

**Disposition of Peer Review Comments For
Toxicological Profile For
Nickel**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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Comments provided by Reviewer #1

ATSDR MRL Update Charge Questions and Responses and Reviewer Comments

Newly Derived Acute-Duration Inhalation MRL

QUESTION: Do you agree with the proposed acute-duration inhalation MRL value and how it was derived? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 1: No comments.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the health endpoint and the point of departure for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 2: I agree.

RESPONSE: *No response needed.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 3: Agree.

A total uncertainty factor of 300 was used here:(10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability).

RESPONSE: *No response needed.*

Newly Derived Intermediate-Duration Inhalation MRL

QUESTION: Do you agree with the proposed intermediate-duration inhalation MRL value and how it was derived? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 4: I agree.

Sine nickel subsulfide for 6 hours/day, 5 days/week for 90 days (Oller et al. 2023) falls within the classical definition of intermediate.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the health endpoint and the point of departure for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 5: I agree.

Since nickel based on alveolitis and perivascular/peribronchiolar inflammation observed in the lungs of rats is the most sensitive indicator.

RESPONSE: *No response needed.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 6: I agree.

A total uncertainty factor of 30 was used: (3 for extrapolation from rats to humans with dosimetric adjustments and 10 for human variability).

RESPONSE: *No response needed.*

Newly Rescinded Chronic-Duration Inhalation MRL

QUESTION: Do you agree with not deriving a chronic-duration inhalation MRL? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 7: I agree.

Though the use of NOAELHEC of 0.0033 mg Ni/m³ as the final POD and a total uncertainty factor of 30 resulted in a chronic-duration inhalation MRL of 0.0001 mg Ni/m³ (1×10^{-4} mg Ni/m³). Since, this value 1×10^{-4} mg Ni/m³ is higher than the intermediate-duration inhalation MRL of 3×10^{-6} mg Ni/m³, therefore a chronic-duration inhalation MRL cannot be derived.

A total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) was assumed in this deduction.

RESPONSE: *No response needed.*

Comments provided by Reviewer #2

ATSDR MRL Update Charge Questions and Responses and Reviewer Comments

Newly Derived Acute-Duration Inhalation MRL

QUESTION: Do you agree with the proposed acute-duration inhalation MRL value and how it was derived? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 1: Affirmative to each part of the question

RESPONSE: *No response needed.*

QUESTION: Do you agree with the health endpoint and the point of departure for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 2: Agree

RESPONSE: *No response needed.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 3: Agree; see below

The ATSDR recommends deriving MRLs for hazardous substances using the NOAEL/uncertainty factor approach. MRLs represent exposure levels high enough to elicit detectable symptoms of toxicity (clinically defined or by biomarkers) in the human population. By selecting the point of departure a priori (i.e., the LOAEL), the ATSDR effectively recommends using linear threshold models in analyzing exposure-response relationships. Such data analysis paradigms are most valid at relatively high exposure doses.

For calculating the MRL for acute-duration, it was presumed that the experimentally determined LOAEL value is equivalent to the toxicity threshold for nickel sulfate hexahydrate. This value (0.2244 mg/m³) was adjusted for continuous duration exposure, converted to a human equivalent concentration (HEC), and then divided by a total uncertainty factor. I do not have any issues with the procedure used or the point of departure for this MRL.

The provisional MRL (100 ng/m³) is well below the nickel content in ambient air particulates across the United States, which are mostly <3 ng/m³, with a maximum mean (reported) concentration of 18 ng/m³ in the last five years (this TOX PROFILE report). The geometric mean concentration of airborne nickel at National Priorities List (NPL) sites is given as 1.47 ng/m³, although values as high as 769.8 ng/m³ have also been reported (Table 5.9 of the TOX PROFILE Report). Does the MRL make sense in relation to the reported concentrations of nickel in the air in this country? The available data suggest that only the most heavily contaminated areas in the United States (NPL sites) are likely to show nickel concentrations in ambient air that may reach the MRL. From this perspective, the value of the MRL, the uncertainty factors used in its derivation, and the field observations seem to be properly aligned.

