TECHNICAL REPORT

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Outcome of a public consultation on the draft update of the risk assessment of nickel in food and drinking water

European Food Safety Authority (EFSA)

Abstract

The European Food Safety Authority (EFSA) carried out a public consultation to receive input from interested parties on a draft Scientific Opinion updating the risk assessment of nickel in food and drinking water. This draft Scientific Opinion was prepared by the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel), supported by the Working Group on Nickel in food. The draft opinion was endorsed by the CONTAM Panel for public consultation on 26 May 2020. The written public consultation was open from 4 June until 15 July 2020. EFSA received comments from six different interested parties. EFSA and its CONTAM Panel wish to thank all stakeholders for their contributions. The present report contains the comments received and explains the way they have been considered for finalisation of the opinion. The opinion was adopted at the CONTAM Plenary meeting on 24 September 2020 and published in the EFSA Journal.

Key words: Nickel, tolerable daily intake (TDI), margin of exposure (MOE), food, dietary exposure, toxicity, public consultation

Requestor: European Commission

Question number: EFSA-Q-2020-00353

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

1.1.1. Background

On 22 January 2015, EFSA's Scientific Panel on Contaminants in the Food Chain (CONTAM) adopted a Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water, in which it established a tolerable daily intake (TDI) of 2.8 µg/kg Ni/kg body weight (bw) per day and concluded that on the basis of the available occurrence data the current chronic dietary exposure raises health concerns for all age groups and that the acute exposure is of concern for nickel-sensitised individuals. The CONTAM Panel noted the need for mechanistic studies to assess the human relevance of the effects on reproduction and development that had been observed in experimental animals and for additional studies on human absorption of nickel from food; for example, in combination with duplicate diet studies.

In its Opinion, EFSA considered occurrence data on nickel in food and drinking water, which were collected in 15 different European countries. However, as 80% of the total collected data were collected in just one Member State, a geographically more widespread data set would be needed to verify the occurrence of nickel in food throughout the EU. Furthermore, for certain food groups, considered as main contributors to dietary exposure in the EFSA Scientific Opinion, only limited occurrence data were available. In order to discuss possible future risk management measures, a better view of the nickel content in food commodities belonging to these food groups was needed. Therefore, by means of Recommendation (EU) 2016/1111[1] , Member States were asked to collect additional occurrence data for several foodstuffs in 2016, 2017 and 2018.

On 17 November 2016, EFSA adopted its updated guidance on the use of the benchmark dose (BMD) approach in risk assessment, which might impact on the previously established TDI for nickel.

It is therefore appropriate to request EFSA to update the EFSA Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water, taking into account the new occurrence data, the updated BMD Guidance and any newly available scientific information.

1.1.2. Terms of reference

In accordance with Art 29 (1) of Regulation (EC) No 178/2002[2], the European Commission asks the European Food Safety Authority for an updated Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water, taking into account the new occurrence data, the updated BMD Guidance and any newly available scientific information.

1.2. Rationale for the public consultation and brief summary of its outcome

In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key issues. Accordingly, the draft opinion together with its annexes was released for public consultation from 4 June 2020 to 15 July 2020 by means of an electronical comment submission tool together with explanatory text on the EFSA website (See Appendix 1). Comments were received from six interested parties from five countries. Table 1 provides an overview on the interested parties that have submitted comments.

[1] Commission Recommendation (EU) 2016/1111 of 6 July 2016 on the monitoring of nickel in food. C/2016/3858. OJ L 183, 8.7.2016, p. 70–71.

[2] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

Table 1: Overview on stakeholder comments received

Stakeholder	Category [a]	Country
National Institute for Public Health and the Environment (RIVM)	National authority	NL
German Federal Institute for Risk Assessment (BfR)	National authority	DE
UK Committee on Toxicity	National authority	UK
NiPERA Inc. (Nickel Producers Environmental Research Association)	International organisation	US
FoodDrinkEurope	Private sector (e.g. industry, consultancy, etc.)	BE
European Coffee Federation	Private sector (e.g. industry, consultancy, etc.)	BE

(a): As specified by the commenter.

2. Assessment of comments and use for finalisation of the opinion

The comments received were duly evaluated by the WG on nickel in food and the CONTAM Panel and wherever appropriate taken into account for finalisation of the draft opinion. Table 2 provides a detailed list with all comments as received from interested parties together with EFSA responses and explanations how the comments were considered for finalisation of the draft opinion.

Table 2: Stakeholder comments and EFSA responses

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
National Institute for Public Health and the Environment (RIVM)	1	Abstract	The exposure to nickel was calculated using a lower-bound and an upper-bound scenario. The abstract mentions only chronic and acute exposure levels. Please indicate which estimates are presented here.	The CONTAM Panel added this information to the abstract.
	2	2.6 Exposure assessment	"Methodology acute exposure assessment (section 2.6), lines 637-716 The CONTAM Panel did not follow the guidance for performing an acute exposure assessment as provided in the 2012 Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues. This was also noted by the RIVM when evaluating the draft opinion of EFSA on glycoalkaloids. However, this procedure was followed by EFSA in 2019 to estimate the cumulative exposure to a group of pesticides (doi: 10.2903/j.efsa.2019.5764). We have several observations regarding this procedure:	
			1. Could the CONTAM Panel make clear why this guidance was not considered for the current risk assessment of nickel.	The Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues (EFSA, 2012) was not used as such (considering that it applies to pesticide residues and not to contaminants). An analogous methodology was used (see replies below within this comment).
			2. The description of the methodology suggests that the probabilistic approach includes random sampling of concentration data, but not random sampling of food consumption data. As described in the 2012 Guidance, also food consumption data should be randomly sampled as part of a probabilistic acute exposure assessment. Could the Panel explain why consumption data were not randomly sampled and what this meant for the outcome of the exposure estimates?	The methodology used was based on random sampling of the occurrence data. Random sampling of consumption events was not performed because all food categories mostly contributing to the acute exposure to nickel are regularly and widely consumed foods. This observation is further supported by the mean acute exposure estimates being very similar to those calculated for the mean chronic exposure to nickel. Thus, the CONTAM Panel concluded this would have a limited impact on the results. Section 2.6 of the Opinion has been revised to make this clearer.
			3. If consumption data were not randomly sampled, the approach is semi-probabilistic rather than full probabilistic. In this case, we suggest	There is not a universal convention for what can be defined as semi-probabilistic or probabilistic. The CONTAM Panel finds that the term

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			to name the approach semi-probabilistic rather than probabilistic to avoid confusion.	'probabilistic' can be considered appropriate and the variables that have been randomly sampled are described in Section 2.6 of the Opinion.
			4. The draft opinion describes that 1000 intake distributions were generated per reporting day. These distributions describe the possible variation in the exposure during one day using different concentration data. It is then written that these 1000 intake distributions were used to calculate the 95% confidence interval. Confidence intervals calculated in this way are not uncertainty intervals, but describe the variation in the exposure during one day due to variation in concentration data. To attain an uncertainty confidence interval, the bootstrap methodology for quantification of uncertainty (proposed in the EFSA Guidance on the Use of Probabilistic Methodology for Modelling Dietary Exposure to Pesticide Residues published in 2012) should be used which includes sampling of the databases with replacement. It seems that in the draft opinion, variation has been equaled to uncertainty. Please consider revising the text if this is correct or to clarify the text to avoid confusion.	The interpretation is correct but the 1,000 iterations and related confidence interval describe the uncertainty, not the variation. The variation is captured by randomly sampling the occurrence within each iteration. So the distribution obtained in each iteration captures the variability linked to consumption and occurrence. The 1,000 iterations capture the uncertainty around the results of each iteration.
	3	3.1.5 Considerations of critical effects and dose–response analysis	Paragraph 3.1.5.2, Line 2150 Could EFSA please clarify why the study of Hindsen et al. (2001) is considered to have important limitations for BMD analysis?	As explained in Section 3.1.5.2, the study by Hindsén et al. (2001) includes a control group and only two exposed groups which limits the reliability of the benchmark dose (BMD) analysis.
			RIVM performed BMD analysis on the data of Jensen et al. (2003) and Hindsen et al. (2001) on the flare-up endpoint using a covariate for study (200 model averaging bootstraps, this analysis could additionally be provided at request). This results in a BMD CI of 0.38 to 3.5 mg Ni/person, which indicates an uncertainty that is not unusual. RIVM suggests that the BMDL of 0.38 mg Ni/person can be used as a reference point to derive the acute MOE for nickel-sensitive persons. Please note that the combined analysis of the Jensen and Hindsen data does indicate a significant dose response. The AICs of the individual models are much (>2) smaller than the AIC of the NULL model.	The CONTAM Panel considered the possibility of combining the studies by Hindsén et al. (2001) and Jensen et al. (2003) in a covariate analysis. However, BMD analysis of the incidence of flare-up reactions reported by Jensen et al. (2003) showed that none of the models were accepted, indicating that there is no observable trend (see Annex A.4) which is in contrast to the assessment of the combined clinical effects. Therefore, the CONTAM Panel did not further use the incidence of flare-up reactions alone, in the assessment.

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			Paragraph 3.1.5.2, Line 2181 The CONTAM Panel noted a large BMDL–BMDU interval with a $BMDL_{10}$ of 0.0124 mg Ni/person outside the dose-range. The Panel relates this to the small sample size that results in a large uncertainty in the response data (Appendix A.5.5), and decided to identify the reference point (RP) based on the NOAEL/LOAEL approach.	
			The conclusion of the Panel that the large BMD CI and the BMDL outside the dose range cannot be attributed to the sample size. Animal studies with a lower (total) number of individuals (e.g. 40 animals of one sex in a typical subchronic study) are often sufficiently informative to derive a BMD(L). Did EFSA consider the possibility that the uncertainty in these data could be due to interindividual variation? In quantal data the interindividual variation is translated into a less steep dose-response. Of course, a less steep curve will result in a larger BMD CI. In this case the steepness parameter (c in most classical quantal models and d in LVMs) is rather low, which could explain it.	The CONTAM Panel does not exclude a contribution from other sources of uncertainty. For example the large uncertainty can be related to interindividual variability in small groups.
			In case a dataset which is considered of insufficient quality to derive a BMDL as a RP, then a NOAEL will be even more unreliable. Therefore such a dataset should not be used to derive a RP at all. When a poor quality dataset is used, it is imperative to indicate the uncertainties surrounding the RP. This can be done by BMD analysis, which accounts for the uncertainty in the data. By deriving a NOAEL/LOAEL the uncertainty in the dataset is ignored and not made visible in the final result (e.g. the ARfD or MOE). Could EFSA please indicate why they first conclude that a dataset is insufficient to derive a BMDL, but in the end consider that the dataset contains sufficient dose-response information to derive a NOAEL/LOAEL? Could EFSA also explain why they consider it unnecessary to reflect the uncertainty in the RP for nickel-sensitive persons in the final result (i.e. the MOE). Please note that these questions can be ignored when the BMDL of 0.38 mg Ni/person is taken as RP for acute exposure for nickel-sensitive persons as suggested in the comments to line 2150	According to the guidance from EFSA's Scientific Committee, BMD analysis is the preferred approach to identify a reference point. The CONTAM Panel performed a BMD analysis of the incidence of clinically cutaneous reactions to nickel following oral exposure in nickel-sensitive persons as reported by Jensen et al. (2003) using a benchmark response (BMR) of 10% and noted that the models showed a dose-response relationship and that all models were accepted (Annex A.3.5). However, very low $BMDL_{10}$ values (< 0.00001 mg nickel/person; see Annex A.3.5 Table A.4) were estimated for four models and the $BMDL_{10}$ - $BMDU_{10}$ interval using model averaging was large (2.66×10^{-5} – 1.63 mg Ni/person). Since no guidance is yet available for how to use the BMD method (in a harmonized manner) for this type of situation (unrealistic BMD results from both model averaging and individual models) the no-observed-adverse-

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				effect-level (NOAEL) approach was considered more appropriate and therefore applied. The CONTAM Panel took the uncertainty in the reference point into account in the interpretation of the MOE as described in (point 2 and 4 under "acute effects") in Section 3.1.6.
	4	3.1.6 Derivation of an HBGV / margin of exposure approach	Line 2193: This TDI corresponds to a 10% extra risk in post implantation loss. What percentage of risk of implantation loss (in human) is acceptable to EFSA? Are extra risks up to 10% acceptable? Or should the TDI also protect against extra risk of e.g. 1% and higher? If the latter is the case, an extra extrapolation factor is advised.	The CONTAM Panel acknowledges the comment. BMD modelling was also performed with a BMR of 5%; see Section 3.1.5.2 and Annex A.2. However, large $BMDL_{05}$-$BMDU_{05}$ CIs (0.06–5.17 and 0.12–4.18 mg nickel/kg bw per day, respectively) were observed. Therefore, the CONTAM Panel decided to apply the default BMR of 10% for quantal data. EFSA has no specific guidance on an acceptable risk for any toxicological effect. To the best knowledge of the CONTAM Panel, no other bodies have such guidance. The TDI is derived from the $BMDL_{10}$ for post-implantation loss in the two-generation rat study (SLI, 2000b) and application of the default uncertainty factor of 100 for interspecies and inter-individual variability. The default factor of 10 for interspecies variability can be split into a sub-factor of 4 for variability in toxicokinetics and a sub-factor of 2.5 for variability in toxicodynamics. The default factor of 10 for inter-individual variability can be split into a sub-factor of 3.16 for variability in toxicokinetics and a sub-factor of 3.16 for variability in toxicodynamics. Nickel (II) is not biotransformed and therefore applying the default factors for interspecies and inter-individual variability in toxicokinetics (4 and 3.16) is conservative as metabolic difference is the major contributor to the variability in toxicokinetics (ECHA, 2012).

