

Public Comments received on the Public Review draft of the proposed REFERENCE EXPOSURE LEVELS FOR NICKEL AND NICKEL COMPOUNDS.

Comments were received from Nickel Producers Environmental Research Association, Inc.
This document lists these comments and provides responses by OEHHA.

Office of Environmental Health Hazard Assessment
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Comments from Adriana Oller, Ph.D., DABT on behalf of NiPERA (Nickel Producers Environmental Research Association, Inc.) on the Draft Nickel RELs

Comment 1.

General Observations on the Selection of Uncertainty Factors

The use of default uncertainty factors (“UFs”) is justified when little information is available about the substance of concern. As more information becomes known about the relative responses of humans, rats and mice to the effects of the substance – and about the substance’s toxicokinetics and metabolism in humans – the scope of uncertainty decreases, and the uncertainty factors should become correspondingly smaller. In addition, while a composite UF typically is derived by multiplying together the various individual uncertainty factors as if they were totally independent of each other, this clearly is not the case. As the European Chemical Agency (“ECHA”) points out in its REACH Implementation Guidance,

“this multiplication [of uncertainty factors] is in general very conservative: when each individual assessment factor by itself is regarded as conservative, multiplication will lead to a piling up of conservatism.”

The goal should be to derive a REL or other limit value that is protective of human health, taking into account all the relevant information that is available, rather than to develop overly conservative values that do not pass even a simple reality check (e.g., ambient air standards that are below background levels in non-industrial areas).

Response :

The appropriate use of uncertainty factors, including appropriate default values, has been extensively documented in the recently published *Air Toxics Hot Spots Program Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* (OEHHA, 2009: http://www.oehha.ca.gov/air/hot_spots/rels_dec2008.html). These guidelines were adopted following an extensive process of public comment and peer review. OEHHA is aware of the EU’s REACH guidance, and has noted a number of interesting features of this program. However, these guidelines are quite distinct from those prepared under the California statutory mandates for the Air Toxics Hot Spots Program (Health and Safety Code Section 44360(b)(2)), and have no authority in this context. Values developed under OEHHA guidance noted above may be more health protective, particularly for infants and children, than comparable values developed under REACH, since the OEHHA has a mandate to explicitly consider impacts on infants and children in accordance with the Children’s Environmental Health Protection Act (“SB25”). This is reflected in the recommended default values for UF_H. With regard to NiPERA’s claim that “the various individual uncertainty factors (are derived) as if they were totally independent of each other, (but) this clearly is not the case”, OEHHA considers this to be neither “clear” nor accurate in the context of the Air Toxics Hot Spots guidelines, which specifically identify the different and independent types of uncertainty and variability covered by

the specified uncertainty factors, and use data-based methods to identify appropriate values for these factors both in the general (default) case and where possible using compound-specific data.

Comment 2.

Intraspecies Variation and the Susceptibility of Children

2.1

Concerns about addressing childhood susceptibility to the effects of chemicals rightly have been brought into the regulatory process in recent years. But it is important to recognize that there is not a “one-size-fits-all” UF to address the possible heightened response of children to the effects of certain chemicals. Knowledge of toxicokinetics, metabolism, consumption, etc, needs to be considered in arriving at an assessment of whether a conservative 10-fold default UF for Intraspecies variability adequately accounts for the potential of unique childhood susceptibility. Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference, and the extent of that difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to the health effects of a particular chemical, and the relationship may change with developmental age. Differences in susceptibility of children, the elderly, and uniquely sensitive individuals in a society are the reason for the incorporation of the almost universally accepted default 10-fold uncertainty factor to account for Intraspecies variation in regulatory risk assessments around the globe. Therefore, increasing the 10-fold Intraspecies uncertainty factor to account for potentially enhanced childhood susceptibility is warranted only where data suggest that a particular substance is going to be absorbed, distributed, metabolized, or excreted by children in a fashion markedly different (e.g., several-fold different) from the way it is handled in adults.

Response:

OEHHA does not agree with this optimistic view of intraspecies uncertainty as it may apply to infants or even sensitive adults such as pregnant women. The Technical Support Document for Noncancer Reference Exposure Levels (OEHHA, 2008) identifies a number of reasons for anticipating greater sensitivity for younger life stages, both pre- and post-natally, and concluded that the traditionally applied uncertainty factor of 10 was insufficient to allow for these sensitive groups within the population. The comment fails to acknowledge the possibility of pharmacodynamic differences (i.e., biological response to absorbed nickel) among the general population. Several authors have noted differences in age-specific dosimetry in predictive PBPK models of various chemicals (e.g, Ginsberg et al. 2003, 2004; Pelekis et al. 2001, 2003; Clewell et al., 2004; Price et al. 2003). These and other related reports are described by OEHHA (2008). Also provided is a rationale for increasing the intraspecies uncertainty subfactor that applies to pharmacokinetic differences from $\sqrt{10}$ to 10 unless specific child related data are available to indicate a lack of difference from adult expectation.

2.2

Assessments of the default 10-fold uncertainty factor to account for population variability (i.e., Intraspecies variation) reveal that a high degree of conservatism already is implicit in the use of

that factor. In a study of several parameters related to toxicokinetics (e.g., metabolism, binding of chemicals to protein and DNA, and levels of enzyme activities), Calabrese reported that 75-95% of the populations (between 1-2 standard deviations) were within a factor of three of the median values. Hattis et al (1987) evaluated toxicokinetic parameters in 101 data sets from 49 chemicals and found that 96% of the variation (2 standard deviations) was within a factor of approximately 3 of the median values. In a study evaluating clinical trials of pharmaceuticals, Burin and Saunders (1999) found that most of the evidence showed that an uncertainty factor of 1- 10 is protective for 99% of human populations, including sensitive subgroups such as children. And, in an evaluation of factors relevant to assessing risk to neonates/infants compared to adults, Renwick et al. (2000) found no consistent evidence to support a generic deviation from an Intraspecies UF of 10 for infants. Similarly, in comparing LC₅₀ values to the highest non-lethal levels of various chemicals, Rusch et al (2009) found that a value equal to 1/3 of the LC₅₀ was lower than the highest non-lethal level. This relationship also was true when values equal to 1/3 of the LC₅₀ were compared to 23 BMCL₀₅ calculations – i.e., the value equal to 1/3 of the LC₅₀ was more conservative than the BMCL₀₅ value. In this survey, the ratio of the nonlethal level to the LC₅₀ was 0.56, and the standard deviation was 0.15. Therefore, as far as acute lethality is concerned, an Intraspecies adjustment for the general population of 3 would be sufficient to account for all but the most uniquely sensitive individuals.