For comparison, the National Ambient Air Quality Standards (NAAQS) for lead in the US is 150 ng/m³ as measured in total suspended particulates. The 2008 rule that set the NAAQS for lead was based on a review of 6,000 scientific studies on the health effects of lead exposure, providing sound data support. Lead in the environment is much more toxic than nickel, and it seems somewhat anomalous that its national ambient air quality target is higher than the MRL corresponding to acute-duration toxicity for nickel. Whether such comparisons should be factored into the selection of uncertainty factors is probably outside the terms of my review.

RESPONSE: *No response needed.*

Newly Derived Intermediate-Duration Inhalation MRL

QUESTION: Do you agree with the proposed intermediate-duration inhalation MRL value and how it was derived? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 4: No; see below. 24 ng/m³ based on linear threshold model for the dose-response relationships.

RESPONSE: *See the Response to Comment 6.*

QUESTION: Do you agree with the health endpoint and the point of departure for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 5: No. See the commentary below.

RESPONSE: *See the Response to Comment 6.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 6: The MRL should be recalculated using the linear threshold model as recommended by ATSDR. Adjustments of intermittent exposure, human equivalent concentration, and uncertainty factors needs to be made accordingly.

The procedure used in estimating the intermediate MRL assumes a curvilinear exposure-response relationship with no threshold value. The incidence data were fit to various dichotomous models in EPA's Benchmark Dose Software (BMDS) using a benchmark response (BMR) of 10% extra risk. Two potential PODs were considered by the authors for calculating the MRL: a BMCL10 of 0.0014 mg Ni/m³ for perivascular/peribronchiolar inflammation and a LOAEL of 0.04 mg Ni/m³ for alveolitis and protein accumulation in the lung. The authors decided to use the BMCL10 of 0.0014 mg Ni/m³ as the POD because it resulted in a lower MRL, hence was presumed to be more protective of public health. Such rationale in making the selection is clearly not science-driven. My opinion is that the choice was wrong, and the reasons for this are summarized below.

The no-threshold models used in assigning the point of departure are based on the premise that an "atom" of nickel (or any dose, however small) can induce some adverse health effect(s) on a cell or tissue. Also

inherent in such models is the assumption that adverse effects are proportional to the exposure dose at the target organ. Numerous studies have shown that such models are unreliable in predicting subclinical effects of toxic metals at low exposure levels. This is not a matter of uncertainty but mainly due to a lack of scientific knowledge. Like most biological phenomena, nickel toxicity can involve both stochastic and deterministic interactions. It is well established, for instance, that gene expression is stochastic by nature – including during trace metal toxicosis (Banerjee et al., 2024). Conversely, it has been suggested that stochastic gene expression can also be employed by cells as a rheostatic mechanism to adapt to rapidly changing exposure to toxic metals in the environment (Hammerlindl & Schaider, 2018). By focusing on the deterministic lockstep changes that occur upon any given exposure, most in vivo studies ignore the stochastic processes that might also play a crucial role in defining the cellular and molecular toxicity of nickel. In essence, the models are not in tune with the genetic and pathological processes that lead to the induction of adverse effects by nickel exposure.

Nickel has low redox activity and is present in blood primarily as a divalent cation (Ni^{2+}). Since nickel is a non-essential trace element, no homeostatic control has evolved to regulate its concentration in the human body, hence the propensity for nickel to accumulate in cells and tissues. There is evidence to suggest that Ni^{2+} does not directly poison tissue or cellular components below the acute exposure dose. Instead, the adverse effects are mediated indirectly through the formation of oxidative stress and mimicry with essential trace elements. Strong binding to sulfhydryl groups and displacement of other divalent metal cations at the cellular and molecular levels play an important role in the pathogenesis of nickel poisoning. These interactions give rise to dysregulation of the metabolic cycles of essential metal cations and functions of numerous biomolecules that contain such chelating ligands, from proteins, enzymes, and antioxidants to cellular structures. The ripples created by interactions of Ni^{2+} with diverse chelating ligands of the sulfoproteome can result in a multiplicative effect in the inhibition or inactivation of many functional or regulatory enzymes. All this is to say that the cellular and molecular processes associated with “sub-acute” nickel exposure are very complicated.

