for inter- and intra-species differences, the CONTAM Panel established a TDI of 13 µg/kg bw for oral exposure to nickel

Acute

22. The CONTM Panel decided to characterise the acute effects based on the LOAEL of 4.3 µg/kg bw as the reference point for acute oral exposure to nickel.

23. In 2015 the CONTAM Panel stated concluded that there wasn't enough information available to justify establishing an acute reference dose and therefore used an MOE approach for the acute effect.

24. Since no new information was identified by the CONTAM Panel, since the previous opinion, that supported a deviation from this approach, the Panel confirmed the use of the MOE approach in this instance. It was considered that an MOE of 30 or more would be indicative of a low concern for human health.

25. The MOE of 30 takes into account:

1. The extrapolation from a LOAEL to a NOAEL (a factor of 3)
2. High incidence of positive reactions at the LOAEL (40 %)
3. Only a limited number of individuals were included in the pivotal study
4. There is uncertainty regarding the threshold and that it can be expected that the threshold is low
5. The effects of nickel on nickel-sensitised individuals have an impact on the quality of life, although not life-threatening (a factor of 10 to cover points 2-5)

Exposure

Chronic

26. The EFSA Update included UK data on occurrence and chronic consumption values. The UK specific chronic exposures (Annex C, Table 1a) are towards the mid and upper end of the range of data from the EU (Table 8, P 59 of the 2020 EFSA Update).

Acute

27. The EFSA Update included UK data on occurrence and acute consumption values. The UK specific acute exposures (Annex C, Table 1b) are closer to the maximum rather than minimum values from the range of data from the EU (Table 9, P. 61 of the 2020 EFSA Update).

Risk Characterisation of UK exposures based on the new health-based guidance values (HBGVs)

Chronic

28. Mean lower bound (LB) and upper bound (UB) UK chronic exposures for all age groups are below the TDI of 13 µg/kg bw. 95th percentile LB and UB chronic exposures for adolescents, adults, the elderly and the very elderly are also below the TDI for nickel. 95th percentile LB and UB exposures for

infants, toddlers and other children exceed the TDI by up to a maximum of 190 % of the TDI.

29. The exceedances of the TDI for LB and UB 95th percentile chronic exposure to nickel may raise a health concern for the young age groups.

Acute

30. MOEs were calculated for the acute exposures comparing them to the reference value of 4.3 µg/kg bw. An MOE of 30 or greater would indicate a low concern for human health. The calculated MOEs are presented in Table 1.

Table 1. MOEs calculated for UK acute oral exposures (µg/kg bw) to nickel taken from the 2020 EFSA Update on nickel.

Age class	Mean exposure	MOE for mean exposure	95th percentile exposure	MOE for 95th percentile exposure
Infants	8.1	0.53	24	0.18
Toddlers	12	0.37	34	0.12
Toddlers	12	0.36	37	0.12
Other children	9.3	0.46	28	0.15
Adolescents	5.2	0.83	16	0.26
Adults	4.0	1.1	12	0.37
Elderly	3.6	1.2	9.4	0.46
Very Elderly	3.6	1.2	9.5	0.45

Values are to 2 significant figures.

31. The MOE values range from 0.12 to 1.2 across the age classes. MOE values for the younger age groups are below 1.

32. The calculated MOEs raise a health concern for nickel sensitised individuals.

Questions to the Committee

33. Members are asked the following questions:

i. Does the Committee agree with the selection of the critical studies for the derivation of the acute and chronic HBGVs?

ii. Do Members agree with the approach used by EFSA for the derivation of the HBGVs?

iii. Do Members agree with the HBGVs established?

iv. Do the Members have any further comments?

Members are invited to read the Opinion and the Annexes attached as Annexes on this paper and comment on the approach used by EFSA.

Secretariat

July 2020

References

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

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. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2133.1986.tb06217.x

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

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. Available at: https://pubmed.ncbi.nlm.nih.gov/11260535/

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. Available at: https://pubmed.ncbi.nlm.nih.gov/14678208/

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. Available at: chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/https://www.nickelinstitute.org/media/3711/sli-springborn-laboratories-inc-2000a.pdf

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. Available at: chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/https://www.nickelinstitute.org/media/3712/sli-springborn-laboratories-inc-2000b.pdf

WHO (World Health Organization) (2017). Guidelines for drinking-water quality, 4th edition incorporating the 1st addendum. 631 pp. Available at: https://www.who.int/water_sanitation_health/publications/drinking-water-quality-guidelines-4-including-1st-addendum/en/