Response:

The relative sensitivity of infants and children compared to adults has been addressed at length in the Technical Support Document for Noncancer Reference Exposure Levels (OEHHA, 2008), and also cites a number of more recent references addressing the toxicokinetic differences. Toxicodynamic differences are also reviewed. The following quotation specifically relates to the arguments made in the comment:

“Several studies have evaluated age-related pharmacokinetic differences in humans using information about drug disposition (Renwick and Lazarus, 1998; Renwick et al., 2000; Ginsberg et al., 2002; Hattis et al., 2003). Calculation of internal doses as the area under the blood concentration times time curve (AUC) for the same doses (mg/kg) indicated that the major difference from adults occurs in preterm and full-term neonates and young infants (Renwick et al., 2000). Higher AUC internal doses in neonates and young infants versus adults were noted for seven drugs which are substrates for glucuronidation, one with substrate specificity for CYP1A2, and four with substrate specificity for CYP3A4 metabolism, and inter-individual variation in elimination by these detoxification pathways did not differ by age group (Renwick et al., 2000). Ginsberg et al. (2002) evaluated pharmacokinetic information on 45 drugs in children and adults metabolized by different cytochrome P450 pathways, Phase II conjugations, or eliminated unchanged by the kidney. These authors noted half-lives in infants three to nine-fold longer than those of adults. In evaluating the inter-individual variability by age, Hattis et al. (2003) noted that the largest inter-individual variability occurred in the youngest children, apparently due to variability in development of critical metabolism and elimination pathways. Notably, these authors observed that for risk assessment modeling, unimodal distributions may be inadequate for young children and for overweight older children.”

The proposed acute REL is not designed to address acute lethality. OEHHA views acute lethality studies as generally having steeper response slopes and not being indicative of more mild effects the aREL is supposed to address. Because the true variability is unknown, there may be a portion of the population for whom the aRELs will not be protective. It is OEHHA's intent that, to the extent possible, the level proposed will protect the general population including those in the high end of susceptibility, particularly children.

2.3

Applying a 10-fold Intraspecies factor leaves an additional factor of 3-fold to protect the uniquely sensitive and to allow for situations where sensitive subpopulations have not previously been identified. This is most likely to occur in the case of new market approval for non-naturally occurring chemicals. In the case of common elements like nickel, the 100-year history of medical study of nickel exposure combined with the ubiquitous nature of the element (nickel is an essential nutrient for plants, some animals and probably humans) precludes the possibility of children responding in a massively different fashion. In recognition of these facts the Food and Nutrition Board of the United States Institute of Medicine set a human Tolerable Upper Intake Level ("UL") for nickel of 1 mg/day for ages 14 years and older based on extrapolations from animal studies showing detrimental effects on reproduction. The ULs for children were set at 0.2 mg/day for ages 1-3 years, 0.3 mg/day for ages 4-8 years, and 0.6 mg/day for ages 9-13 years. The UL is defined as the highest level of daily intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. In this case, the age differences are not related to any known toxicodynamic or toxicokinetic differences but were established as precautionary values. Nevertheless, it can be seen that the Food and Nutrition Board deemed 200 µg Ni/day (or ~28 µg Ni/kg/day for a very young child of 7 kg body weight) to be the lowest "no risk" daily intake value for any segment of the population, while for the majority of the population, the acceptable daily intake value could be up to 5-times higher. Interestingly, this value corresponds well with the WHO (2005) calculation of a Tolerable Daily Intake (TDI) of nickel for the entire population of 12 µg Ni/kg/day, which was based on protecting the most uniquely sensitive subpopulation of people when exposed to nickel, i.e., those who are sensitive to nickel and could experience an exacerbation of an existing dermal reaction as a result of a systemic (oral) exposure.

Finally, assessment of one major determinant of differences in childhood versus adult susceptibility, absorption of a substance into the body, shows no difference between children and adults in the case of nickel (see Table 1 below). Therefore, no more than the default uncertainty factor of 10 for all Intraspecies variability should be used when extrapolating from animal studies to humans with regard to nickel exposure.

Table 1. Gastrointestinal Absorption of Nickel in Rats, Children, and Adults

Study	N	Vehicle or Exposure Media	Duration	Fasting Status	Absorption (% of Dose)
Ishimatsu et al., 1995	Rats	Gavage in starch solution	Acute	not fasted	10
Alexander et al., 1974	8 children	measured nickel in diet	72 hours	not fasted	19
Nielsen et al. 1999	8	food 4hr prior to nickel in water	Acute	12hr fast	23.2
Nielsen et al. 1999	8	food 1.5hr prior to nickel in water	Acute	12hr fast	7.1
Nielsen et al. 1999	8	food and nickel in water together	Acute	12hr fast	3.4
Nielsen et al. 1999	8	food 1.5hr prior to nickel in water	Acute	12hr fast	7.1
Nielsen et al. 1999	8	food 0.5hr after nickel in water	Acute	12hr fast	12.8
Nielsen et al. 1999	8	food 1hr after nickel in water	Acute	12hr fast	16.7

Response:

Table 1 addresses GI tract absorption in eight children and several studies in rats showing a similarity in absorbed dose. The main concern with nickel is airborne exposure, airway deposition, uptake and toxic effects in the lung (as target organ) and distribution to other targets possibly the immune system. The proposed acute, 8-hour and chronic RELs are designed to address population exposures to airborne nickel while acknowledging that parallel oral and/or dermal nickel exposures may also occur and increase overall dosimetry.