While labile Ni^{2+} ions tend to be easily absorbed by diffusion or transported into cells via various divalent cation channels or transporters, insoluble particles can only be absorbed by phagocytosis. Nickel subsulfide transported into cells is likely to persist as a solid phase rather than dissolve in the intracellular milieu, considering that the solubility product constant for NiS is 3×10^{-21} compared to the binding constants of nickel to sulfhydryl groups of biomolecules, including $4.4 \times 10^9 \text{ M}^{-1}$ for cysteine, $1.9 \times 10^9 \text{ M}^{-1}$ for histidine, and $1.5 \times 10^5 \text{ M}^{-1}$ for other amino acids (Costa et al., 1981; Biggart & Costa, 1986). We currently do not know much about the processes that link Ni_3S_2 exposure to toxicological outcomes, i.e., through which pathways the initial chemical–biological interaction extends to the “biological response profiles” reported, how this extension is modulated by adaptive or compensatory processes, as well as by phenotypic traits of the human receptor. The observation (Efremenko et al., 2017a, 2017b; Oller et al., 2023) that aerosolized Ni_3S_2 is more toxic than the easily hydrolysable nickel sulfate is very pertinent. It raises the issue of whether the primary “driver” of the observed effects is due to the unique mechanical-morphological properties of Ni_3S_2 rather than the nickel content of the particles (for instance, see Dumkova et al., 2017). It is remarkable that most of the models used to calculate the benchmark concentration use the “mode of action” approach, which refers to a hypothesized, biologically plausible key event in the sequence from chemical exposure to toxic outcome. They do not implicate mechanistic understanding of the toxic action, especially at the cellular and molecular levels.

The value of 3 ng Ni/m^3 being proposed as an intermediate-duration MRL is $\leq 25\%$ of the concentrations ($0.7 - 72 \text{ ng/m}^3$) found in the outdoor environment and below most of the concentrations in indoor air ($3 - 24 \text{ ng/m}^3$) in many parts of the United States (TOX PROFILE). It is routinely exceeded by the ambient concentration of particulate nickel in New York City (Tables 5.11 and 5.12; TOX PROFILE) and below many values reported in many rural and even remote locations. The implication of the low MRL being proposed is that a large proportion of the US population is being exposed to unhealthy levels of nickel in

their ambient air. There is no epidemiological or monitoring data to support such a claim of serious public health risk at current levels of nickel in the ambient air. It is also inconsistent with the fact that nickel is not a particularly toxic element.

My suggestion is to follow the ATSDR's recommendation by using the NOAEL (0.04 mg/m³) as the point of departure for estimating the MRL. A back-of-the-envelope calculation based on linear extrapolations of the data used in deriving the acute MRL shows the following:

$$\text{Adjustment for Intermittent Exposure} = (0.04 \text{ mg/m}^3) \times [(6 \text{ hrs})/(24 \text{ hrs})] = 0.01 \text{ mg Ni/m}^3$$

$$\text{Human Equivalent Concentration} = (0.01 \text{ mg/m}^3) \times 0.7291 = 0.0073 \text{ mg/m}^3$$

$$\text{Provisional MRL} = (0.0073 \text{ mg m}^{-3})/300 = 0.000024 \text{ mg/m}^3 \text{ (or } 24 \text{ ng/m}^3\text{)}$$

It needs to be noted that the Uncertainty Factor of 300 is used, assuming 10 for a LOAEL, 3 for extrapolation from rats to humans with dosimetric adjustments, and 10 for human variability. The Uncertainty Factor of 30 was used for the no-threshold model.

The MRL (24 ng/m³) estimated with the linear threshold model is lower than 95% of the nickel concentrations measured in ambient air at locations across the United States (Table 5-10). Nickel concentrations around 24 ng/m³ are occasionally found in indoor air during winter (Table 5.12) and near industrial operations (Table 5.11). It seems like a more reasonable benchmark in the context of the available measurement data on nickel concentration in ambient air.