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				In the previous opinion (EFSA CONTAM Panel, 2015) it was concluded "*that data from the available epidemiological studies did not support an association between oral exposure to nickel and reproductive and developmental effects in humans*". From the small number of studies published since the previous opinion, a few suggest that there may be an association between nickel exposure and adverse reproductive and developmental outcomes. However, none of the new studies are sufficient to conclude that nickel is a developmental toxicant in humans. Therefore, applying the default factors for interspecies and inter-individual variability in toxicodynamics (2.5 and 3.16) is conservative. Considering the conservatism in the derivation of the TDI the CONTAM Panel concluded that an additional uncertainty factor for severity of effects is not needed. The opinion has been amended to reflect the conservatism in the approach (Section 3.1.6).
	5	3.4.1 Chronic effects	Lines 2711-2712: EFSA concluded that the 95th percentile chronic dietary exposure to nickel may raise a health concern for the young age groups. The TDI of 13 µg/kg bw is based on a BMDL10 of 1.3 mg Ni/kg bw per day for the increase of post-implantation loss (see 3.1.6. lines 2189-2194). As infants, toddlers and other children are not of a child-bearing age, exceeding this TDI is not directly associated with an increased health concern for this endpoint. For a risk assessment in case the TDI is exceeded, it is important to know what other effects for these age groups may be expected and at which level of exposure. Could EFSA add more discussion about the relevance of exceeding this TDI for young age groups, and discuss what the level of exposure is at which other effects may be expected?	As a general approach, EFSA establishes only one TDI for a chemical substance / group of substances. This is also the case for nickel in this opinion. The CONTAM Panel has selected post-implantation loss in the two-generation rat study (SLI, 2000b) as the critical effect for the TDI. For infants, toddlers and other children who are not of a childbearing age this is a conservative approach, hence the TDI will also be protective for effects that might occur in these age groups. Likewise, this is also a conservative approach for other population groups such as all male age groups, as well as elderly and very elderly women who also are not of a childbearing age. The opinion has been amended to reflect the conservatism in the approach (Section 3.4.1).

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				It is not a part of the current mandate to re-evaluate all the data already evaluated in the previous Opinion. Effects on pups in several studies have already been addressed in the previous Opinion. And to some extent also in the current Opinion. For example "*No effect on the growth of surviving F1 pups during lactation and no effect on the survival or growth of F1 pups from postnatal day (PND) 22 for several weeks following weaning was observed)*" (Section 3.1.2.5) and discussed in more detail in the previous Opinion. In addition, no clinical signs of toxicity or macroscopic changes in the examined organs and tissues were observed among the offspring surviving the peri-natal period in this study (SLI, 2000a). The highest dose in this study of 17 mg Ni/kg bw per day can therefore be considered as a NOAEL for surviving pups and as being relevant for the young age groups. The CONTAM Panel acknowledges that findings in surviving pups in the two-generation rat study (SLI, 2000b) described in the previous opinion were not taken forward to the current opinion, e.g. "*No effect on F1 or F2 pup viability and growth was observed in the offspring of rats administered up to the highest dose tested, 2.2 mg Ni/kg bw per day.*" In addition no treatment-related clinical signs of toxicity or histopathological changes in the examined organs and tissues were observed among the offspring surviving the peri-natal period in this study (SLI, 2000b). This study was performed according to the OECD TG 416 (OECD, 2001), i.e. a wide range of endpoints were evaluated. The highest dose in this study of 2.2 mg Ni/kg bw per day can therefore be considered as a

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				NOAEL for surviving pups and as being relevant for the young age groups. The Opinion has been amended (see Section 3.1.2.5). The studies retrieved after the previous Opinion did not have any influence regarding the conclusion on the critical effect for the TDI. On this background, the CONTAM Panel concluded that the TDI is also protective for the young age groups, i.e. infants, toddlers and other children.
	6	3.4.2 Acute effect	Lines 2714-2723: The CONTAM Panel selected a LOAEL of 4.3 µg Ni/kg bw as the reference point for the acute oral exposure to nickel based on eczematous flare-up reactions in the skin (see 3.1.6. lines 2196-2199). An MOE approach was applied and an MOE of 30 or higher was considered to be of a low health concern. The MOEs calculated for acute dietary exposure are around or below 1 for all age groups. This is relevant for nickel-sensitized individuals, but not for the general population. There are however also indications of acute effects that are relevant for the general population, e.g. malformations and early resorptions observed in developmental toxicity studies and acute neurotoxicity. It is therefore important to know whether acute exposure of the general population may pose a health concern. Could EFSA elaborate on the question whether acute effects may occur due to the acute dietary intake of nickel in the general population and at which exposure level such acute effects may be expected?	The CONTAM Panel has selected eczematous flare-up reactions in the skin as the critical effect for the risk characterisation of acute exposures for nickel-sensitised individuals. It is not a part of the current mandate to re-evaluate all the data already evaluated in the previous Opinion. In the previous Opinion, it was concluded that nickel is a developmental toxicant inducing fetotoxicity, embryotoxicity and teratogenicity. And based on the available data it was concluded that "*the most suitable and reliable dose–response information for developmental and reproductive effects are those reported in the studies by SLI (2000a,b).*" The endpoint 'post-implantation loss' in the two-generation rat study (SLI, 2000b) was identified as the critical effect for the derivation of the TDI – not for risk characterisation of acute exposure. This is also the conclusion by the current CONTAM Panel. The NOAEL identified for post-implantation loss in the two-generation study (SLI, 2000b) was 1.1 mg Ni/kg bw per day. Malformations and early resorptions were not reported in this study at the highest dose level (2.2 mg Ni/kg bw per day), but only reported in studies at higher doses as evaluated in the previous Opinion. The

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				two studies retrieved after the previous Opinion did not have any influence regarding the conclusion on the critical effect cf. the following text in the draft Opinion (Section 3.1.2.5) "*Two recent studies confirmed that nickel caused developmental toxicity in mice when administered during different gestational periods at doses higher than those resulting in developmental toxicity in rats.*" In conclusion, exposure levels at which developmental effects may be expected are much higher than the LOAEL of 4.3 µg Ni/kg bw for eczematous flare-up reactions in the skin. The three studies on neurotoxicity retrieved after the previous opinion only reported effects at higher dose levels than the LOAEL of 4.3 µg Ni/kg bw for eczematous flare-up reactions in the skin. As the critical effect is related to the most sensitive population group, i.e. nickel-sensitised individuals, this is a conservative approach and will also be protective for other acute effects that might occur in non-nickel-sensitised individuals.
	7	3.5.5 Summary of uncertainties	Lines 2860-2867: EFSA concludes that the assessment is more likely to overestimate than to underestimate the risks. However, when looking at table 11, there are more – than + present indicating in our view an underestimation rather than an overestimation. Could EFSA elaborate on why the assessment is more likely to be overestimated?	The plusses and minuses indicate whether the identified uncertainty has the potential to over- or underestimate the risk. No quantification of the uncertainties was performed. However, the CONTAM Panel took into account that some uncertainties have a larger impact on the risk assessment. Particularly the uncertainty linked to the use of fasting condition in the pivotal study for the acute risk assessment was considered to be a major source of uncertainty (except for the scenario on acute exposure from

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				drinking water on an empty stomach) which has been explained in Section 3.5.4 of the Opinion.
German Federal Institute for Risk Assessment (BfR)	8	Abstract	Line 15-34, p. 1: Key elements and results are described without considering the uncertainties. The uncertainties should be summarised in short and mentioned in the context of the results to avoid misinterpretation and generalisation of the findings.	The limited number of words of the abstract does not allow a meaningful summary of the uncertainties. Instead a paragraph on the uncertainties has been added to the Summary.
	9	Summary	Line 40-51, p. 2: The summary of uncertainties is missing. A short statement about the uncertainties provides an overview of the limitations of this opinion.	The overall conclusion on the uncertainties has been added to the Summary.
	10	2.2.1 Collection and selection of evidence	Line 544-559, p. 13: It is proposed to clarify in the text, whether the information in the REACH-registration dossiers was taken into account when drafting the opinion. The registration dossiers are disseminated on ECHA's web site.	The registration dossiers were published before the previous Opinion was adopted and published in 2015. It is the understanding of the current CONTAM Panel that the information in the registration dossiers was evaluated in the risk assessment reports (RARs) under the former 'Existing Substances Regulation' as the RARs were taken into account in the previous Opinion. A literature search has been performed under the current mandate in order to locate new information since the publication of the previous Opinion. The new information has been evaluated in the current Opinion.
	11	2.4 Food consumption data	line 620-621 (p. 14): Age groups are presented that did not exactly match with the survey descriptions in the Comprehensive Database. It would be helpful to clarify whether the age groups were standardised in all surveys or how this was proceeded. Further it would be helpful to address these sub-populations also in the descriptions on exposure in section 2.6.	Seven dietary surveys providing information for pregnant and lactating women are additional to other surveys which are intended to represent the general population. These dietary surveys were designed and conducted specifically for these population groups of women and consequently the age range does not perfectly match with other dietary surveys. These surveys are included in the description on exposure in Section 2.4. These population groups had a similar exposure to nickel as compared to other adult population groups. Therefore, the CONTAM Panel does not consider further details on these surveys to be useful.
	12	2.6 Exposure assessment	Line 712-715, p. 17: An amount of 500 ml tap water or bottled water for assessing the acute	The purpose of this scenario is to estimate the dietary exposure from a volume of water that

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			exposure from water seems to be very low. Half-life of Ni is given in the opinion with more than 24h. Therefore, the amount of water consumed on one day should be considered and this is more than 2 L in the upper percentile. Further it is noted, that a considerable part of the European population consumes more than 500 ml water also in the morning on empty stomach. Some weight reducing diets (intermittent fasting) combine periods of fasting with periods of balanced diet and recommend an adequate consumption of water during fasting period up to 700 ml in the morning on empty stomach.	can be consumed during one drinking occasion under fasted conditions; therefore this scenario is not reflecting the daily exposure. The CONTAM Panel is aware that different consumers have different habits and these cannot be captured in one scenario. This scenario gives an estimation of the exposure due to the consumption of 500 mL and allows stakeholders to easily calculate the exposure if the consumption would be 1.4, 1.5, 2… times higher.
			Line 672 ff, p. 16: For some infant formulas the dilution factor used was reported for others not. Would be helpful to have it for foods under consideration. If there are data for both forms submitted to EFSA it would be helpful to see whether ratio of Ni-concentrations in dried/powder or fresh/ reconstituted forms are in the range of the factors used.	For all infant formulas a dilution factor of 8 was used as indicated in the second bullet point. For other food categories, the dilution factor is not included in the opinion, due to the long list of the food categories adjusted by a dilution factor. It was considered more appropriate to invite the reader to consult the dilution factors in the reference inserted at the end of the paragraph. For clarity, the reference has been included now also directly after the first bullet point of the paragraph. For the food categories for which the data were robust enough and permitted to check the consistency, the nickel concentrations of the reconstituted forms were in the range of the factors used.
			Line 680-682, p. 16: Could you please discuss whether water and milk used for reconstitution can be differentiated in the National surveys from milk/ water drunken. Same is for water, which is not specified as bottled water or tap water. How often is this the case?	The reconstituted foods (e.g. baby foods) are reported as such and no recipe indicating the amount or type of water (or milk) is provided. EFSA's comprehensive consumption database does not allow to differentiate between liquids used for reconstitution and liquids consumed as such. Data providers can specify the type of water consumed as bottled or tap. However, it is often reported as unspecified drinking water.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Line 696, p. 16: It is not clear for which parameters the confidence interval was applied.	The 95% confidence interval (CI) defined as the interval between the 2.5th and 97.5th percentiles obtained from the 1,000 iterations was determined to indicate the uncertainty around the mean and P95 values. This clarification has been added to the text in Section 2.6.
	13	3.1.3. Observations in humans	Chapter 3.1.3.4. Immunotoxicity including sensitisation Line 1348, p. 35: It is stated: "It is a sensitiser, hence exposure may lead to adverse hypersensitivity reactions." Since it is not clear yet that nickel may play an additional essential role in the human body, please add a sentence such as: However, if nickel would also be regarded as a kind of ultra-trace element or essential co-factor of the human microbiome (e.g. in nickel-binding urease of Helicobacter pylori), additional immunological (self-) reactions may play a role. Nielsen FH, 1993. Ultratrace elements of possible importance for human health: an update. Prog Clin Biol Res, 380:355-376. Nielsen FH, 1996,How should dietary guidance be given for mineral elements with beneficial actions or suspected of being essential? J Nutr, 126:2377S-2385S. Zeer-Wanklynn CJ and Zamble DB, 2017. Microbial nickel: cellular uptake and delivery to enzyme centers. Current Opinion in Chemical Biology 37:80–88.	The evaluation whether nickel is essential for humans is not in the remit of the CONTAM Panel. In addition, it is currently not clear what the impact of an interaction between nickel and the microbiome would be on the immune system and more in particular on nickel-specific allergic reactions. Therefore, the CONTAM Panel decided not to include such a statement in the Opinion.
			Line 1353, p. 35: As the authors stated very shortly "also in humans … repeated oral exposure to nickel may prevent or diminish sensitisation", thus this essential issue needs to be further elaborated in this section. Immunologically it represents the other side of the coin and should not be mentioned only in section 3.1.4.4. Otherwise, it may lead to misinterpretation in risk assessment of oral nickel exposure and human nickel reactivity or non-reactivity. The authors also mentioned that they	The CONTAM Panel agrees that oral exposure to nickel may diminish skin sensitization. Indeed, this may occur in nickel sensitized individuals. The opinion indicates in several places, that not all the nickel-sensitized individuals will show flare-up reactions. Indeed, this was true in the study used for risk assessment by the CONTAM Panel. Hypersensitization or oral tolerance may