The considerations laid out by the IoM's Food and Nutrition board relate specifically to oral intake, rather than to the inhalation exposures which are the subject of the present analysis. In the absence of specific child or other sensitive individual data, OEHHA would apply a UF of ten for pharmacokinetic uncertainty (and variability) and $\sqrt{10}$ for pharmacodynamic uncertainty (and variability). For example, in the proposed nickel aREL we apply only a $\sqrt{10}$ UF to address possible intraspecies sensitivity differences between adult and child asthmatics. Such differences may relate to the underdeveloped nature of the child respiratory tract (i.e., smaller airways) and its greater sensitivity to airborne toxicants.

OEHHA's use of an additional $\sqrt{10}$ uncertainty factor for intraspecies is in accordance with our updated guidance on non-cancer risk assessment mandated by the California Children's Environmental Health Protection Act of 1999 (Health and Safety Code Sections 39669.5 *et. seq.*). Since these guidelines have already been subject to extensive peer review and have been adopted as the effective risk assessment guidelines for use in the Air Toxics Hot Spots program, OEHHA will not engage here in further discussion of the general case. However, we will comment on the specific issues with regard to nickel. Notwithstanding the views of other bodies (whose decisions were intended to apply in different contexts than the Air Toxics Hot Spots program) our view is that there are insufficient data on nickel exposure to children to allow a lower UF to be used at this time. Since nickel targets the lung, a particularly susceptible organ in the developing human, we think that a cautious health protective approach is justified.

NiPERA's proposed alterations would increase the RELs from 3 to 13 fold. The UFs employed by OEHHA are reasonable in view of our legal mandate, which requires a health protective approach.

Comment 3.

The Acute REL

The current Acute REL for nickel is $6 \mu\text{g Ni/m}^3$. It was derived from Cirla et al. (1985), in which seven metal platers with occupational asthma (at least three of whom also were nickel sensitive and had positive reactions to skin testing) were exposed to 0.3 mg/m^3 nickel sulfate hexahydrate ($67 \mu\text{g Ni/m}^3$) for 30 minutes. Six of the seven exhibited $>15\%$ reduction in FEV_1 which was considered the "critical effect." OEHHA considered $67 \mu\text{g Ni/m}^3$ to be a LOAEC for 30-minute exposure and extrapolated it to $33 \mu\text{g Ni/m}^3$ for a 1-hour concentration. It then applied a LOAEC Uncertainty Factor ("UF") of 6, an Interspecies UF of 1 (since it was a human study), and an Intraspecies UF of 1 (presumably because these were sensitive asthmatics). That produced a Cumulative UF of 6 and an Acute REL of $6 \mu\text{g Ni/m}^3$.

The new proposed Acute REL of $1.1 \mu\text{g Ni/m}^3$ also is based on Cirla et al. (1985) with a LOAEC of $67 \mu\text{g Ni/m}^3$ for 30-minute exposure, extrapolated to $33 \mu\text{g Ni/m}^3$ for a 1-hour exposure. But, instead of applying a LOAEC UF of 6, as it had earlier, OEHHA applied a LOAEC UF of 10. And instead of applying an Intraspecies UF of 1 (where the test subjects were already the most sensitive subpopulation of nickel sensitive asthmatics), OEHHA applied an Intraspecies UF of $\sqrt{10}$ to account for possible pharmacodynamic differences between adults and infants/children with respect to lung or other adverse effects of nickel inhalation. This resulted in a cumulative UF of 30 and an Acute REL of $1.1 \mu\text{g Ni/m}^3$.

NiPERA believes OEHHA's use of a composite UF of 30 is not justified. A more supportable composite UF would fall in the range of 3-9. A 15% decline in FEV1 is a mild effect for this population of nickel-sensitive, asthmatic workers. There certainly is no basis for applying a LOAEL UF of 10 (which is an unexplained increase from the LOAEL UF of 6 that OEHHA applied in its prior calculation of an Acute REL for nickel). To the contrary, as the European Chemical Agency ("ECHA") states in its REACH Implementation Guidance, when the starting point for deriving a no effect level is a LOAEL, it is recommended that a LOAEL uncertainty (or "assessment") factor "between 3 (as minimum/majority of cases) and 10 (as maximum/exceptional cases)" be selected. The reductions in FEV1 seen in six of the seven nickel-sensitive asthmatics studied by Cirla et al. (1985) certainly does not mark this as an "exceptional case" warranting application of the maximum LOAEL UF of 10. In these circumstances, a UF of 3 should be more than sufficient to translate the LOAEC in the Cirla et al. (1985) study into a point of departure for application of an Intraspecies uncertainty factor (assuming one is needed at all).

Since the subjects in Cirla (1985) were particularly nickel sensitive, the use of an Intraspecies UF >1 is questionable. With a LOAEL UF of 3 and an Intraspecies UF of 1, the Acute REL would be $11 \mu\text{g Ni/m}^3$. But even if one uses an Intraspecies UF of $\sqrt{10}$ to account for the possibility that asthmatic children are ~ 3 times more sensitive than asthmatic adults to the effects of nickel in air, the cumulative Uncertainty Factor (using a LOAEC UF of 3) would be 9,

and the resulting Acute REL would be $3.7 \mu\text{g Ni}/\text{m}^3$ (rounded up to $4 \mu\text{g Ni}/\text{m}^3$). We believe an Acute REL value of $4 \mu\text{g Ni}/\text{m}^3$ is as low as can reasonably be justified – particularly since exposure in the Cirla et al. (1985) study was to an aerosol containing 100% nickel sulfate, while ambient air is expected to have approximately 50% of the nickel content as soluble nickel.