RESPONSE: For most profiles, ATSDR uses one of two approaches for identifying the point of departure (POD) for the MRL: the benchmark dose modeling approach and the NOAEL/LOAEL approach. In the benchmark dose (BMD) approach, the experimental data (in the case of the nickel MRL, the perivascular/peribronchiolar inflammation incidence data) are modeled and a BMD is estimated. The POD used to derive the MRL is 95% lower bound on a benchmark dose (referred to as the BMDL). ATSDR agrees that a no-threshold response would not be appropriate for nickel due to the reasons stated by the Reviewer. It is noted that the BMD methodology used for the MRL did not apply no-threshold extrapolation, as the threshold response was defined by the benchmark response (BMR) of 10% (Haber et al. 2018). Thus, the selected POD is not based on the assumption that an "atom" of nickel can induce a pulmonary effect, it is based on the 95% lower bound of an estimate of a value that would induce the lesion in 10% of the study population. In the NOAEL/LOAEL approach, the POD is the highest NOAEL for the critical effect; if a NOAEL is not identified, then the lowest LOAEL is used as the POD. There are several limitations to the NOAEL/LOAEL approach including high dependence on study dose selection, lack of consideration of the shape of the dose-response curve, and inability to derive a NOAEL when the lowest dose/concentration tested is a LOAEL. When the lowest dose is a LOAEL (as is the case for the nickel intermediate-duration inhalation MRL), an uncertainty factor is applied to account for this limitation; however, this may under- or overestimate the no-effect level. Given these limitations, preference is given to the BMD approach over the NOAEL/LOAEL approach since BMD modeling takes into consideration the dose-response over a range of doses rather than a single dose. Thus, for the intermediate-duration inhalation MRL for nickel, the BMCL₁₀ was selected as the POD over the LOAEL value.

The Reviewer commented that the MRL is within the range of ambient air levels. As noted in the introduction in Appendix A, MRLs are intended only to serve as a screening tool to aid public health professionals in assessing potential risks. A conservative approach is used to derive MRLs to be consistent with the public health principle of prevention.

Newly Rescinded Chronic-Duration Inhalation MRL

QUESTION: Do you agree with not deriving a chronic-duration inhalation MRL? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 7: I disagree; see the comments below.

The effort to estimate the point of departure (POD) using various no-threshold models failed to provide an adequate fit to the data – not really surprising. The NOAEL of 0.03 mg Ni/m³ was consequently used as the benchmark concentration in calculating the MRL. After adjusting for continuous exposure and human equivalent concentration using the methodology and equations shown in the intermediate-duration MRL section and the values shown in Tables A-11 and A-12, the POD was calculated to be 0.0033 mg/m³. I suggest that the uncertainty factor should be 300, instead of 30, to be consistent with the values for chronic- and intermediate-duration exposures. Otherwise, an explanation for the use of different uncertainty factors should be mentioned in the report. With an uncertainty factor of 300, the chronic-duration inhalation MRL is estimated to be 0.00001 mg Ni/m³ (10x10⁶ mg Ni/m³), instead of 1x10⁴ mg Ni/m³. This value is lower than the proposed intermediate-duration inhalation MRL of 24x10⁶ mg Ni/m³ obtained with the compatible linear threshold model.

An MRL value of 10 ng/m³ falls in the top 5% of reported nickel concentrations measured in ambient air at locations across the United States (Table 5.10) and most NPL sites in the country (Table 5.9). It is less than the average of reported maximum concentrations (18 ng/m³) of particulate nickel in ambient air in the United States during the last five years (this TOX PROFILE report). In the context of the reported ambient air concentration of nickel in the United States, the MRL would seem reasonable as it can be used to benchmark the top 5% of the population or areas with the highest risk for likely health impairment from nickel exposure.