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			will include desensitisation / hyposensitisation (see line 3876; PubMed > 60 citations; last call 2020-07-03). Suggestion, please implement new paragraph after line 1352: Also in humans, like in animal studies, repeated oral exposure to nickel may prevent or diminish skin sensitisation. As everybody is affected by daily nickel uptake, this will be the case in the majority of Ni-sensitive persons. Studies have shown that an increased oral exposure to Ni, e.g. by wearing dental braces, can help prevent Ni-allergy through tolerance induction. Several molecular processes may play a role here, such as anergy, cytokine switch, suppression or deletion of immune cells. Hensten-Pettersen A (1992) Casting alloys: side-effects. Adv Dent Res 6:38–43 Jensen CS, Lisby S, Baadsgaard O et al. (2002) Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. Br J Dermatol 146:636–642 Kerosuo H, Kullaa A, Kerosuo E et al. (1996) Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. Am J Orthod Dentofacial Orthop 109:148–154 Mortz CG, Lauritsen JM, Bindslev-Jensen C et al. (2002) Nickel sensitization in adolescents and association with ear piercing, use of dental braces and hand eczema. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). Acta Derm Venereol 82:359–364 Todd DJ, Burrows D (1989) Nickel allergy in relationship to previous oral and cutaneous nickel contact. Ulster Med J 58:168–171 van Hoogstraten IM, Andersen KE, von Blomberg BM et al. (1991) Reduced frequency of nickel allergy upon oral nickel contact at an early age. Clin Exp Immunol 85:441–445	play a role in the population, with the consequence that most individuals are not sensitized to nickel, even if there has been exposure, and not all individuals that are sensitized show flare-up reactions. The risk assessment performed is based on a study with sensitized individuals showing flare-up reactions, even though also in these individuals the regulatory mechanisms indicated by this stakeholder must have been active. The text in Section 3.1.4.4 was amended accordingly. The CONTAM Panel acknowledges BfR for providing the references, however did not consider these references of added value for the risk assessment under the current mandate.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Line 1420, p. 36: Please mention that this is a very rare case under millions of Ni-sensitive people in Europe. It is not correct to say "Very severe skin … do occur in sensitive individuals after consuming …". How many other cases are known? Please exclude cross-reactivity to other ingredients and give numbers plus references.	The CONTAM Panel agrees that the statement "very severe" may be an overstatement and has amended the sentence. The real incidence of flare-up reactions is not known; there are no formal registrations of this phenomenon. So the CONTAM Panel also considers the term "very rare" as an overstatement and has not put this in. The paragraph indicated by this stakeholder is sufficiently prudent in the sense that it only states that increased reactions have been associated with nickel containing foods. In the case study mentioned, it is stated that the exposure to nickel by injection was likely the cause of the reaction noted; this implies not fully proven. In both reports, nickel containing foods are mentioned, but obviously foods contain much more than nickel alone, which leaves other causes of reactions open, even if there are no molecules known which cross react with nickel.
			Line 1462, p. 37: According to the German IVDK (Information Network of Departments of Dermatology at the University Medical Center Göttingen, collecting ACD data from German/Swiss hospitals) flare-up reactions to nickel are rare, and are neither systematically investigated nor understood up to now. Thus this likely indicates a low risk.	There is around 15% of the population with nickel sensitivity and consequently these are at risk for flare-up reactions. However, it is true that not all of the sensitised individuals will show these reactions. The CONTAM Panel agrees with the notion that flare-up reactions are neither systematically investigated nor understood. In the absence of formal reporting systems in Europe, no reliable data regarding the incidence of flare-up reactions to nickel are available.
			Line 1375-1381, p. 35: All patients included in the study by Gawkrodger et al. (1986) have also been challenged with a placebo either the week before or the week after treatment with nickel. Interestingly, 10 out of the 26 placebo treatments resulted in a skin reaction, indicating a high spontaneous incidence for systemic contact dermatitis (SCD). Since this information	In this double-blind cross-over study, subjects were challenged with a placebo either the week before or the week after treatment with nickel. Whereas it is clear that certain lesions were noted in sensitized individuals treated with placebo capsules, this may be explained by the

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			could be also relevant to the dose-response assessment, especially with regard to the identification of a LOAEL, the high incidence of positive reactions after placebo treatment in the study by Gawkrodger et al. (1986) should be discussed.	relative short period of the placebo treatments after the initial nickel treatment, and that these reactions may have been caused by the earlier nickel treatment which was not considered by the authors. Nevertheless, in all subjects exposed to the higher dose, lesions were observed in contrast to the subjects exposed to the lower doses and placebo. The excess effect determines the NOAEL or, in the absence of a NOAEL the LOAEL. The CONTAM Panel added the information on the placebo treatment by Gawkrodger et al. (1986) to the Opinion.
	14	3.1.4. Mode of action	Chapter 3.1.4.4. Immunotoxic activity of nickel Line 1821, p. 44: A clear immunotoxicological mechanistic description of human nickel allergy is still missing in this section. Since nickel is known as a non-classical hapten and novel information on nickel-binding proteins has been published – representing the first step in human skin sensitization – the consideration of recent publications is recommended. After last sentence "…I or type IV hypersensitivity", please specify e.g. with: "Such Ni-binding proteins may include immunomodulatory and nickel T cell activating human serum albumin (HSA-Ni) or stress and cytoskeletal proteins in human immune cells or in keratinocytes from human skin (Thierse et al., 2004; Heiss, et al., 2005; Koppes et al., 2017)". Koppes SA, Engebretsen KA, Agner T, Angelova-Fischer I, Berents T, Brandner J, Brans R, Clausen ML, Hummler E, Jakasa I, Jurakić-Tončic R, John SM, Khnykin D, Molin S, Holm JO, Suomela S, Thierse HJ, Kezic S, Martin SF, Thyssen JP. Current knowledge on biomarkers for contact sensitization and allergic contact dermatitis. Contact Dermatitis. 2017, 77:1-16. doi: 10.1111/cod.12789 Heiss K, Junkes C, Guerreiro N, Swamy M, Camacho-Carvajal MM, Schamel WW, Haidl ID, Wild D, Weltzien HU, Thierse HJ. Subproteomic	Thank you for this suggestion. The text is amended to cover this.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			analysis of metal-interacting proteins in human B cells. Proteomics. 2005, 5:3614-22. doi: 10.1002/pmic.200401215. Thierse HJ, Moulon C, Allespach Y, Zimmermann B, Doetze A, Kuppig S, Wild D, Herberg F, Weltzien HU. Metal-protein complex-mediated transport and delivery of Ni2+ to TCR/MHC contact sites in nickel-specific human T cell activation. J Immunol. 2004, 172:1926-34. doi: 10.4049/jimmunol.172.3.1926. PMID: 14734778 Line 1825, P. 44: After "…may result in sensitisation." A novel Ni-specific study concerning Ni-specific human T cell clone reactivity, which is mandatory in human allergic immune responses to nickel, has been published and should be integrated here. Such as: "A study from Aparicio-Soto et al. (2020) just recently published demonstrates the dominance of a specific T cell receptor alpha (TRAV9-2) in Ni-specific T cell activation in allergic and non-allergic individuals, thus indicating immunologically a privileged recognition of nickel by the human immune system, thereby possibly co-explaining high numbers of nickel-reactive individuals, whether developing clinical symptoms or not. Moreover, a dominant binding of non-classical hapten nickel to amino acid histidine – in this case a CDR3 histidine – could be confirmed (Thierse et al., 2005) " Aparicio-Soto M, Riedel F, Leddermann M, Bacher P, Scheffold A, Kuhl H, Timmermann B, Chudakov DM, Molin S, Worm M, Heine G, Thierse HJ, Luch A, Siewert K. TCRs with segment TRAV9-2 or a CDR3 histidine are overrepresented among nickel-specific CD4+ T cells. Allergy. 2020 Apr 16. doi: 10.1111/all.14322. Thierse HJ, Gamerdinger K, Junkes C, Guerreiro N, Weltzien HU. T cell receptor (TCR) interaction with haptens: metal ions as non-classical haptens. Toxicology. 2005, 209:101-7. doi: 10.1016/j.tox.2004.12.015. Line 1847 ff, p. 45: Compare comment for line 1353, p. 35. Line 1894, p. 46:	Thank you for this addition. The text has been adapted accordingly.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Please, adapt and include reference information to: "Lower or same concentrations may result in activation of nickel-specific T cells (Thierse et al., 2004; Aparicio-Soto et al, 2020)." Thierse HJ, Moulon C, Allespach Y, Zimmermann B, Doetze A, Kuppig S, Wild D, Herberg F, Weltzien HU. J Immunol. 2004, 172:1926-34. doi: 10.4049/jimmunol.172.3.1926. PMID: 14734778 Aparicio-Soto M, Riedel F, Leddermann M, Bacher P, Scheffold A, Kuhl H, Timmermann B, Chudakov DM, Molin S, Worm M, Heine G, Thierse HJ, Luch A, Siewert K. TCRs with segment TRAV9-2 or a CDR3 histidine are overrepresented among nickel-specific CD4+ T cells. Allergy. 2020 Apr 16. doi: 10.1111/all.14322.	Thank you. The text was amended accordingly.
	15	3.1.5 Considerations of critical effects and dose-response analysis	Chapter 3.1.5.2 Dose–response analysis (including BMD modelling) Line 2097 ff, p. 50-51: Please specify calculation, with respect to limited data being available and to varying individual threshold responses in human nickel sensitisation as well as in the elicitation phase. Please reconsider 5% nickel as a non-sensitising concentration in human patch testing. Further qualitative uncertainties should be addressed with regard the different study designs and possible cross-reactivities.	The detailed description of the BMD calculations as well as the input data can be found in Appendix III and Annex A. The CONTAM Panel considers elicitation reactions in sensitised individuals and has not identified a threshold for sensitisation. See reply to comment 13 regarding cross-reactivities.
			Line 2103, p. 50: Is the version 61.3 of Proast software correct? In Appendix III, it is stated that Proast v. 67.0 was used.	Thank you for spotting. Indeed version 67.0 was used. The opinion was revised accordingly.
			Line 2117 ff, p. 50: Please specify, what time point you used to identify post implantation losses (PND 0 or PND 4).	The current CONTAM Panel modelled the post implantation loss which was calculated as follows: implantation scar count minus the number of live pups at delivery. This information has been added to the opinion.
			Line 2117 ff, p. 50: From remodeling the data, we guess, that PND 0 was taken. Please explain, why this time point was taken - in contrast to the former	Also in 2015, the CONTAM Panel used the post implantation loss at delivery. The CONTAM Panel

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			opinions, where PND 4 was taken. In our opinion, PND 4 might be the more relevant time point, since perinatal (postnatal) effects would be also included. In addition, if PND 4 was used, the BMDL10 would be roughly 50 % higher and the BMDU/BMDL ratio 50 % lower – hence this dataset appears to be more reliable and informative. Line 2183-2186, p. 51 / table 6: The robustness of the identified LOAEL of 0.3 mg seems to be unclear since it is based on the lowest dose tested and no dose-dependent increase of the response was observed compared to the 1 mg treatment. Taking into account the entire data shown in table 6, the identified LOAEL could be also a result of a very low background response (1/10) in the control group in the study by Jensen et al. (2003). This is also supported by the data of Gawkrodger et al. (1986), who observed a much higher incidence of positive reactions (10/26) after placebo treatment.	noted the higher $BMDL_{10}$ value when using the data at postnatal day (PND) 4 and decided to use the more sensitive endpoint. See reply to comment 3 regarding the insufficient quality of the dataset to derive a reference point.
	16	3.1.6 Derivation of an HBGV / margin of exposure approach	Line 2187 ff, p. 52: It is welcomed, that also nickel-sensitised persons are taken into account when selecting the points of departures. It is noted that the TDI of 13 µg/kg bw is larger than the tolerable acute exposure of 0.14 µg/kg bw based on the MOE (4.3 µg/kg bw / 30). This would indicate that the chronic daily exposure could be higher than the acute exposure on one day only. This is a highly unusual situation; normally the acute exposure can be higher than the chronic exposure. Please add more reasoning, why the effects in nickel-sensitised persons are not taken into account for the assessment of the chronic exposure situation. The reported chronic exposure levels reach and exceed the effect doses in nickel-sensitised persons.	The establishment of a TDI and the application of an MOE approach for risk characterisation imply fundamental differences that do not allow the comparison of the TDI with a value derived from the reference point for the critical acute effects divided by the MOE. The most sensitive population group for adverse effects from acute exposure to nickel is nickel-sensitised individuals and therefore an appropriate approach for the risk characterisation of acute exposure in nickel-sensitised individuals. The CONTAM Panel acknowledges that the MOE approach for risk characterisation of acute exposure in nickel-sensitised individuals would also be protective against chronic effects.
	17	3.2.1. Occurrence data on food submitted to EFSA	Line 2317-2318, p. 55: From these sentences it is not absolutely clear whether the higher levels result from non-detects with high LOQ/LODs or whether there were a relevant number of detects excluded before because they had high LODs/ LOQs.	The CONTAM Panel acknowledges the lack of clarity within this sentence and explained in the draft opinion that some of the samples, which were excluded in the previous assessment due to limits of quantification (LOQs) above 4 µg/kg, had a high nickel concentration measured.
	18	3.3.1 Current dietary	Line 2563, p. 62: What is the justification to select 12 consuming days as cut-off?	Due to limited number of consumption data, it was not possible to base the scenario on acute