Response:

As noted in the response to Comment 2 our revised guidance on non-cancer risk assessment requires a more health protective assessment to account for young children. OEHHA has a specific obligation to consider possible special sensitivities of children under California's Children's Environmental Health Protection Act. Even though the Cirla et al. (1985) study was conducted in nickel-sensitive asthmatics, the study subjects were adults and not children, whose developing respiratory tract may be more sensitive to asthma-provoking chemical exposures. Also in the Cirla study the effects noted were substantial, exceeding a 15% decrease in FEV₁, which was the lower cut off, for 6 of the 7 subjects studied. In addition, it is possible that children in the general population might be sensitized to nickel through exposures from consumer products, especially jewelry. Asthmatic children have generally poorer outcomes due to smaller airways, poorer asthma management, and other factors. A 15% or greater decline in FEV₁ may be a mild effect in normal adults, but may be regarded as severe in children. OEHHA thinks that this endpoint (decrease in lung function) is suitable for the development of an acute REL, and that in view of the concerns noted above, an additional margin of safety is appropriate for acute inhalation exposure of young children to nickel. OEHHA also notes that the standard intermediate value for uncertainty factors is consistently described as $\sqrt{10}$ (which rounds to 3, but is in fact 3.162...), so two such factors multiply to 10, not 9 as stated in the comment. We pointed out previously (in the response to Comment 1) that although the ECHA's REACH guidelines are of interest, they have no particular authority in the context of the Air Toxics Hot Spots program.

Comment 4.

The 8-Hour REL

4.1

OEHHA has proposed an 8-hour REL of $0.08 \mu\text{g Ni}/\text{m}^3$ based on Graham et al. (1978) in which SPF female Swiss mice exposed to nickel chloride by inhalation for 2 hours at levels of 0, 100, 250, 375, or $490 \mu\text{g Ni}/\text{m}^3$ exhibited a dose-related significant decrease in splenic antibody-forming cells following a challenge with a T-lymphocyte dependent antigen. OEHHA identified $250 \mu\text{g Ni}/\text{m}^3$ as the LOAEC in this study and asserted that the NOAEC of $100 \mu\text{g Ni}/\text{m}^3$ was "unreliable" because no control values are given.

Graham et al. (1978) should not be used to derive an 8-hour REL for nickel. The fact that OEHHA considers the NOAEC of $100 \mu\text{g Ni}/\text{m}^3$ to be unreliable (although ATSDR identified $100 \mu\text{g Ni}/\text{m}^3$ as a NOAEC in this study) is symptomatic of the fact that Graham (1978) was a research study that is short on details needed to evaluate adverse effect levels. Moreover, the critical effect in Graham (1978) was subtle and of uncertain significance. Thus, ATSDR identified $250 \mu\text{g Ni}/\text{m}^3$ in this study as a "less serious" LOAEC. See ATSDR (2005) page 60.

As OEHHA recognizes, an alternative to Graham et al. (1978) for deriving the 8-Hour REL is the NTP inhalation study (NTP 1996c) in which rats were exposed 6.2 hours/day, five days/week to nickel sulfate hexahydrate for durations ranging from 16 days to 24 months. We believe the NTP (1996c) study is preferable to Graham et al. (1978) for this purpose, but, for comparison, we will calculate the 8-Hour REL using each of the two studies separately – first Graham et al. (1978); then NTP (1996c).

If Graham et al. (1978) is used as the key study, as it was done by OEHHA, the 8-hour REL should be higher than the value of $0.08 \mu\text{g Ni}/\text{m}^3$ calculated by OEHHA – for two reasons: First, it is not clear why a BMDL UF of $\sqrt{10}$ was applied once the BMDL itself had been calculated. As the European Chemical Agency observes, a BMDL05 value “has, on average, been proposed to be comparable to a NOAEL.” That being the case, there is no reason to apply an additional uncertainty factor to arrive at the point of departure.

Response:

It is true that Graham et al. (1978) is a research study and that it supports a similar 8-Hour REL value as the NTP study with the lung toxicity endpoint. Several other reports on nickel immunotoxicity are reviewed in the draft Nickel RELs document. However the Graham study provides a quantitative assessment of an endpoint relating to the immunotoxicity of nickel. The study was conducted with sufficient animals (14-28 per dose) and each group of animals served as their own controls. The authors identified a NOAEL of $100 \mu\text{g Ni}/\text{m}^3$ based on a lack of a significant difference between pre- and post-treatment at the $100 \mu\text{g}/\text{m}^3$ level. Despite this the dose response is linear across all treatment levels raising the question of whether $100 \mu\text{g}/\text{m}^3$ is truly a NOAEL. Our approach was to replace the LOAEL with a BMDL on a benchmark representing a doubling of the background effect level. Because we used a benchmark dose response model we applied a reduced UF to what amounts to an adjusted LOAEL, namely $\sqrt{10}$. As for the “uncertain significance” of a compromised immune system resulting from nickel exposure, there are probably many susceptible subgroups including the ill, hospital inpatients, the very young and the elderly that would be adversely affected by additional immunocompromise.