RESPONSE: *ATSDR disagrees with the Reviewer's suggestion of adding an additional uncertainty factor of 10 to the potential chronic-duration inhalation MRL value. ATSDR utilizes uncertainty factors to account for the uncertainty in extrapolating from a LOAEL rather than a NOAEL, for extrapolating from animals to humans, and for human variability in sensitivity. Not all of these uncertainty factors are applicable for each MRL. In addition to these uncertainty factors, ATSDR will sometimes utilize a modifying factor to account for database deficiencies. The proposed chronic MRL was based on a NOAEL identified in a rat study and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) was used. A modifying factor was not considered warranted since there is a fairly strong database consisting of National Toxicology Program (NTP) studies in rats and mice for three nickel compounds, as well as four additional studies in rats.*

It appears that the Reviewer is proposing the same total uncertainty factor (300) that was used for one of the potential intermediate-duration inhalation MRLs. The following uncertainty factors were used for this potential MRL: 10 for the use of a LOAEL, 3 for extrapolation from animals to humans using dosimetric adjustments, and 10 for human variability. This total uncertainty factor of 300 is not appropriate for the chronic MRL since the POD is a NOAEL rather than a LOAEL. The Reviewer commented that an explanation for the use of different uncertainty factors should be added to the profile. Since uncertainty factors are specific to each MRL, a comparison of uncertainty factors across MRLs is not warranted.

References Provided by the Reviewer

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Costa M, Abbracchio MP, Simmons-Hansen J. Factors influencing the phagocytosis, neoplastic transformation, and cytotoxicity of particulate nickel compounds in tissue culture systems. *Toxicol Appl Pharm.* 1981;60(2):313–23.

Dumková J, Smutná T, Vrlíková L, et al. 2017. Sub-chronic inhalation of lead oxide nanoparticles revealed their broad distribution and tissue-specific subcellular localization in target organs. *Particle and Fibre Toxicology* (2017) 14:55. <https://doi.org/10.1186/s12989-017-0236-y>

Efremenko AY, Campbell JL, Dodd DE, et al. 2017a. Time- and concentration-dependent genomic responses of the rat airway to inhaled nickel sulfate. *Environ Mol Mutagen* 58(8):607-618. <https://doi.org/10.1002/em.22139>.

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Hammerlindl H, Schaidler J. 2018. Tumor cell-intrinsic phenotypic plasticity facilitates adaptive cellular reprogramming driving acquired drug resistance. *Journal of Cell Communication and Signaling* (2018) 12:133–141. <https://doi.org/10.1007/s12079-017-0435-1>

Comments provided by Reviewer #3

ATSDR MRL Update Charge Questions and Responses and Reviewer Comments

Newly Derived Acute-Duration Inhalation MRL

QUESTION: Do you agree with the proposed acute-duration inhalation MRL value and how it was derived? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 1: No comments.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the health endpoint and the point of departure for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 2: I agree with the health endpoint and the POD used to derive the MRL..

RESPONSE: *No response needed.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 3: I agree with the uncertainty factors.

RESPONSE: *No response needed.*

Newly Derived Intermediate-Duration Inhalation MRL

QUESTION: Do you agree with the proposed intermediate-duration inhalation MRL value and how it was derived? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 4: No comments.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the health endpoint and the point of departure for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 5: I agree with the health outcome; however, I am struggling with the POD and in particular the benchmark dose modeling. The BMD modeling rests on inclusion of the control incidence data and the exposure concentrations for the control chamber provided in Table S1 of the Oller et al (2022) study. Absent this data the incidence data for the three remaining dose groups (7/8; 8/8; 8/8)

would likely have precluded BMD modeling. The controls in the nickel subsulfide study per Table S1 were exposed to a mean gravimetric concentration of 0.02 ± 0.01 mg Ni/m³ (note although the table legend states mg compound/m³ based on information in the manuscript this appears to be the concentration of Ni rather than nickel subsulfide). Elsewhere in the manuscript (p 736) the authors report the following: Ni₃S₂ aerosols were generated using Wright Dust Feeders (BGI Incorporated, Waltham, MA, USA). Final exposures were 0, 0.05, 0.15, or 0.6 mg Ni₃S₂/m³ (0, 0.04, 0.11, or 0.44 mg Ni/m³) – they don't report the control chamber concentration given in Table S1 in the main body of the manuscript. Likewise, they do not provide any information in the materials and methods section regarding how chamber concentrations were monitored in the control chamber.