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		exposure assessment		exposure from seaweed on the 95th percentile (P95) seaweed consumption. Therefore, the P75 has been selected as a highest reliable percentile for which the availability of at least 12 data has been identified as an appropriate minimum requirement. This was based on a common approach and expert judgement.
			Line 2585, p. 62: As already commented above it is not totally clear why only water ingested on empty stomach without food was considered. The estimated half-life is more than 24h and it is not described that this is only on empty stomach. As described above, 500 ml is definitely an underestimation considering half-life of >24h and might be an underestimation also for at least some people following dietary restrictions.	See reply to comment 12.
	19	Appendix III – Benchmark dose analysis	III.1.1. Data description; Line 4022 ff, p. 96: Please give a detailed table on the database used for modelling. With the data from SLI 2000a,b we are not able to exactly reproduce the results presented in EFSA opinion (2020).	Following this comment, EFSA has asked and received permission to include the individual data in the Scientific Opinion. The individual data used in the BMD analysis reported in Appendix III have been included in Section III.1.6. In addition, the individual data have been added to Annex A.1 and Annex A.2 which report other BMD analyses using the data from SLI (2000a,b).
UK Committee on Toxicity	20	1.3.4 Previous assessments	The UK Committee on Toxicity considered that it would have been useful to include the paper by Haber et al. 2017 (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) in this section.	The CONTAM Panel reports in this section only previous risk assessments from national and international public organisations.
	21	3.1.5 Considerations of critical effects and dose–response analysis	Line 2061-2: The UK Committee on Toxicity does not support the post-implantation loss as being a representative endpoint for infants and other younger age groups, but agree that there are no new better studies for adults.	See reply to comment 5.
NiPERA Inc. (Nickel Producers	22	Abstract	Lines 26-27: In the revised Opinion a LOAEL of 4.3 µg Ni/kg b. w. and a MOE of 30 are proposed. As described in our comments below, while the choice of a LOAEL or BMDL may not significantly change the	See reply to comment 28.

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Environmental Research Association) [The atttachment[3] submitted by NiPERA Inc. is also available in **Annex A** of this Technical Report]			starting value, we strongly disagree with the recommendation of a MOE of 30 and the finding of health concerns for the Ni sensitive subpopulation. In our view, the MOE of 30 is not justified when considering the built-in conservatism associated with the study on which the LOAEL is based.	
	23	Summary	Lines 84-88 (expanded further in lines 964-969 for mice and lines 1022-1030 for rat). The micrographs published in Pandey et al. (1999) are consistent with changes seen in testes that were improperly fixed with formalin which can result in incomplete penetration of the fixative and allows degradation of the tissue prior to fixation. It is interesting to note that after the Pandey group changed to a fixation method that is now recommended (Bouin's fluid), they found no changes in the testes of treated mice, although they did report a change of columnar to cuboidal epithelium in the seminal vesicles (Pandey and Singh, 2001). Such a change is seen under normal physiologic conditions as the secretory activity of a tissue changes.	The text regarding such effects in mice is taken from the previous opinion as mentioned in Section 3.1.2.5 where it is also stated "*Limitations in these studies preclude their use for the establishment of a reference point.*" The text regarding rats is based on the Lambade et al. (2015) study where the CONTAM Panel noted the following limitations "*The CONTAM Panel noted that except for a figure of a slide, the histopathological changes in the testes are only descriptive and no information on incidence and severity in the various groups is presented.*" None of these studies are used further for the risk characterisation. The CONTAM Panel would also like to point at the conclusion in a very recent paper (Ellenburg et al., 2020) "*Compared to Bouin solution, formalin fixation of rat testicular tissue produced adequate histology for the evaluation of spermatogenesis and may be superior to Bouin solution for certain cytologic features.*"
			Lines 88-89. The draft report indicates that mice are more "sensitive" than rats to the reproductive effects of nickel. This wording could be interpreted to mean that these effects are seen at lower exposure levels in mice than in rats. This is not the case. Mice show some effects (such as teratogenicity) that are not seen in rats, and these effects	The CONTAM Panel, like other scientific bodies, distinguishes between reproductive toxicity and developmental toxicity. Teratogenicity and developmental effects are covered under developmental toxicity. The observation "*Mice*

[3] The attachment submitted by NiPERA Inc. includes the comments submitted via the electronical comment submission tool, although sometimes with different phrasings, and Annex 1. Annex 1 is a review of the draft EFSA Update of the Risk Assessment of Nickel in Food and Drinking Water presented to NiPERA and prepared by Lynne Haber and Bruce Allen. The Content of Annex 1 is included in comment 37 with the exception of a table. For comments that were submitted via the electronical comment submission tool and as part of the attachment, the phrasing as submitted via the tool is included in this technical report.

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			always occur at higher doses than the developmental effects in rats that were chosen by EFSA as the point of departure. We recommend EFSA clarify the wording in the report to reflect this point.	*appear to be more sensitive than rats regarding reproductive effects.*" is included in the paragraph regarding reproductive toxicity (lines 84-89 in the draft opinion for public consultation) whereas developmental toxicity is addressed in the following paragraph (lines 90-96). For further details on these specific reproductive effects see Section 3.1.2.5. The CONTAM Panel finds that this is clear from the text.
			Line 113 and line 115: The text here and throughout the scientific opinion should clarify that only "some" nickel-sensitized individuals are susceptible to oral nickel elicitation reactions, since only a small subfraction of the nickel sensitive subpopulation has dermatitis reactions to oral nickel exposure (Di Gioacchino et al., 2000 Lymphocyte subset changes in blood and gastrointestinal mucosa after oral nickel challenge in nickel-sensitized women. Contact Dermatitis. 43(4):206-11). This means that the value provided to protect nickel-sensitized population from oral exposure effects is not applicable or necessary for all nickel-sensitized individuals.	The CONTAM Panel agrees that not all sensitized individuals will develop flare-up reactions and the text has been adapted to acknowledge this throughout the opinion. Yet, the risk assessment for this outcome was based on a study where certain individuals do show flare-up reactions, whereas others do not.
			Line 205: It could be noted that the relevance of using a chronic TDI based on reproductive effects for infants, toddlers, and young children is not a relevant effect so may not be appropriate.	See reply to comment 5.
	24	1.3.4 Previous assessments	Line 485: Reference is made to the most recent version of the WHO Guidelines for drinking water (WHO, 2017). It would be useful to clarify in the text what is the exact study used by WHO for deriving a TDI of 12 µg Ni/kg b.w.. The current text refers to WHO 2005 as the latest assessment. Yet, WHO 2005 cites the Nielsen et al (1990) dietary study as the basis for the TDI (nickel administered in Ni-rich diet). There is a second WHO amendment of 2007 that cites the Nielsen et al. (1999) study with fasting individuals and nickel administered in water. EFSA (line 486) indicates that "… a TDI of 12/ug/kg bw derived form a LOAEL established after oral provocation of fasted patients with an empty stomach" and it seems to be referring to the Nielsen et al. (1999) study.	The WHO 2017 version does not give a reference to the critical study. In the version of the WHO 2005 available to the CONTAM Panel (link in the reference list) the reference is to the Nielsen et al. 1999 study. Text in Opinion amended.
	25	3.1.2. Toxicity in	Section 3.1.2.5 Toxicity in experimental animals/Reproductive and developmental toxicity	

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
		experimental animals	Lines 1806-1807: The draft report indicates that mice are more "sensitive" than rats to the reproductive effects of nickel. This wording could be interpreted to mean that these effects are seen at lower exposure levels in mice than in rats. This is not the case. Mice show some effects (such as teratogenicity) that are not seen in rats, and these effects always occur at higher doses than the developmental effects in rats that were chosen by EFSA as the point of departure. We recommend EFSA clarify the wording in the report to reflect this point.	See reply to comment 23.
			Lines 964-969 (mice), lines 1022-1030 (rats): Testicular effects are discussed for mice (Pandey et al., 1999; Pandey and Srivastava, 2000) and rats (Lambade et al., 2015). The micrographs published in Pandey et al. (1999) are consistent with changes seen in testes that were improperly fixed with formalin which can result in incomplete penetration of the fixative and allows degradation of the tissue prior to fixation. It is interesting to note that after the Pandey group changed to a fixation method that is now recommended (Bouin's fluid), they found no changes in the testes of treated mice, although they did report a change of columnar to cuboidal epithelium in the seminal vesicles (Pandey and Singh, 2001. Seminal toxicity of nickel sulfate in mice. Biol. Trace Element Res. 82:211-215.). Such a change is seen under normal physiologic conditions as the secretory activity of a tissue changes. EFSA already notes that except for a figure of a slide, the histopathological changes in the testes reported in Lambade et al. (2015) using formalin for testes fixation are only descriptive and no information on incidence and severity in the various groups is presented. Therefore, the reliability of the reported effects in testes in mice and rats should be qualified.	See reply to comment 23.
	26	3.1.3. Observations in humans	Section 3.1.3.3. Observations in humans /Reproductive and developmental toxicity Lines 1231-1234. The CONTAM panel previously concluded that the data from the available epidemiological studies did not support an association between oral exposure to nickel and reproductive and developmental effects in humans. The panel then reviews new studies that have been published since 2015 and this may leave the impression with the reader that the new studies change the conclusion that such an association is not supported. However, this is not the case and this important point should made clearer in the text. Moreover, it should be noted that the human epidemiological literature regarding	The conclusion (Chapter 4) was slightly amended and reads: "*From the small number of studies published since the previous opinion, a few suggest that there may be an association between nickel exposure and adverse reproductive and developmental outcomes.*" The CONTAM Panel finds that this observation does not give an impression that the new studies change the conclusion of the previous opinion, but only that a few new studies suggest an association.

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			environmental nickel exposure and reproductive effects is generally of low quality, due to the lack of appropriate statistical approaches to assess potential confounding, poor to no exposure measurements in many studies, and an inability to assess the temporal relationship between nickel exposure and the outcome of interest. For example, the study of Zhang et al. (2019) examined the relationship between congenital heart defects of offspring and nickel in maternal hair. This study did not account for many known confounders of malformations; this and the difference in control and cases characteristics (e.g., folic acid intake, 50% smoking in cases and 35% in controls) are enough to call into question the reported associations. This is more of a hypothesis generating study than firm evidence of causality, as acknowledged by the authors. To illustrate this point, in a similar study of neural tube defects and Ni in hair, the cases had lower Ni levels than the controls (Yan et al., 2017. Birth Defects Res. 109(3):234-243). Ni et al. (2018) reported associations between orofacial malformations and umbilical cord blood nickel concentrations. However, this study also reported some differences between control and cases characteristics, and associations between orofacial malformations and other metals besides nickel in cord blood were found. A similar study by Zheng et al. (2014) found that controls had higher levels of nickel in umbilical cord blood than cases. A limitation of these types of studies involves temporality, as the key period of Iip and palate development occurs during 4-12 weeks of gestation while the umbilical cord blood is collected at the end of pregnancy. Thus, these types of studies are not able to provide evidence of causality. Chen et al. (2018) reported that statistically significant higher urinary nickel concentrations were found for mothers who underwent pre-term delivery (< 37 weeks). No other metals were studied. The mean urinary nickel concentration for the cohort was reported as 3.97 µg Ni/l (11.2 µg Ni/g creatinine), with the 5th to 95th percentiles ranging from 0.22 to 9.74 µg Ni/l. These urinary levels can be compared against a large epidemiological study of female refinery workers in Monchegorsk, Russia, that found no adverse effects of nickel exposure on pregnancy outcomes (Vaktskjold et al., 2006. Genital malformations in newborns	

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			of female nickel-refinery workers. Scand J Work Environ Health 32(1):41-50. Vaktskjold et al., 2008. Spontaneous abortions among nickel-exposed female refinery workers. Int J Environ Health Res 18(2):99-115). In that study, background urinary nickel levels in female non-refinery workers had a geometric mean of 5.9 µg Ni/l. The low exposure refinery workers had a geometric mean of 15.5 µg Ni/l with a P95 of 21 µg Ni/l (~3-fold increase in urinary levels) and the high exposure workers had a geometric mean of 122 µg Ni/l with a P95 of 163 µg Ni/l (~20-fold increase in urinary levels). This study, in which 24-fold higher nickel levels did not have adverse pregnancy outcomes, calls the associations reported by Chen et al. (2018) and other studies reviewed in section 3.1.3.3 of the EFSA scientific opinion into question. In our view, the Vaktskjold et al. studies are more relevant than the additional epidemiological studies discussed in this section because of the lack of effects found at very high nickel exposures (translated into very high urinary levels) of the female worker study population and the limitations of the newly published epidemiological studies. Environmental epidemiological studies of gestational outcomes can suggest hypotheses for further study but give incomplete and possibly misleading information regarding causality for exposure to individual agents. Results across the literature regarding human reproductive and developmental studies associated with nickel exposure are largely inconsistent or null, with no clear evidence for causal associations between nickel and any particular outcome. This is supported by a large occupational study of nickel workers showing no reproductive effects. We respectfully request that EFSA clarifies that the new human epidemiology studies still do not provide evidence that nickel or nickel compounds present a reproductive or developmental hazard to humans.	
	27	3.1.5 Considerations of critical effects and dose-response analysis	Section 3.1.5.2. Dose-response analysis (including BMD and modelling) Chronic effects Lines 2105-2134. We support the comments provided by L. Haber and B. Allen (Annex 1 in attached NiPERA comments) regarding the adult TDI derivation based on reproductive effects in rats. One minor comment about the adult TDI is the EFSA-derived BMDL10 of 1300 µg Ni/kg b.w. did not consider the nickel in the diet of the rats. Rats in the Springborn study were fed a Purina Mills, Inc. diet with a nickel content typically around 1.45 µg Ni/g feed, and the amount of	The SLI reports specify the following "… *within generally accepted limits, there were no contaminants in the diet or drinking water which would interfere with the conduct of the study*".