4.2

Second, OEHHA’s use of an Intraspecies UF of 30 is unjustified. As discussed in Sections I and II above, the Intraspecies UF should be 10 at most. There is no basis for using a pharmacodynamic (“PD”) UF of 10 as a component of the Intraspecies UF in the calculation of the 8-Hour REL, particularly since the critical effect in Graham et al. (1978) was of uncertain significance. At most, a PD UF of $\sqrt{10}$ should be used, as it was in deriving the Acute REL. OEHHA says it “anticipates that repeated exposures to airborne nickel will have a greater impact on infants and children than on adults due to its targeting of lung function and asthma inducing capability.” As discussed in Section II, this assumption is not well supported in the OEHHA report. See Draft Nickel REL Document page 88. In any case, the minor immunologic effect in the Graham study does not involve lung function or asthma. Furthermore, the pharmacodynamic or pharmacokinetic (“PK”) differences between adults and children would be expected to be most significant in the case of infants. See OEHHA, Technical Support Document For the Derivation of Noncancer Reference Exposure Levels (June 2008) (“Noncancer REL

TSD”) page xii; Haber et al., Poster presented at Society for Risk Analysis Annual 2009 Meeting (submitted as Attachment 1 hereto). But infants spend little time outdoors and will not be exposed repeatedly to 8-hour ambient air levels of nickel associated with “hot spot” sources. Eliminating the BMDL UF of $\sqrt{10}$, and applying an Interspecies UF of 10 and an Intraspecies UF of 10 (for a cumulative UF of 100) to the Extrapolated 8-hour concentration of $82 \mu\text{g Ni/m}^3$ produces an 8-hour REL of $0.8 \mu\text{g Ni/m}^3$ ($82 \mu\text{g Ni/m}^3 \div 100 = 0.82 \mu\text{g Ni/m}^3$ rounded to $0.8 \mu\text{g Ni/m}^3$).

Response:

OEHHA does not view the Graham et al. findings as of “uncertain significance”. The uncertainty is in the extrapolation to an acceptable human exposure for repeated 8-hour exposures. The repeated exposures and longer time for human sensitivities to be manifested, compared to a one hour exposure for the aREL, requires a larger PD UF factor. The test system in Graham was depressed antibody response to sheep red blood cells. This is a general test for immunotoxicity which may affect a number of organs including the lung’s response to inhaled infectious agents. The fact that the test system did not involve the lung is irrelevant. The 8-hour REL is intended to address repeated exposures that may occur in a workplace, a school, a preschool, etc. It is entirely possible that children may be placed in an environment relevant to the 8-hour REL.

Comment 5.

The 8-Hour REL (NTP 1994c)

Alternatively, the 8-hour REL can be derived by conservatively using the 24-month NTP inhalation study of nickel sulfate hexahydrate (NTP 1996c). In that study, a NOAEC of 0.03 mg Ni/m^3 (MMAD $2.5 \mu\text{m}$ and GSD = 2.38) for pulmonary effects was identified. The value of 0.03 mg Ni/m^3 can be considered a very conservative estimate of the NOAEC for a single 8-hour exposure (or even repeated 8-hour exposures over a limited period of time), since this value was the NOAEC in a lifetime study, which typically is used to derive a Chronic REL, not the much more limited 8-Hour REL. That being the case, there should be no need to extrapolate the exposure duration from 6.2 hours to 8 hours or to adjust the five day/week lifetime exposure downward to seven day/week exposure for a much shorter period. However, if the adjustment from 6.2 to 8 hours is made, the extrapolated 8-hour NOAEC concentration would be $23.25 \mu\text{g Ni/m}^3$; if both adjustments are made, the extrapolated 8-hour NOAEC concentration would be $16.6 \mu\text{g Ni/m}^3$. These two values represent very conservative alternative points of departure.

As discussed further in Section V below, for the purpose of REL derivation, the dosimetric adjustment should be made for the exact particle size used in the animal study. Table 13 in the Draft Nickel REL document reports the DAF for two different particle size distributions for nickel sulfate (MMAD = $1.8 \mu\text{m}$; GSD = 1.6 and MMAD = $3.1 \mu\text{m}$; - 13 -GSD = 2.9), but neither of them matches the one corresponding to the $30 \mu\text{g Ni/m}^3$ exposure group in the NTP study (MMAD = $2.5 \mu\text{m}$ and a GSD = 2.38). For this reason and because there are significant differences in the calculated Dosimetric Adjustment Factor (“DAF”) depending on the particle size used, we recommend that OEHHA recalculate the DAF for the exact particle size corresponding to the $30 \mu\text{g/m}^3$ dose in the two-year study (MMAD = $2.5 \mu\text{m}$; GSD = 2.38). The

resulting DAF is likely to be in the range 0.35-0.40. Conservatively using the lower end of this range as the DAF would yield a Human Equivalent Concentration (“HEC”) of 10.5 $\mu\text{g Ni}/\text{m}^3$ from the NOAEC of 30 $\mu\text{g Ni}/\text{m}^3$; a HEC of 8.1 $\mu\text{g Ni}/\text{m}^3$ from the extrapolated 8-hour NOAEC concentration of 23.25 $\mu\text{g Ni}/\text{m}^3$; and a HEC of 5.8 $\mu\text{g Ni}/\text{m}^3$ from the extrapolated 8-hour NOAEC concentration of 16.6 $\mu\text{g Ni}/\text{m}^3$.

Response

Our original particle size distributions used in the MPPD2 modeling for the NTP(1994c) study in the public review draft were based on the ranges observed for all dose levels with NiSO₄. These values were given in Tables K1 and K3 in the NTP report appendix, namely MMAD of 1.08 to 3.08 μm and geometric standard deviations of 1.6 to 2.9 μm with a density of 2.07 g/m^3 . In the revised draft we have repeated the airway deposition modeling with the low dose average distribution values of MMAD = 2.50 μm , gsd = 2.38 and density = 2.07 g/cm^3 . Using these low dose values the rat airway deposition fraction was 0.089 (TB + Alv.). The corresponding human values ranged from 0.25 to 0.40 giving an average DAF of 0.26. Applying this to the current value of 21.4 $\mu\text{g}/\text{m}^3$ (30 $\mu\text{g}/\text{m}^3 \times 5/7$ days/week) and using a UF of 300 would give a proposed REL of 0.02 $\mu\text{g}/\text{m}^3$. This revision has been noted in Table 9. This supporting study for the 8-Hour REL is used for the cREL with different UFs. The 8-Hour RELs are developed to address repeated exposures, which may approach chronic exposures but are not continuous. In our derivation of the comparison 8-Hour REL from the NTP study we have not adjusted for 6.2 hours/8 hours but have applied a 5/7 days/week adjustment. It should be noted that the MPPD2 model predicts airway deposition only, not subsequent airway removal or systemic uptake, distribution, excretion etc.