A second related concern is the control chamber concentrations themselves which seem high for this type of study. In both the nickel subsulfide and nickel sulfate studies (0.02 ± 0.01 mg Ni/m³ and 0.03 ± 0.02 mg Ni/m³) “background” concentrations of 20 to 30 ng Ni/m³ were present in the control chambers. These measurement exceed 95th percentile measurements in outdoor air (e.g., see Table 5-10. Percentile Distribution of Mean Nickel Concentrations Measured in Ambient Air at Locations Across the United States) – although these mean values are lower than some maximum values reported in Table 5-10.

It may be appropriate to evaluate “background” Ni concentrations in other studies to determine whether the control chamber data is an outlier or is in line with the experiences of other inhalation studies. For example, I couldn't find data for control chambers in the following NTP study: NTP technical report on the toxicology and carcinogenesis studies of nickel oxide (CAS No. 1313-99-1) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 451 and assume it may be lacking in others.

I believe ATSDR needs to critically reevaluate the quality of the Oller et al (2022) study considering these concerns since it not only impacts derivation of the intermediate duration MRL but also led ATSDR to not derive a chronic MRL as well.

RESPONSE: *It is appropriate to include the control group in the BMD modeling to account for background incidences of lesions. Although it is less than ideal to have some nickel exposure in the control group, this low-level exposure was accounted for in the BMD modeling.*

ATSDR agrees that some critical information regarding exposure were not included in the published paper; however, this information was included in the published supplemental information.

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 6: I agree with the uncertainty factors – but I also raised concerns above.

RESPONSE: *See the response to the previous comment.*

Newly Rescinded Chronic-Duration Inhalation MRL

QUESTION: Do you agree with not deriving a chronic-duration inhalation MRL? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 7: Please see my comments above. Depending on actions ATSDR takes regarding the Intermediate MRL then either not deriving the chronic duration MRL is appropriate (i.e., the Intermediate MRL remains unchanged) or using the chronic proposed in the earlier ATSDR draft could be appropriate.

RESPONSE: *ATSDR re-considered derivation of the intermediate-duration inhalation MRL based on the Reviewer's comments and has opted to not revise the MRL (see Response to Comment 5).*

Annotated Comments

The Reviewer provided annotated comments on the toxicological profile. Many of these comments are identical or nearly identical to specific comments above. This section focuses on comments not previously addressed.

COMMENT 8: (Section 1.2, page 6, line 23) delete extraneous studies (...and other studies studies involving...)

RESPONSE: *The suggested revision was made in Section 1.2:*

Conflicting findings have been reported in oral studies examining fertility, with one study reporting decreased fertility following male-only or male and female exposures but not after female-only exposure (Käkelä et al. 1999) and other studies involving male and female exposure (EPA 1988a, 1988b; Springborn Laboratories 200b) not finding effects.

COMMENT 9: (Section 1.2, page 6, line 23) change to: ... epidemiological data on the potential of nickel...

RESPONSE: *The suggested revision was made in Section 1.2:*

The limited available epidemiological data on the potential of nickel to induce developmental effects have not found associations (Vaktskjold et al. 2006, 2007, 2008a).

COMMENT 10: (Section 1.3, page 7, line 23) an acute MRL was developed; correct? (The acute- and chronic-duration inhalation database was insufficient for derivation of an MRL)

RESPONSE: *The referenced text in Section 1.3 was corrected:*

The inhalation database was adequate for the derivation of acute- and intermediate-duration inhalation MRLs for nickel but was insufficient for derivation of a chronic-duration inhalation MRL.

COMMENT 11: (Section 2.1, page 13) use of low and high evidence. Low quality? I realize this likely fits ATSDR's SOPs but terms like limited and sufficient would be more transparent to the user.

RESPONSE: *The Reviewer is referring to the level of evidence ratings from the systematic review. The evidence levels are defined in Section C.7. There is a statement in Section 2.1 referring the reader to Appendix C for details on the systematic review.*

COMMENT 12: (Section 2.2, page 81, line 25) duplicate text (see Page 80, Line 22)

RESPONSE: *The duplicated paragraph in Section 2.2 was deleted.*

COMMENT 13: (Section 2.3, page 84, line 4) change to: Most studies did not find significant body weight alterations in rats and mice...