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			daily food ingested by the animals ranged from 25-28 g for males to 18-20 g for females. The weight of the animals (e.g., F0) increased during the study from 230 to 520 g (males) and 180 to 280 g (females). Considering averages weights and average food consumption rates, on average, males ingested ~102 µg Ni/kg/day and females ingested ~120 µg Ni/kg b.w. The total BMDL10 would have been 1450 µg Ni/kg b.w. for females (1300 + 120= 1450 µg Ni/kg b.w.), resulting in a TDI of ~14 µg Ni/kg b.w. (when using UF=100).	The level of nickel in the basal diet was not reported in the final study reports. No correction of the doses was conducted in the SLI studies. Both the control group and the treated groups were fed the basal diet. The CONTAM Panel therefore concluded that no correction of the doses is required.
			While a chronic TDI based on reproductive effects can be relevant to adults, and perhaps adolescents, this endpoint is not relevant to infants, toddlers or other children, and even its applicability to the elderly and the very elderly could be debatable. A TDI for children could be based on sensitive health endpoints from studies specifically designed to assess repeated exposures in young children, as was addressed in Haber et al. (2017. Regul Toxicol Pharmacol. 15;87 Suppl 1:S1-S). Studies of relevance would evaluate effects in young animals exposed to nickel for a comparable portion of their lifetime such as between birth and sexual maturity. In rodent two-generation reproduction studies, the exposure period for the F1 animals not only encompasses the period of interest in humans, but also begins earlier (during gestation) and continues past childhood into puberty and early adulthood, making systemic health effects in F1 animals particularly useful for evaluating effects in children. Subchronic toxicity studies also provide useful information on potential effects and effect levels, in particular since they include evaluation of a number of sensitive toxic endpoints that are not typically evaluated in reproductive studies. Unlike the study in F1 animals, the subchronic studies will not, however, identify endpoints where children are more sensitive than adults.	See reply to comment 5.
			A review of four two-generation reproductive studies (Ambrose et al.,1976; RTI, 1988; Smith et al., 1993; SLI, 2000b), focusing on general toxicity observed in the F1 rats, indicated that decreased body weight appears to be the most sensitive systemic adverse effect. Ambrose et al. (1976) measured body weights in the F1 generation only twice and no toxicity was noted in F1 animals exposed to up to ~64 mg Ni/kg-day. Smith et al. (1993) only measured body weights at postnatal day 21 and observed no body weight changes at the highest	See reply to comment 5.

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			exposure level of 31.6 mg Ni/kg-day. The RTI (1988) and the SLI (2000b) studies contain the more detailed information on body weights for the F1 generation. Exposures took place first in utero (from mothers exposed to those nickel levels in drinking water or by gavage), then through lactation up to postnatal week 3 (again from exposed mothers), and finally from drinking water or gavage, from weaning until adulthood. In the SLI (2000b) study body weights were measured on postnatal day 1, 4, 7 and 21 and then weekly until mating. No adverse effects on F1 pups' body weights were observed at any of the time points and exposure levels included in this study and the NOAEL in this study is 2.2 mg Ni/kg-day, which is lower (and therefore supported) by body weight data from the three other reproductive studies, is the same as the NOAEL in a chronic study (Heim et al., 2007), and is lower than NOAELs in subchronic studies. We respectfully request that EFSA acknowledges this issue and derives a separate TDI for these age groups or refers to the one derived in Haber et al (2017), and by at least noting in Section 3.4.1 that the conclusions may overestimate concerns for these age groups.	See reply to comment 5.
			Acute effects Lines 2184-2186. The Jensen et al. (2003) was selected in 2015 and the draft 2020 EFSA documents to derive a point of departure value for the risk assessment of nickel sensitive individuals acutely exposed to Ni from the diet. Use of the LOAEL from this study (instead of a BMDL) can have significant impact in the risk assessment, particularly when a MOE of 30 is selected.	See reply to comment 28.
	28	3.1.6 Derivation of an HBGV / margin of exposure approach	**Chronic effects** Lines 2189-2194. The TDI of 13 µg Ni/kg b.w. was calculated by applying an uncertainty factor of 100, which accounts for toxicokinetic and toxicodynamic differences between rats and humans and assumes that humans are more susceptible to the reproductive effects of Ni than rats. As indicated in Haber et al. (2017), it should be noted that the epidemiological studies of female nickel workers (Vaktskjold et al., 2006; 2008) have not shown an association between Ni exposures and adverse reproductive effects in a highly exposed female population. In our view, these studies are more relevant than the new epidemiological studies discussed in section 3.1.3.3 because of the very high nickel exposures (translated into very high urinary levels) of the female	The Vaktskjold et al. (2006, 2008) articles are already addressed and evaluated in the previous opinion. Based on the available data the previous CONTAM Panel identified reproductive and developmental toxicity as the critical effect for the risk characterisation of chronic oral exposure to nickel, and identified the incidence of litters with post-implantation loss per treatment group as the relevant and sensitive endpoint. The current CONTAM Panel wants to emphasise that negative epidemiological studies can never

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			worker study population and the limitations of the newly published epi studies.	revoke positive animal studies. Therefore, the CONTAM Panel still identified reproductive and developmental toxicity as the critical effect for the risk characterisation of chronic oral exposure to nickel, and identified the incidence of litters with post-implantation loss per treatment group as the relevant and sensitive endpoint for the dose–response assessment. See also reply to comment 4 for more details regarding the epidemiological studies and the animal data.
			For infants, toddlers and young children, a TDI based on age appropriate studies would be more relevant. If an uncertainty factor of 100 was applied to the NOAEL of 2.2 mg Ni/kg b.w. described under Section 3.1.5.2, a chronic TDI could be set at 22 µg Ni/kg b.w.	See reply to comment 5.
			Acute effects Lines 2212-2220: We urge EFSA to reconsider the MOE of 30 in favor of a lower MOE (e.g., 1- 3) based on the following considerations addressing their points 2-5: • In Jensen et al. (2003), 4 of 10 patients reacted to 0.3 mg Ni (and the same number to 1.0 mg Ni), with 1/10 reacted, indicating 10% of the patients might have had a non Ni-specific reaction on sites of previous dermatitis and the Ni-specific response to 0.3 mg Ni was 30%. • Although the sample size in the Jensen et al. (2003) was fairly small, the dosing protocol maximized the internal dose and the resulting nickel-specific ED30 value (0.3 mg Ni), making it a very conservative value. Resulting ED5s from Jensen et al. (2006) for three separate groups of studies (9 studies including ~150 people) were 0.41, 0.65, and 1.00 mg, respectively, which are consistent with, and do not contradict, the ED30 of 0.3 mg Ni from the Jensen et al., (2003) (although Jensen et al., 2006 is not suitable as a key study by itself) • Subjects were fasted prior to dosing, increasing absorption as much as 10-fold higher than in a fed state and doses were bolus (capsule), maximizing peak serum levels much higher than if the same dose were administered over the course of the day.	The CONTAM Panel identified the lowest-observed-adverse-effect-level (LOAEL) of 0.3 mg as 4/10 individuals reacted at that dose level. According to the Guidance on default values (EFSA Scientific Committee, 2012) "*In cases where the BMD approach cannot be applied, the LOAEL approach might be used and an additional uncertainty factor will be needed, the size of which should be determined on a case-by-case basis and justified.*" The CONTAM Panel considered a factor of 3 as justified referring to the REACH Guidance Document (ECHA, 2012) recommending a factor of 3 for the majority of cases. According to the EFSA Guidance on default values (EFSA Scientific Committee 2012) "*... use of an additional UF to take account of the deficiency of a database should be considered on a case-by-case basis and justified.*" The CONTAM Panel considered an additional factor of 10 as justified to reflect other deficiencies in

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			• The dermal response in Jensen et al. (2003) at 0.3 mg was a flare-up at a previous sites of dermatitis, not a severe reaction. More severe widespread cutaneous reactions indicative of a systemic reaction were only seen at the much higher dose of 4.0 mg nickel, consistent with findings in other studies. • Patients in Jensen et al. (2003) and the other supporting studies in Jensen et al. (2006) were from dermatology clinics, representing more sensitive nickel-allergic individuals than the general population. Jensen et al. (2006) stated "It should be emphasized that the tested individuals included in the studies do not represent the majority of the population but are persons allergic to nickel, who have consulted a dermatologist. In the majority of the cases, the patients had symptoms which could indicate a systemic component in their disease, and many patients had had chronic hand eczema which flared up after the oral exposure." • Only a small subfraction of the nickel sensitive subpopulation has dermatitis reactions to oral nickel exposure (Di Gioacchino et al., 2000. Contact Dermatitis. 43(4):206-11). The text should clarify that it is only "some" nickel-sensitized individuals who are susceptible to oral nickel elicitation reactions, and a low nickel diet is not necessary or recommended for all nickel-sensitized individuals (Mislankar and Zirwas, 2013. Dermatitis. 24(4):190-5). • The value of draft EFSA value of 4.3 µg Ni/kg b.w. is in addition to Ni intake from the diet. In Jensen et al. (2003), as described in the manuscript, "No other dietary intervention was conducted, hence each individual was exposed to nickel or placebo, in addition to the nickel exposure from the normal dietary intake. The additional nickel exposure from the diet was not estimated." The paper also states that "4 of 10 nickel-sensitive individuals reacted to 0.3 mg nickel or to the amount equivalent to that contained in a normal daily diet." Therefore, the patients were exposed to 0.3 mg (100% bioaccessible Ni) + ~0.3 mg dietary nickel (<100% bioaccessible) = 0.6 mg total Ni, making the actual "diet-equivalent" dose eliciting a response as high as 9 µg Ni/kg bw (0.6 mg Ni/70 kg b.w.=9). • Since only 1/10 patients in Jensen et al., (2003) were male, the	the data available for the assessment as described in points 2-5, i.e. 40% positive reactions at the LOAEL, limited number of individuals in the pivotal study, uncertainty regarding the threshold and critical effect has an impact on the quality of life in nickel-sensitised individuals. The CONTAM Panel emphasises that a specific factor is not considered for each of these pieces of limitations in the database, but finds that an overall factor of 10 for these limitations is justified. The CONTAM Panel acknowledges that this might be a conservative approach.