Comment 6.

The cumulative UF to be applied in this case should be in the range of 10 - 30. Having applied a DAF, there is no need to apply an uncertainty factor to account for pharmacokinetic (“PK”) differences between rats and humans. And there is no reason to apply an uncertainty factor >1 to account for pharmacodynamic (“PD”) differences in response between rodents and humans – because rats and mice appear to be more, not less, sensitive to the respiratory effects of nickel than non-human primates and humans. Thus, the Interspecies UF should be 1 in this case – or, at the very most, $\sqrt{10}$. Combining those values with an Intraspecies UF of 10, which would include any possible children’s increased susceptibility to nickel effects, results in a conservative cumulative UF in the range of 10-30. Applying a UF of 30 to the HEC of 10.5 $\mu\text{g Ni}/\text{m}^3$ (derived from unadjusted NOAEC) results in an 8-hour REL of 0.35 $\mu\text{g Ni}/\text{m}^3$. For the very conservative, time adjusted HECs of 8.1 and 5.8 $\mu\text{g Ni}/\text{m}^3$, a UF of 10 would be sufficiently protective, yielding 8-hour REL values of 0.81 and 0.58 $\mu\text{g Ni}/\text{m}^3$, respectively.

Thus, if Graham et al. (1975) is used as the key study, the resulting 8-Hour REL would be 0.8 $\mu\text{g Ni}/\text{m}^3$; while if the NTP (1996c) study is used, the resulting 8-Hour REL would be in the range of 0.35 to 0.81 $\mu\text{g Ni}/\text{m}^3$.

Response

We have found no conclusive evidence that humans are less sensitive to the pneumotoxic effects of nickel than rodents. In general, human epidemiological studies have less well-defined exposures and toxic endpoint measurement than experimental studies in rodents. As noted in the response to Comment 5, the modeling of the NTP exposure addresses only airway deposition and not subsequent uptake, distribution and excretion etc. Therefore we have applied an uncertainty factor for pharmacokinetic differences that may go beyond airway deposition. OEHHA does not agree with NiPERA's proposed UF of 100 for the Graham et al. (1975) study supporting an 8-Hour REL for prolonged, if discontinuous, airborne nickel exposures. As noted in the response to Comment 2 our revised guidance on non-cancer risk assessment requires a more health protective assessment to account for young children. In accordance with the guidance we have adopted uncertainty factors, which appear appropriate to this end: for a BMDL which approximates an adjusted LOAEL we have used a UF_L of $\sqrt{10}$; for interspecies differences we have used a UF_A of 10 since there is insufficient data showing that experimental animals respond the same as all human age-groups with respect to kinetic and dynamic differences; finally we have used a UF_H of 30 to account for intraspecies differences in the human population including sensitive subgroups such as children with asthma, giving a cumulative UF of 1000. In the latter UF_H we think that individual responses of children to airborne nickel exposures probably vary by more than $\sqrt{10}$ so we have increased the PD subfactor to 10 until further data become available.

Comment 7.

The Chronic REL for Nickel and Nickel Compounds (except NiO).

Currently, the Chronic REL for all forms of nickel other than nickel oxide is $0.05 \mu\text{g Ni/m}^3$. This was derived from the NTP lifetime study of nickel sulfate hexahydrate in which the LOAEC for male and female rats was $60 \mu\text{g Ni/m}^3$ and the NOAEC was $30 \mu\text{g Ni/m}^3$. The new proposed Chronic REL of $0.015 \mu\text{g Ni/m}^3$ is based on the same NTP study. Using a Benchmark Dose approach, OEHHA calculated a BMDL05 value of $30.5 \mu\text{g Ni/m}^3$ (based on alveolar proteinosis), which is essentially the same as the NOAEC. The average lifetime experimental exposure for the NOAEC group males was calculated to be $5.4 \mu\text{g Ni/m}^3$, and the Human Equivalent Concentration ("HEC") was calculated to be $1.5 \mu\text{g Ni/m}^3$, which OEHHA derived by applying a dosimetric adjustment factor ("DAF") of 0.27 to the average lifetime experimental exposure of $5.4 \mu\text{g Ni/m}^3$. OEHHA purportedly selected the DAF of 0.27 using the MPPD2 Model and the following particulate characteristics: MMAD = $1.8 \mu\text{m}$; GSD = 1.6. See Draft Nickel REL Document page 93. In fact, Table 13 on page 92 of the Draft Nickel REL Document indicates that the correct DAF for those particulate characteristics is 0.43, not 0.27. A DAF of 0.43 would yield an HEC of $2.3 \mu\text{g Ni/m}^3$, not $1.5 \mu\text{g Ni/m}^3$.

Apart from that apparent confusion, it is not clear where or how OEHHA came up with the particulate characteristics that it used. NTP (1996) reports a range of particle sizes for the two-year aerosols as follows: MMAD from 2.24 to $2.5 \mu\text{m}$ and GSD from 2.08 to 2.38. In particular, the aerosol used in the exposure to $30 \mu\text{g Ni/m}^3$ in the two year study had an MMAD = $2.5 \mu\text{m}$ and a GSD = 2.38. For the purpose of REL derivation, the dosimetric adjustment should be made for the exact particle size used – because a different particle size distribution would have

resulted in a lower or higher deposition and a greater or lower response in animals, respectively.