RESPONSE: *The suggested revision was made in Section 2.3:*

Most studies did not find significant body weight alterations in rats and mice exposed to inhaled nickel oxide.

COMMENT 14: (Section 2.3, page 84, line 27) change to: ...decreased food and/or water intake

RESPONSE: *The suggested revision was made in Section 2.3:*

Decreases in body weight gain have been observed in a number of oral exposure studies of soluble nickel compounds.

COMMENT 15: (Section 2.4, page 92, line 15; Section 2.4, page 93, line 11) update (An intermediate-duration inhalation MRL was derived from the NOAEL (0.06 mg Ni/m³) and LOAEL (0.11 mg Ni/m³) identified from the NTP (1996c) study of nickel sulfate.)

RESPONSE: *The referenced statement was deleted from Section 2.4.*

COMMENT 16: (Section 2.4, page 94, line 3) some caution since there are a limited number studies with either overlapping Ni concentrations or assessment of nasal and lung pathology within a study (The nasal lesions are typically observed at higher concentrations than the lung effects)

RESPONSE: *The statement in Section 2.4 was revised:*

In studies examining the lungs and nasal cavity, the nasal lesions were typically observed at higher concentrations than the lung effects.

COMMENT 17: (Section 2.5, page 95, line 23) replace hears with hearts (...were observed in the hearts of rats or mice...)

RESPONSE: *The typographical error in Section 2.5 was corrected:*

Inhalation and oral exposure studies in animals have not reported cardiovascular effects. No histopathological alterations were observed in the hearts of rats or mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate 6 hours/day, 5 days/week for acute, intermediate, or chronic durations.

COMMENT 18: (Section 2.5, page 96, line 1) change to: Exposure of male mice to metallic nickel at 0.0004 mg Ni/m³ for 6 hours/day...

RESPONSE: *The suggested revision in Section 2.5 was made:*

Exposure of male mice to metallic nickel at 0.0004 mg Ni/m³ 6 hours/day, 5 days/week for 14 weeks resulted in vascular endothelial dysfunction indicated by increased aortic relaxation in ApoE^{-/-} mice (Ying et al. 2013).

COMMENT 19: (Section 2.5, page 96, line 11) duplicative text (see Page 95)

RESPONSE: *The duplicated paragraph was deleted from Section 2.5.*

COMMENT 20: (Section 2.21, page 142, line 24) reported MMAD not consistent with a NP, double check (cited study authors stated: Despite the small nanoscale size of the primary NPs, the mass median aerodynamic diameter (MMAD) of the aerosolized NPs ranged from 3 to 4 μm).

RESPONSE: *The particle size reported in the profile is correct.*

COMMENT 21: (Section 3.1.1, page 148, line 32; Section 3.1.2, page 152, line 27) distribution patterns for inhaled nanomaterials can result in higher nasal deposition (e.g., see Kreyling WG, Geiser M. In: Nanoparticles in Medicine and Environment, Inhalation and Health Effects. Marijnissen JC, Gradon L, editor. Springer Berlin; 2009. Dosimetry of Inhaled Nanoparticles; pp. 145–171.)

RESPONSE: *The profile does not discuss nanoparticles in Chapter 3 of the profile. A discussion of the distribution and deposition of nanoparticles in the respiratory tract was added to Section 2.21:*

Research on nanoparticles in general suggest that particle size will influence respiratory distribution and deposition (Oberdörster et al. 2005). The percentage of regional deposition in the nasal, pharyngeal, and laryngeal regions decrease with increasing nanoparticle size and alveolar region deposition increases. Additionally, the translocation of nanoparticles to extrapulmonary sites appears to be greater for nanoparticles compared to larger particles.

COMMENT 22: (Section 3.1.2, page 152) nickeloplasmin. There is very little peer reviewed published data on this protein and one study seems to suggest that it doesn't exist (see: Weischer CH, Kördel W, Hochrainer D. Effects of NiCl₂ and NiO in Wistar rats after oral uptake and inhalation exposure respectively. Zentralbl Bakteriell Mikrobiol Hyg B. 1980 Sep;171(4-5):336-51).

RESPONSE: *The reference to nickeloplasmin was deleted from Section 3.1.2.*