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			LOAEL should consider female body weights. Values of 4.3 to 5 µg Ni/kg b.w can be calculated by dividing 0.3 mg by a range of body weights for female (60-70 kg). The actual (total) "diet-equivalent" dose eliciting a response could be significantly higher than 4.3 µg Ni/kg b.w. We urge EFSA to reconsider the MOE of 30 in favor of a lower MOE (e.g., 1- 3).	
	29	3.2. Occurrence data	It should be noted that nickel is not a contaminant but rather a naturally occurring element. Nickel (Ni) is essential to plants (i.e., it forms the core of the plant urease enzyme) and thus it is present in the food we eat. In addition to naturally occurring Ni in foods, small amounts of Ni could be transferred to the food from food contact materials and from cooking pots, pans and utensils. In plants and food, Ni is not present as 100% bioaccessible Ni (II) ion but rather as part of complex organic molecules. As such it is neither easily bioaccessible for subsequent absorption into the blood stream after consumption nor is it possible to remove it from food sources. The absorption and systemic bioavailability of Ni(II) ion from food (<< 100% bioaccessible) and water (100% bioaccessible) is different. Furthermore, there are differences in absorption of Ni from drinking water (100% bioaccessible) when water is ingested with food (1-5% nickel absorption) versus when it is consumed under fasting (from 10% to up to 27% nickel absorption). Thus, the mere fact of mixing 100% bioaccessible Ni (from water) with food in the stomach already decreases its absorption by at least 6-fold. Studies have shown a good correlation between the relative bioaccessible fraction of Ni in gastric fluid from various Ni compounds, the systemically absorbed fraction, and the acute toxicity after oral exposure (Henderson et al., 2012. Oral Bioaccessibility Testing and Read-Across Hazard Assessment of Nickel Compounds. Regul Toxicol and Pharmacol. 63(1):20–28.). While there is now more data on the bioaccessibility of Ni from different types of food, data on absorption is lacking. It is however safe to assume that the absorption will not be any higher than 3-5%. These are important considerations when assessing the overall risks to human health from oral ingestion of nickel in the diet (food + beverages).	The CONTAM Panel acknowledges the uncertainty related to the lack of information on bioaccessibility and has addressed this point in Section 3.5.4.
	30	3.4.1 Chronic effects	Lines 2700-2712. The report states: "Mean chronic dietary exposure was the highest for the young age groups and particularly for toddlers. The mean LB chronic dietary exposure for toddlers ranged from 6.23 to 12.5 µg/kg bw and the mean UB from 7.77 to 14.6 µg/kg bw per day,	See reply to comment 5.

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			across dietary surveys. For one survey in toddlers, the mean chronic dietary exposure was at the level of the TDI (LB–UB: 12.5–14.6 µg/kg bw per day) and this may indicate a concern." Then it goes on to add: "The 95th percentile chronic dietary exposure was also the highest for the young age groups and particularly for toddlers." And "The 95th percentile LB chronic dietary exposure exceeded the TDI in 10 out of 14 dietary surveys in toddlers and in 11 out of 19 dietary surveys in other children. Also in infants, an exceedance of the TDI was observed in some surveys." The fact that the TDI value, in reference to which exceedances are noted, is not based on health effects relevant to these study populations should be noted here and in Section 3.5 Uncertainty Analysis. Please see comments under section 3.1.5.2 and 3.1.6 for an alternative TDI that would be relevant for infants, toddlers and young children. Looking at table 8 of the draft EFSA Scientific Opinion, dietary Ni intake would only present a risk for infants and toddlers exposed to the maximum values of the 95% percentile dietary exposure when compared to a TDI of 22 µg Ni/kg b.w.	
	31	3.4.2 Acute effect	Lines 2714-2716. The draft reports states: "The CONTAM Panel concluded that the calculated MOEs raise a health concern for nickel-sensitised individuals." The LOAEL for acute effects of 4.3 µg Ni/kg b.w divided by a MOE of 30 equals 0.14 µg Ni/kg b.w g. According to EFSA's Draft Opinion, in order for all nickel sensitive individuals to not have a health concern regarding the risk of dermatitis after oral intake of Ni from the diet, the exposure should be ≤0.14 µg Ni/kg b.w (~10 µg Ni/day). As noted in the comments above, we disagree with the need for a MOE of 30 given the conservatism built into the derivation of the LOAEL. The EFSA report provides estimates of upper bound (UB) acute exposure only, which overestimates true consumption. If we look at adults as an example, the mean and 95% acute Ni dietary exposure values (Table 9 of EFSA report) are as follows: general mean values have min-max of 2.2 and 4.7 µg Ni/kg b.w, while 95% have min-max values of 6-11.6 µg Ni/kg b.w. The lowest values from the summaries of the European surveys (Table D4) are the C2.5 (lower CI) of the mean dietary exposure in total population (1.75-12.57 ug/kg bw/day).	The MOE is the ratio between a defined point on the dose-response curve for the adverse effect (i.e. the reference point) and the human intake. Therefore, it makes no implicit assumptions about a "safe" intake. Therefore, the MOE approach is used for substances for which the available data are too limited for establishing an acute reference dose (ARfD). Consequently, the reference point used for MOE calculation should not be applied in the same way as a reference point for the establishment of a health-based guidance value (HBGV), as suggested in the comment.

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			The reported daily nickel intake for a low Ni diet is 150 µg/day (Mislankar and Zirwas, 2013), resulting in 2.1-2.5 µg/kg b.w. Given all of this information, a value of less than 0.14 µg Ni/kg b.w or 10 µg Ni/day is not achievable under realistic conditions. If 0.14 µg Ni/kg b.w or 10 µg Ni/day are put forward as the target value below which no concerns are expected, the question is how will this message be interpreted by the public and of what benefit will it be, if such a low nickel diet is not achievable? Is the message that this risk is unavoidable? If the MOE of 30 was warranted based on the totality of the data, it could be justified to raise such a strong warning. However, based on the points discussed above, it appears that a much lower overall MOE (e.g. 1-3) can also be justified. The resulting values of 0.1-0.3 mg Ni or 1.4-4.3 µg Ni/kg b.w. would be more achievable with a low Ni diet and would encourage the nickel-sensitized individuals reacting to oral nickel exposure to switch their eating habits towards lower Ni content diets. Otherwise, by EFSA concluding that all the nickel sensitive individuals (~10% of the general population) are at risk from all possible types of dietary nickel exposure, no helpful information would be provided to the nickel-susceptible individuals, and the non-susceptible individuals would be alarmed unnecessarily. Furthermore, attempts to dramatically decrease nickel in the diet to levels so far below normal dietary intake levels could have unintended consequences and result in other more serious health effects (e.g., animal food-based diets with lower Ni content can lead to heart disease).	
	32	3.5.4 Other uncertainties	Lines 2798-2867. Table 11 summarizes the sources of uncertainty and provides a qualitative evaluation of its impact. However, there is no information provided on the relative weight of the + or – effect associated with each source. For example, not considering the additional exposure from Ni released from food contact material (FCM) is listed as "–" (underestimates exposure), while basing the acute reference value on a study that uses fasting is given a "+" (overestimate exposure). However, while the Ni absorption between fasting and not can be a 10-fold difference (30% vs 3%), the contribution of Ni from the highly regulated FCM may add a few percent to the dietary Ni.	See reply to comment 7. Consequently, the Panel concluded that the assessment is more likely to overestimate than to underestimate the risks although Table 11 contains more minuses than plusses.

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	33	3.5.5 Summary of uncertainties	Table 11: Sources of Uncertainty addressed specifically: 1. An additional exposure from nickel released from food contact materials not considered (-): This source should be removed. Minimal amounts of nickel are released from food contact materials compared to the diet. In addition, there is no reference or known reference for the statement in the document noting "However, leaching of nickel into food may not be negligible for food contact materials made of poor quality stainless steel, or of other metal alloys containing nickel." Also, some of the cited papers incorrectly report the contributions of nickel or report the wrong information (e.g., Muller et al., 2015; Khaniki et al., 2016; Guarneri et al., 2016; Flint and Packirisamy, 1995, 1997). Further details can be provided upon request.	The CONTAM Panel concluded in 2015 the following: '*Migration from food contact material could represent an additional source for the presence of nickel in food and drinking water. The CONTAM Panel concluded that the extent of nickel migration into food and drinking water due to the use of good quality stainless steel cookware, tableware, and in general food contact materials has likely little or no relevance compared to the dietary exposure determined by the intrinsic presence of nickel in diet constituents. However, leaching of nickel into food may not be negligible for food contact materials made of poor quality stainless steel, or of other metal alloys containing nickel.*' Reference to the 2015 opinion is included in Section 1.3.2 of the current opinion where this conclusion is repeated as a citation from the 2015 opinion. Considering that the available database is too limited to draw up a scenario on dietary exposure to nickel resulting from food contact material, the CONTAM Panel considers that it is appropriate to include this source of uncertainty in Table 11.
			Upon request from EFSA, the following additional information was provided by NiPERA Inc[4]: [1) Lines 2392 – 2395: page 57: Müller et al. (2015). EFSA state that "Nickel can be released from coffee machines and concentrations above the SRL (up to 780 µg/kg) have been reported after decalcification (Müller et al, 2015)." This statement conveys the message that Ni release from coffee machines exceeds the SRL. However, of the coffee machines tested, only one exceeded the SRL, and that was only for the	The supplemental tables show that the SRL was exceeded in 2 out of 8 coffee machines tested; the portafilter machine PF2 and the pod machine PM3. For PF2 the specific release limit (SRL) was exceeded on one day and in one sample. For PM3, the SRL was exceeded in 6 samples taken

[4] The clarification submitted by NiPERA Inc. is also available in **Annex A** of this Technical Report.

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			one measurement after decalcification. The elevated nickel release is only brief and returns to significantly below the SRL for the rest of the measurements. These study results should be put into perspective with the low nickel release data of the rest of the tested items and the other time points of the one item that briefly exceeded the nickel SRL.	on 3 days. The CONTAM Panel revised the sentence to improve clarity.
			2) Lines 2396 – 2398: page 57: Khaniki et al. (2016). This study is cited as evidence that cast irons can have high Ni releases. However, the quality and relevance of this study should be considered when reporting on the information derived from this study. This paper was written in Persian and the English translation is, to say the least, unclear and the content of the article is difficult to follow. a. One critical deficiency in the paper is the authors did not specify the type of cast iron or shape of the container tested in their study, describing the containers only as "four cast iron containers purchased from only production unit in Iran that had standard symbol". Much of what is on the market (and what is referred to as been increasing in supply in the Introduction of the paper) is porcelain cast iron, but this does not appear to be what was tested. b. The 72 hour length of time for testing cast iron is unrealistic for cooking (domestic or professional) and cast iron cookware is not used for storage of food. The FDA indicates that cast-iron equipment is for use in the food industry for cooking surfaces and in utensils for serving food "if the utensils are used only as part of an uninterrupted process from cooking through service." For all other uses, cast iron may not be used as a food-contact surface. Iron without a protective material is too vulnerable to corrosion and oxidation. c. The highest nickel release value is seen in used containers which were "…prepared through quite corrosive by wire." This method is not explained and seems quite aggressive, with no relevance to simulation of use of the cast iron cooking vessels over time. d. A further factor questioning the relevance of the study is the lack of seasoning of unenamelled cast iron cookware (if that is what was tested) that is done by individuals (and recommended by manufacturers) for this type of cooking material before use in order to prevent food from sticking to the surface, to reduce metal transfer to food, and to prevent corrosion during cleaning after use.	The CONTAM Panel is aware of the limitations in the reporting as well as the limited applicability of the procedures for actual use. A sentence was added to the Opinion to reflect this limitation.

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			3) Lines 2413 – 2420: page 58: Guarneri et al (2016). The study summary should be corrected to state that tomato sauce and lemon marmalade were only tested in used pans. The testing comparison of used and unused pans was conducted only in fluids of different pHs. In addition, consideration may be given to the fact that conditions of testing new pans may not mimic the "home scenario" as the Methods and Materials section notes washing between, but not before, testing. Suppliers of stainless steel cookware advise customers, at a minimum, to wash the goods prior to use and preferably to boil water in the cookware at least twice prior to use. This latter advice is in alignment with the Council of Europe Technical Guide (2013), where compliance with SRL values is determined using the results obtained from the third consecutive test of pan.	It has been clarified in the text that the tomato sauce and lemon marmalade were tested in used pans.
			4) Lines 2421 – 2424: page 58: Flint and Packirisamy (1995, 1997). EFSA's statement that the results reported by Guarneri et al (2016) contradict those reported by Flint and Packirisamy (1995, 1997) (who only observed an increase of the nickel concentration for the first and/or second cooking operation when using new 19/9 stainless steel pots for cooking acidic foods) is not strictly correct. The increases in nickel release observed by Guarneri et al are entirely consistent with the results reported by Flint and Packirisamy (1995, 1997), because the passivation of stainless steel follows a sequence of events where the protective oxide layer on its surface undergoes the loss of iron and the chromium content of the layer is enriched. This process commences with an initial increase in metal release upon contact with aqueous media as indicted in the diagram below. The nickel releases from new (unused) pans reported in the Guarneri et al (2016) study were obtained while the test samples were in the active zone of the passivation process, while the nickel releases reported by Flint and Packirisamy spanned both the active and passive regions of the passivation process. As EFSA acknowledges in its draft report (line 2420) nickel release was higher from unused pots than used pots (i.e. after an initial active period, nickel releases from stainless steel decrease with time). It is, however, correct to state that the authors of the two papers differed in their interpretation of the results regarding the potential impact of diet prepared in stainless steel cookware for nickel-sensitised	For this statement, the CONTAM Panel refers to the results reported by Guarneri et al. (2016) regarding used pots.