For these reasons and because there appear to be significant differences in the calculated DAF depending on the particle size used (e.g., DAF of 0.43 versus DAF 0.27 in Table 13 of the Draft Nickel REL Document for two different MMADs for nickel sulfate, neither of which matches the ones used in the animal study), we recommend that OEHHA recalculate the DAF. The recalculation should be based on either (1) the exact particle size corresponding to the 30 $\mu\text{g}/\text{m}^3$ dose in the two-year study (MMAD = 2.5 μm ; GSD = 2.38); or (2) the mean of the particle sizes used for all three dose levels (MMAD = 2.3 μm ; GSD = 2.2). The resulting DAFs are likely to be in the range 0.35- 0.40. Applying the DAF to the average experimental exposure of 5.4 $\mu\text{g Ni}/\text{m}^3$ will likely produce an HEC of $\sim 2 \mu\text{g Ni}/\text{m}^3$.

Response

See the response to Comment 5. The particle size distribution values used in the draft Nickel RELs document were based on the ranges observed for all dose levels rather than the average values for a particular dose level. We have repeated the deposition modeling with the average values observed in the low dose animals as shown in NTP Appendix K2 (NiSO₄). The revised DAF is 0.26 rather than 0.27 resulting in a slight adjustment of the proposed cREL.

Comment 8.

OEHHA's selection of uncertainty factors also is questionable. Since rats appear to be at least as sensitive to the inhalation respiratory effects of nickel as humans, there is no need to apply a pharmacodynamic UF >1 in extrapolating between species, and the MPPD2 Model already accounts for PK differences between rats and humans, as OEHHA recognizes. The Interspecies UF, therefore, should be 1 or, at the very most, not greater than $\sqrt{10}$. And, as explained in Sections I and II above, the Intraspecies UF should be no higher than 10. There are no data or other bases for concluding that a PD UF $>\sqrt{10}$ or a PK UF $>\sqrt{10}$ is needed to account for any potential differences between adults and children in susceptibility and kinetic handling of nickel. This is particularly true as far as a Chronic REL is concerned – because the vast bulk of lifetime exposures for which a Chronic REL is supposed to be protective will occur during adulthood. Using the HEC of $\sim 2 \mu\text{g Ni}/\text{m}^3$, an Interspecies UF of 1 and an Intraspecies UF of 10 produces a Chronic REL of $0.2 \mu\text{g Ni}/\text{m}^3$. We believe that this is the most justifiable Chronic REL value for Nickel and Nickel Compounds other than NiO. Alternatively, if a very conservative Interspecies UF of $\sqrt{10}$ is used (rather than a UF of 1), the Chronic REL would be $0.067 \mu\text{g Ni}/\text{m}^3$.

Response

As noted in the response to Comment 5, the modeling of the NTP exposure addresses only airway deposition and not subsequent uptake, distribution and excretion etc. OEHHA does not agree with NiPERA's view of the small uncertainty accompanying prolonged continuous airborne nickel exposures. NiPERA's proposal of an interspecies UF of 1 is unacceptable to OEHHA since there are insufficient data in young animals and humans to justify it and this implies no pharmacodynamic or kinetic differences between animals and humans. In accordance with the guidance, we have adopted uncertainty factors which appear appropriate to this end.

Since a chronic study NOAEL was identified, we used UF of 1 for both UF_L and UF_S; for interspecies differences we used a UF_A of $\sqrt{10}$ mostly for pharmacodynamics; and finally for UF_H we used 30 which assumes greater uncertainty and variability in kinetics and dynamics among the human population than between rodents and humans.

Comment 9.

Chronic REL NiO

OEHHA's derivation of a Chronic REL for nickel oxide appears to reflect some confusion between the results for rats and mice in the 2-year NTP study of nickel oxide (NTP, 1996b). Thus, in calculating the Chronic REL for NiO, OEHHA incorrectly identified the LOAEC for alveolar proteinosis in female mice in the NTP nickel oxide study as 500 $\mu\text{g Ni/m}^3$. See Draft Nickel REL Document page 94. In fact, the LOAEC for mice in the NTP study was 1.0 mg Ni/m³, which was the lowest dose tested for mice, a point OEHHA recognizes earlier in the Document. See id. page 62. The 500 $\mu\text{g Ni/m}^3$ LOAEC in the NTP study of nickel oxide was for effects seen in rats, not mice. Despite this apparent confusion, OEHHA seems to have correctly calculated a BMDL₀₅ value of 117 $\mu\text{g Ni/m}^3$ based on the alveolar proteinosis observed in female mice. Extrapolating the BMDL₀₅ value from 6 hours/day, 5 days/week to continuous lifetime exposure produces an average experimental exposure of 20.9 $\mu\text{g Ni/m}^3$.

Response

Thank you for catching this typographical error. It will be corrected in the final version of the document.

Comment 10.

Chronic REL NiO

At this point, it is necessary to identify the particle size to use for dosimetric adjustment. One could use the mean particle size of all aerosols used in the female mouse study (MMAD = 2.38 μm ; GSD=2.11). However the DAF should be calculated for human equivalent to mice and not for human equivalent to rats, as is currently done in the Draft Nickel REL Document (Table 13 and page 94). On the assumption that deposition fractions in mice will be roughly similar to deposition fractions in rats, applying a DAF (mice-human) of ~0.35 (which is the approximate value expected for an MMAD = 2.38 μm ; GSD=2.11) to the average experimental exposure of 20.9 $\mu\text{g Ni/m}^3$, produces an HEC of 7.3 $\mu\text{g Ni/m}^3$.

Response

We agree. As noted in previous responses we have repeated the airway deposition modeling with the average values for the low dose animals (1.25 mg NiO/m³): MMAD = 2.46 μm , gsd = 1.89, density = 6.67 g/cm³. The rat airway deposition fraction was 0.1289 and the human deposition fractions ranged from 0.30 to 0.45 with a mean DAF of 0.338. This would result in a slightly higher proposed cREL of 0.07 $\mu\text{g/m}^3$ for NiO. However, since the MMPD model is only set up for rat and human airway deposition predictions, we have revised Table 13 to include

mouse deposition values from Hsieh et al. (1999c). These authors concluded that deposition of nickel compounds in the mouse airway was significantly lower than in the rat. DAFs for NiO calculated based on Hsieh et al. (1999c) average only 0.096. Applying the DAF of 0.096 to the results of the NTP mouse data gives rise to a revised cREL of $0.02 \mu\text{g}/\text{m}^3$. Hsieh et al. (1999c) used an MMAD = $2.80 \mu\text{m}$, gsd = 1.87, density of $7.45 \text{ g}/\text{cm}^3$ and concentrations of 1.25 to 5.0 mg NiO/m³.