Abbreviations

2GEN F0F1	The F0/F1 generation of the two-generation study
2GEN F1F2	The F1/F2 generation of the two-generation study
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMR	Benchmark response
CI	Confidence interval
CONTAM	Contaminants in the Food Chain
DRF	Dose range finding study
EFSA	European Food Safety Authority
HBGV	Health-based guidance value
LOAEL	Lowest observed adverse effect level
MOE	Margin of exposure
TDI	Tolerable daily intake
WHO	World Health Organisation

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

Discussion paper for the EFSA Public Consultation on the draft "Update of the risk assessment of nickel in food and drinking water"

The link below is to the EFSA draft "Update of the risk assessment of nickel in food and drinking water" and its associated annexes:

http://www.efsa.europa.eu/en/consultations/call/public-consultation-draft-scientific-opinion-update-risk

Secretariat
July 2020

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

Discussion paper for the EFSA Public Consultation on the draft "Update of the risk assessment of nickel in food and drinking water"

The following are the references for the studies used in the derivation of the health-based guidance values:

Chronic

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. Available at: chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/https://www.nickelinstitute.org/media/3711/sli-springborn-laboratories-inc-2000a.pdf
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. Available at: chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/https://www.nickelinstitute.org/media/3712/sli-springborn-laboratories-inc-2000b.pdf

Acute:

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. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2133.1986.tb06217.x

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. Available at: https://pubmed.ncbi.nlm.nih.gov/11260535/

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. Available at: https://pubmed.ncbi.nlm.nih.gov/14678208/

Secretariat
July 2020

TOX/2020/ ANNEX C

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

Discussion paper for the EFSA Public Consultation on the draft "Update of the risk assessment of nickel in food and drinking water" UK exposures

UK exposures from the EFSA Update on nickel have been tabulated for ease. The values were taken from Annex D, Table D1 and D4. Only data from UK surveys were included.

Table 1a. Mean and 95th percentile **chronic exposures** to nickel (µg/kg b.w. per day) for total population across age classes

Age class	Country	Survey	Number of subjects	Mean LB	Mean UB	P95 LB	P95 UB
Infants	United Kingdom	DNSIYC 2011	1369	6.09	8.15	15.37	17.44
Toddlers	United Kingdom	DNSIYC 2011	1314	10.05	11.59	23.17	24.82
Toddlers	United Kingdom	NDNS Rolling Programme Years 1-3	185	10.74	12.03	19.66	21.61
Other children	United Kingdom	NDNS Rolling Programme Years 1-3	651	8.34	9.30	18.23	19.79
Adolescents	United Kingdom	NDNS Rolling Programme Years 1-3	666	4.63	5.19	10.19	11.17
Adults	United Kingdom	NDNS Rolling Programme Years 1-3	1266	3.54	4.00	7.33	8.05
Elderly	United Kingdom	NDNS Rolling Programme Years 1-3	166	3.21	3.60	6.01	6.69
Very elderly	United Kingdom	NDNS Rolling Programme Years 1-3	139	3.24	3.64	6.74	6.98

LB: Lower bound; UB: Upper bound. Exposures are to 2 significant figures

Table 1b. Mean and 95th percentile upper-bound **acute exposures** to nickel (µg/kg b.w. per day) across age classes with their corresponding confidence intervals (2.5th and 97.5th percentiles)

Age class	Country	Survey	Number of consuming days	Mean (CI 2.5; 97.5)	P95 (CI 2.5; 97.5)
Infants	United Kingdom	DNSIYC 2011	5400	8.14 (7.91; 8.40)	24.04 (22.79; 25.32)
Toddlers	United Kingdom	DNSIYC 2011	5200	11.60 (11.27; 11.92)	34.44 (32.40; 36.63)
Toddlers	United Kingdom	NDNS Rolling Programme Years 1-3	740	12.02 (11.17; 13.00)	36.77 (30.84; 43.34)
Other children	United Kingdom	NDNS Rolling Programme Years 1-3	2600	9.31 (8.95; 9.71)	27.97 (25.78; 30.36)
Adolescents	United Kingdom	NDNS Rolling Programme Years 1-3	2700	5.18 (4.94; 5.45)	16.28 (14.97; 17.77)
Adults	United Kingdom	NDNS Rolling Programme Years 1-3	5000	4.00 (3.87; 4.13)	11.61 (10.92; 12.32)
Elderly	United Kingdom	NDNS Rolling Programme Years 1-3	660	3.60 (3.38; 3.86)	9.40 (8.26; 10.74)
Very elderly	United Kingdom	NDNS Rolling Programme Years 1-3	550	3.63 (3.40; 3.90)	9.47 (8.33; 10.82)

CI: Confidence interval. Exposures are to 2 significant figures

Secretariat
July 2020