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			individuals. Had Guarneri et al taken into consideration the typical passivation process for stainless steel and given sufficient consideration to the differences in nickel release from used and unused pots, they may have come to a different conclusion	
			5) Lines 2423-2424: page 58: Flint and Packirisamy (1995, 1997). The EFSA draft report incorrectly states that Flint and Packirisamy tested 19/9 stainless steel pots, where the pots tested were made of UNS S30400 (18/8) stainless steel.]	The CONTAM Panel noted that in the paper by Flint and Packirisamy (1995) reference is made to 19 Cr/9 Ni stainless-steel saucepans with the inclusion of UNS S30400 between brackets. Flint and Packirisamy (1997) makes reference to UNS 30400 containing 19% Cr/9% Ni. The material and methods section of the papers do not specify the Ni and Cr content of the used materials. Considering that this specific information is not needed in the opinion, it was deleted from the text.
			2. Limited number of subjects and lack of information on degree of sensitisation in the pivotal study for the acute risk assessment (+/-): This can only be + based on comments made on Section 3.1.6. Derivation of HBGV/Margin of Exposure Approach, noting the conservatism in the key study and supporting studies for acute effects.	The CONTAM Panel agrees that it is likely that the subjects in the pivotal study had a relatively high degree of sensitisation, which might have led to an overestimation of the risk. The low number of individuals may have led to either an underestimation or overestimation of the risk.
			3. Not including systemic nickel allergy syndrome in the risk assessment (-): This source should be removed. SNAS is not expected to occur at doses lower than those triggering flare ups of dermatitis at previous sites. In Jensen et al. (2003) reactions at previous sites occurred at 0.3 mg (4/10 patients) but widespread dermatitis only occurred at 4.0 mg Ni (6/10 patients), and general reactions significantly higher than at other doses and controls only occurred at 4.0 mg Ni (6/10 patients).	Whereas the expectation of NiPERA that systemic nickel allergy syndrome (SNAS) may only occur at higher doses that those triggering flare-up reactions may eventually be proven to be valid, currently such proof does not exist. The CONTAM Panel considers that the study by Jensen is not sufficient to make that conclusion. Currently, there is not enough information on SNAS to take studies dealing with this condition further for risk assessment.
			4. Uncertainty in the reference point for acute effects: use of LOAEL that results in a high incidence (40%) of skin reactions (-): The use of this LOAEL is very conservative based on all other studies available and will not result in an underestimate of risk. See comments made in	The CONTAM Panel emphasises that conservatism in the hazard / risk characterisation should not be mixed up with uncertainty.

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			Section 3.1.6. Derivation of HBGV/Margin of Exposure Approach noting the conservatism in the key study and the existence of supporting studies for acute effects. 5. Using a chronic TDI based on reproductive effects for infants, toddlers and young children (+): It could be noted that a TDI based on body weight effects in studies relevant to the exposure period of the younger target populations could be higher than the TDI based on reproductive effects.	See also reply to comment 28. The CONTAM Panel emphasises that conservatism in the hazard / risk characterisation should not be mixed up with uncertainty. See also reply to comment 5.
	34	4. Conclusions	Comments made in previous sections should be considered where relevant in the Conclusions.	The CONTAM Panel revised the conclusions according to the changes in the main body of the text.
	35	5. Recommendations	We agree with the recommendations for research mentioned in the EFSA report.	
	36	Appendix III.0 – Benchmark dose analysis	Based on the information provided in Appendix III, it is not possible to reproduce the results of the modelling We encourage EFSA to include in the report all the model input parameters and data as well as modelling results so that the modelling can be independently reproduced. Additional comments, more detailed comments are provided in Annex 1 of the attached NiPERA comments (written by L. Haber and B. Allen), which concluded: "for the chronic TDI we recommend that EFSA provide additional details and explanations of the parameters used in the modeling and that it provide in the Annex both the actual data used for modeling, and the final modeling results that were used to calculate the RP. For the acute assessment, we recommend that EFSA use model averaging to avoid having the assessment driven by a model with low biological plausibility. In addition, we note the many aspects of conservatism related to the Jensen study that counterweight the concern about the small sample size, supporting a final UF of 1."	See reply to comment 19. It has been specified in the Appendix and Annex that the litter effect was taken into account. All fitted dose-response models are listed in the Appendix and Annex, as well as the results including the estimated model parameters, the weights for model averaging and the graphs (for each model and the bootstrap curves based on model averaging).
	37	Unspecified	We are happy to see the revisions to the EFSA assessment, and appreciate the enhancements that have been made that have improved the scientific basis of the EFSA chronic TDI. Our comments document key differences among the 2015 EFSA assessment, the 2020 EFSA assessment, and our evaluation (Haber et al., 2017), with the goal of identifying areas for potential improvement of the reference point (RP, also known as the point of departure) for the acute assessment and of the documentation for the chronic TDI.	

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Chronic TDI All three assessments (EFSA, 2015, 2020; Haber et al., 2017) were based on modeling conducted on the incidence of litters with post-implantation loss from some combination of the data from the 1-generation dose range finding study (DRF) and the first generation or second generation of the 2-generation (2-GEN) study (SLI, 2000a, 2000b). The recent draft (2020) from EFSA includes a number of improvements over the 2015 assessment, reflecting substantial enhancements to the available software that have been made in the intervening years. In particular, the most recent assessment used model averaging, and included a wider variety of models than was available in 2015 (or 2017). Modelling was conducted using the PROAST software via the EFSA website, using the individual data, with study as a covariate. The full range of dichotomous models available from PROAST was used, rather than focusing on dedicated models for nested data, as was done in the Haber et al. (2017) assessment. Although the modeling conducted by EFSA has the advantage of using a broader range of dichotomous models to model the individual data than what was done in previous assessments, there are a number of aspects of the modeling that were not fully documented, resulting in several uncertainties for the reader. As in the 2015 documentation, the individual input data modeled were not presented, making it harder to reproduce the EFSA (2020) results. The website for the modeling shows an option for addressing nested quantal data, and includes the option for including a "litter effect," although the manner in which the litter effect is included is unclear. Is this a litter-specific covariate (LSC), intralitter correlation (IC), or something else? It is also not clear whether litter-specific probabilities of response were modeled for this data set. Does the "alfa" parameter reflect the "litter effect"? Note also that Annex A1 (modeling of the F1/F2 generation of the 2GEN study) provides a BMR of 10%, but Annex A2 (modeling of DRF and the F0/F1 generation of the 2GEN study) uses a BMR of 5%. This means that the complete modeling results with the final data set used for the analysis (DRF and 2GEN studies), with the BMR of 10%, are not presented. We urge EFSA to provide in the Annex both the actual data used for modeling, and the final modeling results (including explanation of model parameters) that were used to calculate the RP.	See reply to comment 36. More information regarding the manner in which the litter effect is handled in PROAST is provided in section 5.7 of the PROAST manual (menu version) which is available at https://www.rivm.nl/documenten/proast-manual-menu-version. The manual describes the following: "In PROAST clustering in quantal data is taken into account as follows. It is assumed that the response at each dose (= value of x) has a betabinomial rather than binomial distribution. The betabinomial distribution results from assuming a Beta distribution for the expected response for a particular cluster (e.g. litter) and a binomial distribution for the experimental units (e.g. embryos) within the cluster (litter). In this way all models available for quantal models, as discussed in Section 5.4, can be similarly applied

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			All of the assessments used an uncertainty factor of 100, based on a factor of 10 for interspecies differences and a factor of 10 for intraspecies variability. Overall, the absence of key details on the modeling, and absence of the model output for the final model, create uncertainty for the reader and make it harder to follow the details of the EFSA (2020) approach, since it is not clear exactly what data were used, and how the nested nature of the data was accounted for. However, overall, the EFSA (2020) assessment appears to be a step in moving the science forward, by including a larger variety of models and by including model averaging. **Acute Assessment** In contrast to the chronic assessment, the acute assessment in EFSA (2020) moves the science forward in some ways, but in other aspects does not use the state of the science approach. By modifying only part of the assessment, but not including other new methodological approaches, the 2020 draft does not reflect the current best state of the science.	to quantal data with clustering. The difference between fitting a model as if the data were not clustered is just one additional parameter, called alfa in PROAST. This parameter alfa is one of the parameters of the Beta distribution. In PROAST alfa is defined such that the lower its value the wider the Beta distribution (higher variation). The addition of the parameter alfa can be regarded as a nested extension of the dose-response model. Therefore, the log-likelihood value associated with the best fit of the betabinomial dose-response model (with alfa) can be compared to the equivalent binomial model (without alfa) in the usual way (repeat the same analysis, but select data type quantal data, option 4 from the first PROAST question)." The (fitted) dose-response model reflects the frequency of response in the average litter, as a function of dose. Therefore, the $BMDL_{10}$ relates to the average litter as well. As specified in the first paragraph of Section 3.1.5.2: "The detailed description of the BMD analysis performed by the Panel can be found in Appendix III and Annex A. Appendix III shows the detailed BMD analysis from which the reference point was selected, and all other BMD analyses are shown in Annex A." Appendix III.1 presents the results from the modelling of the data from the DRF and the 2GEN F0F1 studies for a BMR of 10%.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			The EFSA (2015) report identified three studies with dose-response information on systemic contact dermatitis (SCD) (Gawkrodger et al., 1986; Hindsén et al., 2001; and Jensen et al., 2003), and conducted BMD modeling on each of them. The Jensen et al. (2003) study was identified as the most sensitive, and EFSA calculated a BMDL10 of 0.08 mg Ni per person, corresponding to 1.1 µg Ni/kg. EFSA noted that the test population consisted of sensitized individuals, and the nickel was consumed in the form of nickel sulphate in lactose capsules, consumed in a fasted state, which would result in absorption much higher than that from food. Based on these considerations and the low severity of the response on the one hand, and the high interindividual variability on the other hand, EFSA concluded that a margin of exposure (MOE) of 10 or higher would be indicative of low health concern. Our acute assessment (Haber et al., 2017) was also based on modeling of the Jensen et al. (2003) study, and we obtained the same modeling results as those obtained by EFSA (2015). However, EFSA (2015) chose the lowest BMDL10 of the acceptable models, resulting in a BMDL10 of 0.08 mg Ni, based on the multistage model. This approach is consistent with the then-current EFSA (2009) BMD guidance. Our final BMDL10 of 0.3 mg Ni was based on the holistic approach described in Haber et al. (2018). All of the models had acceptable goodness of fit p-values and scaled residuals, but comparative visual fit was difficult to evaluate, and there was no clear reason to prefer one model over another. Therefore, we averaged the BMDLs from unique models to obtain a final BMDL. (Note that this averaging of model results is different from model averaging, which was not available with BMDS at the time.) Consistent with US EPA (2012) guidance, all models were run in the restricted (also known as constrained) form. The draft EFSA (2020) assessment also focused on the Jensen et al. (2003) study. However, unlike the previous modeling, which had constrained the slope parameters to avoid extremely steep slope in the low-dose region, the 2020 assessment used unconstrained models. This is consistent with the EFSA (2017) guidance on BMD modeling. The issue of whether to constrain the slope parameter has been one of ongoing disagreement between EPA and EFSA. The EPA (2012) guidance recommends the use of constrained models, due to the potential for excessively conservative BMDLs, sometimes approaching zero when the slope is not constrained. In contrast, the EFSA (2017) guidance expresses concern about constrained models having bounds	

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			that are too narrow to adequately characterize the within-model uncertainty, with the resulting BMDL not being sufficiently health protective. Experts worldwide have recently reached consensus that the slope parameter should not be constrained, but that model averaging, using soft constraints with a Bayesian approach, should be used to avoid biologically unreasonable results[5]. The Bayesian approach has the advantage that it can better account for the model uncertainty, while avoiding biologically unreasonable results by putting low weights on models with very steep slope parameters. The problem of very low BMDLs with unconstrained models was evident in the EFSA (2020) draft, which reported a BMDL10 – BMDU10 interval of 2.66 x 10-5 – 1.63 mg Ni/person. In obtaining this result, EFSA used model averaging, but not Bayesian model averaging (which is not currently an option with the PROAST software on the EFSA website). Because of the wide BMDL10– BMDU10 interval for the Jensen et al. (2003) study, EFSA (2020) also explored combining the results of that study with those of Gawkrodger et al. (1986), but the interval was still considered too large, and the BMDL10 was outside the dose range. Therefore, EFSA (2020) based the RP on the LOAEL of 0.3 mg Ni in the Jensen et al. (2003) study, corresponding to 4.3 µg Ni/kg. In light of the extrapolation from a LOAEL with a 40% response, EFSA concluded that an MOE of 30 or higher would indicate a low health concern. Unlike PROAST, BMDS 3.1.2 can conduct Bayesian model averaging, and the prior distributions in BMDS have low a priori probabilities for curves with supra-linear slopes (i.e., curves that are very steep in the low-dose region). Therefore, we modeled the same data as used by EFSA (clinically cutaneous reactions in the Jensen et al. (2003) study) using BMDS 3.1.2. All of the dichotomous models were run in the unrestricted/unconstrained form, and Bayesian model averaging was conducted. The resulting BMDL10 was 0.17 mg Ni/person, and the BMDU10 was 2.55 mg Ni/person. Thus, the use of Bayesian model averaging allowed the use of unconstrained models without resulting in an extremely wide BMDL10 – BMDU10 interval. Interestingly, this BMDL10 of 0.17 is between the BMDL10 of 0.30 mg Ni identified by	Being involved in the discussions on the dose-response chapter of the EHC 240, EFSA acknowledges this approach which is still under development and evaluation. So far, the influence of the choice of the specific prior distribution for the parameters in the models on the results obtained has not been sufficiently studied. Therefore, the CONTAM Panel did not apply this approach in the current mandate for identifying a reference point.

[5] This consensus has not yet been published, but was reached in the context of the update to the dose-response chapter of the WHO/IPCS EHC 240, and has been presented at a webinar associated with the cancelled 2020 SOT annual meeting.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Haber et al. (2017) and that identified by EFSA (2015) of 0.08 mg. The BMDL10 of 0.17 mg Ni corresponds to 2.4 µg Ni/kg for a 70 kg person. Our 2017 assessment recommended an uncertainty factor of 1, based on a number of areas of conservatism in the Jensen et al. (2003) study: (1) the dosing protocol maximized the internal dose by treating fasted subjects, meaning that absorption was as much as 10-fold higher than in a fed state; (2) dosing was in a bolus (capsule), so peak serum levels were higher than would have occurred if the same amount were ingested in drinking water or food; and (3) subjects were patients at a dermatology clinic and so were likely to be more sensitive than people with systemic nickel dermatitis who did not seek treatment. These areas of conservatism were considered sufficient to counter the small sample size, particularly in light of the IPCS (2012) guidance that an intraspecies factor of 1 can be appropriate for a TDI based on elicitation, since the response is already based on effects in the most sensitive individuals. Therefore, we still consider an uncertainty factor (UF) of 1 to be adequate. We also note that the reported doses did not include nickel in food, and so the TDI in Haber et al. (2017) is in addition to the normal dietary intake. A similar concept would apply here. However, we recognize that such an approach might be difficult to implement in the context of EFSA's work. Therefore, the fact that the doses in the Jensen study were in addition to dietary nickel provides additional support for the choice of a UF of 1, and should be considered in EFSA's consideration of an appropriate MOE when applied to total dietary intake. It is noted that the UF is a risk assessment parameter, while the MOE is a risk management value, but MOEs of at least the size of the UF that would be used in the scenario of interest are generally considered to be of low health concern. **Summary of Key Decision Points and Results for the Acute Assessment** Table (see pdf on page 5 and 6 of Annex 1 in the document provided by NiPERA) **Conclusion** In summary, for the chronic TDI we recommend that EFSA provide additional details and explanations of the parameters used in the modeling and that it provide in the Annex both the actual data used for modeling, and the final modeling results that were used to calculate the	In the consideration of the MOE of 30 the CONTAM Panel did not apply an uncertainty factor for inter-individual variability as nickel-sensitised individuals are the most sensitive human population, or in other words a factor of 1 for inter-individual variability has been applied. The MOE of 30 has been considered justified due to limitations in the database, see reply to comment 28, as well as text in the opinion (Section 3.1.6).

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			RP. For the acute assessment, we recommend that EFSA use model averaging to avoid having the assessment driven by a model with low biological plausibility. In addition, we note the many aspects of conservatism related to the Jensen study that counterweight the concern about the small sample size, supporting a final UF of 1. **References** EFSA (European Food Safety Authority). (2009). Guidance of the Scientific Committee on a request from EFSA on the use of the benchmark dose approach in risk assessment. EFSA Journal; 1150:1-72. EFSA (European Food Safety Authority). (2015) Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water. EFSA Panel on Contaminants in the Food Chain (CONTAM). Eur Food Saf Auth J 13(2): 4002. EFSA (European Food Safety Authority) EFSA. (2017) Update: Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal;15(1):4658, 41 pp. doi:10.2903/j.efsa.2017.4658. EFSA Scientific Committee. EFSA (European Food Safety Authority). (2020) Update of the risk assessment of nickel in food and drinking water. EFSA Panel on Contaminants in the Food Chain (CONTAM). Draft. Doi: 10.2903/j.efsa.2020.xxxx Gawkrodger DJ, Cook SW, Fell GS, Hunter JA. (1986) Nickel dermatitis: The reaction to oral nickel challenge. Br J Dermatol 115: 33–38. Haber LT, HK Bates, BC Allen, MJ Vincent, and A.R. Oller. (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 Haber LT, ML Dourson, BC Allen, R Hertzberg, A Parker, MJ Vincent, A Maier, and A Boobis. (2018) Benchmark Dose (BMD) Modeling: Current practice, issues and challenges. Crit Rev Toxicol. 8:1-29. https://doi.org/10.1080/10408444.2018.1430121	

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Hindsén M, Bruze M, Christensen OB. (2001) Flare-up reactions after oral challenge with nickel in relation to challenge dose and intensity and time of pervious patch test reactions. J Am Acad Dermatol 44(4):616-23. IPCS (International Programme on Chemical Safety). (2012) Guidance for immunotoxicity risk assessment for chemicals. World Health Organization, Geneva. http://www.who.int/ipcs/methods/harmonization/areas/immunotoxicity/en/. Jensen CS, Menné T, Lisby S, Kristiansen J, Veien N. (2003) Experimental systemic contact dermatitis from nickel: A dose–response study. Contact Dermat 49: 124-132. SLI (Springborn Laboratories Inc.). (2000a) A one-generation reproduction range-finding study in rats with nickel sulfate hexahydrate. Springborn Laboratories Inc., Spencerville, SLI Study No. 3472.3. SLI (Springborn Laboratories Inc.). (2000b) An oral (gavage) two-generation reproduction toxicity study in Sprague-Dawley rats with nickel sulfate hexahydrate. Final Report. Springborn Laboratories Inc., Spencerville, SLI Study No. 3472.4. US EPA (United States Environmental Protection Agency). (2012) Benchmark dose technical guidance document. Final Draft. US EPA, Washington, DC, EPA/100/R-12/001, June 2012. https://www.epa.gov/risk/benchmark-dose-technical-guidance.	
FoodDrinkEurope	38	3.2.1. Occurrence data on food submitted to EFSA	We welcome the opportunity to comment on the Public consultation on the draft scientific opinion on update of the risk assessment of nickel in food and drinking water. Regarding Occurrence data considered for dietary exposure assessment Line 2307- In the draft of the updated EFSA risk assessment for nickel, the food category "sugar and confectionary" is associated with high nickel contents. EFSA notes that these high levels are mainly due to the sub-category "chocolate (cocoa) products". In this context, we would	The FoodEx food categories are consistently reported at FoodEx level 1 throughout the main body text of the document. The reporting of one of them at level 2 would be rather confusing.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			therefore recommend that the sub-category "chocolate (cocoa) products", which is already explicitly stated in the summary, is used along the document for consistency rather that the broader category "sugar and confectionary". Or at least that it is clearly shown that within the food category "sugar and sweets" only one sub-category has high contents. Without any detailed clarification, it can be assumed that all products in this broad category are associated with high nickel content and would consequently be subject to a negative interpretation for no reason.	The CONTAM Panel considers that it is clearly and sufficiently stated that the cub-category "chocolate (cocoa) products" drives the nickel concentration within the whole food category "sugar and confectionary" in every point of the document where this food category is discussed.
	39	3.2.2 Previously reported occurrence data in the open literature	Regarding Release of nickel from food contact materials Line 2390 to 2392- In respect to the coffee machine as food contact material, it would be useful to have a have a foot note reference to the EU Food Contact Materials Framework Regulation 1935/2004 and the Regulation 2023/2006 on good manufacturing practices for materials and articles intended to come into contact with food, when referring to food contact materials/ packaging material/ domestic appliances. Line 2399-2405 - A further clarification would be required considering that no content for canned food at the beginning of shelf life is mentioned. If the preserved foods themselves contained nickel, this information is required in order to assess an increase.	Both regulations have been added to the legislation Section (1.3.5). The CONTAM Panel added information to the text to improve clarity. However, the concentration at the beginning of the shelf life was not provided for all samples in the paper.
European Coffee Federation [The contribution submitted by the European Coffee Federation is also available in **Annex B** of this Technical Report]	40	Summary	We welcome the opportunity to comment on the public consultation on the draft scientific opinion on the update of the risk assessment of nickel in food and drinking water. As a follow-up to the 2015 EFSA opinion and Recommendation (EU) 2016/1111, the coffee industry monitored the presence of nickel in coffee and is working on better understanding the main sources of contamination. We would thus like to make the following observations. Green Coffee. Nickel is, as for all plants, an essential micronutrient relevant for example in the nitrogen metabolism. Therefore, it can be present and detected in green coffee. Literature reports a variation of nickel composition in green coffee beans in correlation with the geographical origin. This could be a consequence of differences related to coffee varieties, and soil composition.	Thank you for sharing this information with the CONTAM Panel. EFSA would like to invite the European Coffee Federation to submit the occurrence data to EFSA for consideration in future risk assessments. Please contact data.collection@efsa.europa.eu to obtain further information regarding the submission.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
			Roasted Coffee. Nickel is not formed during the roasting process. The measured amounts are related to the green coffee. Beverage. Nickel values found in the beverage are a consequence of the brewing method and water used for the infusion. Overall, the industries sampling results are mostly in line with those referred to the 2020 EFSA opinion.	
	41	3.2.2 Previously reported occurrence data in the open literature	To be noted that coffee machines acquired by the consumer are to comply with the EU Food Contact Materials Framework Regulation 1935/2004 and the Regulation 2023/2006 on good manufacturing practices for materials and articles intended to come into contact with food, when referring to food contact materials/ packaging material/ domestic appliances. As for the water that is used for brewing, it would be compliant with the 1998 Drinking Water Directive. Thus, we kindly request the following inclusion: Line 2390 to 2392. In respect to the coffee machine as food contact material, it would be useful to have a foot note reference to the EU Food Contact Materials Framework Regulation 1935/2004 and the Regulation 2023/2006 on good manufacturing practices for materials and articles intended to come into contact with food, when referring to food contact materials/ packaging material/ domestic appliances.	See reply to comment 39.

(a): Comments are shown as received from the commenters.

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Abbreviations

2GEN F0F1	F0/F1 generation of the two-generation study
ARfD	Acute reference dose
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDU	benchmark dose upper confidence limit
BMR	benchmark response
bw	body weight
CI	confidence interval
CONTAM	Panel on 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
LOQ	limit of quantification
MOE	margin of exposure
NOAEL	no-observed-adverse-effect-level
OECD	Organisation for Economic Co-operation and Development
PND	postnatal day
RAR	Risk assessment report
SNAS	systemic nickel allergy syndrome
SRL	specific release limit
TDI	tolerable daily intake

Appendix A – Explanatory note to Public Consultation

EFSA's Panel on Contaminants in the Food Chain (CONTAM) has launched an open consultation on the draft scientific opinion on the update of the risk assessment of nickel in food and drinking water. This document presents an estimation of the acute and chronic human dietary exposure to nickel from food and drinking water, and an assessment of the human health risks related to this dietary exposure.

Interested parties are invited to submit written comments by **15 July 2020**.

Please use the electronic template provided: https://ec.europa.eu/eusurvey/runner/public_consultation_nickel to submit comments and refer to the line and page numbers. To submit additional data to support your comments or files, there is an upload function available in the tool (for a maximum size of 1Mb file). Otherwise you can also contact specific unit's functional mailbox: biocontam@efsa.europa.eu

Please note that comments will not be considered if they:

- are submitted after the closing date of the consultation
- are presented in any form other than what is provided for in the instructions and template
- are not related to the contents of the document
- contain complaints against institutions, personal accusations, irrelevant or offensive statements or material
- are related to policy or risk management aspects, which are out of the scope of EFSA's activity.

EFSA will assess all comments which are submitted in line with the criteria above. The comments will be further considered by the relevant EFSA Panel and taken into consideration if found to be relevant. Due to time constraints, EFSA cannot use additional occurrence data submitted during the public consultation for the dietary exposure assessment in this risk assessment. However, occurrence data submitted in SSD format will be stored and used for future risk assessments.

Copyright-cleared contributions

Persons or organizations participating in a Public Consultation of EFSA are responsible for ensuring that they hold all the rights necessary for their submissions and consequent publication by EFSA. Comments should inter alia be copyright cleared by taking into account EFSA's transparency policy and practice to publish all submissions. In case the submission reproduces third-party content in the form of charts, graphs or images, the required prior permissions of the right holder(s) should have been obtained by the PC respondent

Publication of contributions

Contributions will be published (as part of an EFSA report published together with the final opinion) and may be re-used by EFSA in a different context. It should be noted that contributions submitted by individuals in a personal capacity will be published as such, indicating the author's first and family name, unless a substantial justification for protection is provided by the respondent. Contributions submitted on behalf of an organization are also made publicly available and attributed to the organization in question.

Submit comments (deadline: **15 July 2020**)

Published: 4 June 2020

Annex A – Contribution submitted by NiPERA Inc.

The following file was submitted by NiPERA Inc. together with their contribution to the public consultation:

- 2020_Draft_EFSA_Opinion_on_Nickel_NiPERA_comments

This file is available on the EFSA Knowledge Junction community on Zenodo at: https://doi.org/10.5281/zenodo.4081886

The following file was sent by NiPERA Inc. following a request from EFSA to provide further details regarding comment 33:

- NiPERA response to EFSA detailed comment request

This file is available on the EFSA Knowledge Junction community on Zenodo at: https://doi.org/10.5281/zenodo.4081886

Annex B – Contribution submitted by the European Coffee Federation.

The following file was submitted by the European Coffee Federation together with their contribution to the public consultation:

- ECF_response_draft_to_EFSA_scientific_opinion._Final

This file is available on the EFSA Knowledge Junction community on Zenodo at: https://doi.org/10.5281/zenodo.4081892