Comment 11.

Chronic REL NiO (Uncertainty factors)

As in the case of the Chronic REL for Nickel and compounds other than NiO, the most appropriate Interspecies UF to apply here is 1 – because the DAF adjustment already accounts for PK differences between rodents and humans, and because rodents are at least as sensitive to the respiratory effects of nickel as humans. At the same time, as explained in Sections I and II above, the Intraspecies UF should be no greater than 10, consisting of a PD UF of $\sqrt{10}$ and a PK UF of $\sqrt{10}$. Although OEHHA proposed using a PD UF of 10, there is no basis for believing that children or infants are 10 times more susceptible to the pulmonary effects of nickel than adults. And, bear in mind, this is a Chronic REL, which is based on exposures for a full lifetime, most of which is spent as an adult.

Using the HEC of $7.3 \mu\text{g Ni}/\text{m}^3$, an Interspecies UF of 1 and an Intraspecies UF of 10 produces a Chronic REL of $0.7 \mu\text{g Ni}/\text{m}^3$ for Nickel Oxide based on the NTP study results for female mice. Alternatively, if an Interspecies UF of $\sqrt{10}$ is used (rather than a UF of 1), the Chronic REL would be $0.24 \mu\text{g Ni}/\text{m}^3$.

Response

The proposal to use a UF_A of 1 is incorrect: the DAF procedure used allows for toxicokinetic differences between species but not toxicodynamic differences. In accordance with guidelines (OEHHA, 2008) a UF_{A-d} of $\sqrt{10}$ is used. OEHHA does not agree with the proposed UF_H of 10 for the NiO cREL, which does not adequately address increased sensitivity of infants and children. The NTP study was not based on lifetime exposure but rather was initiated with young adult mice. In our derivation of the proposed cREL we have used a UF_H of 30 to adequately address intraspecies uncertainty in potential effects of lifetime exposures to airborne nickel oxide. This UF is weighted to address uncertainty in the response of young animals and humans to the toxic effects of nickel. The use of a UF_H of 30 does not imply that “children or infants are 10 times more susceptible”: the increased uncertainty for infants and children is only by a factor of 3 since a UF of 10 has always been assumed by default for variability in the adult population. This proposed chronic REL has been significantly revised based on the published airway deposition results of Hsieh et al., 1999c in mice. The new value is $0.02 \mu\text{g Ni}/\text{m}^3$.

Comment 12.

The Oral cREL

OEHHA has proposed a new Oral Chronic REL for nickel of 0.0013 mg Ni/kg-day, based on a study by Smith et al. (1993) in which nickel chloride was administered to rats in drinking water. The critical effect was increased perinatal mortality (measured as dead pups per litter) on postnatal days 1 and 21. OEHHA identified the LOAEL for perinatal mortality as 10 ppm (equivalent to 1.3 mg Ni/kg-day), which was the lowest exposure level in the G2 breeding. In the G1 breeding, by contrast, 50 ppm (6.8 mg Ni/kg-day) was a NOAEL. OEHHA applied a LOAEL UF of 10, an Interspecies UF of 10, and an Intraspecies UF of 10 to the LOAEL of 1.3 mg Ni/kg-day in the G2 breeding, producing an Oral Chronic REL of 0.0013 mg/kg-day. The Oral Chronic REL should not be based solely on Smith et al. (1993), a study that is difficult to interpret for several reasons, including the following:

- *Treatment effects were based on pup deaths, an endpoint that is prone to measurement bias (underestimation due to cannibalism).*
- *The control group used for comparisons had significantly smaller litter sizes than several of the other treatment groups. This may be reflective of higher than ordinary rates of cannibalism in the controls and, consequently, unobserved stillborn pups. Even if there was not increased cannibalism, the smaller litters in the control group present fewer opportunities for pup deaths.*
- *The inference of a nickel-related effect in the second breeding – and not the first – came about largely because of a reduction in observed mortality in the second breeding control group, not because of increased severity of response.*
- *Interpretation of the data is complicated by maternal toxicity, notably a decrease in maternal body weight gain. Also, changes in food and water intake were observed.*
- *The results may have been confounded by decreases in plasma prolactin levels in the dams and pups at one week after weaning of the second litter. As the authors noted, the possible involvement of changes in prolactin levels on the reproductive effects observed in the rats could not be eliminated. But there are key differences in the functions of prolactin in rats and humans such that decreased prolactin levels in humans would not be expected to result in fetal deaths.*

Rather than relying solely on Smith et al. (1993), OEHHA should base the Oral Chronic REL on the reproductive toxicity study in rats, Springborn Laboratories (2000a & 2000b), supplemented by Smith et al. (1993). That is the approach OEHHA took in setting the Public Health Goal (“PHG”) for nickel in drinking water and the Child-Specific Reference Dose (“chRD”) for school site risk assessment. There is no reason to depart from that approach here.

[OEHHA mistakenly states that Smith et al. (1993) was used to derive the PHG for nickel in drinking water. That was true of an early draft of the PHG, but the PHG ultimately was based on Springborn Laboratories (2000a & 2000b), supplemented by Smith et al. (1993), as was the chRD for Nickel. See Development Of Health Criteria For School Site Risk Assessment Pursuant To Health And Safety Code Section 901(G): Child-Specific Reference Doses (chRDs) For School Site Risk Assessment – Cadmium, Chlordane, Heptachlor, Heptachlor Epoxide,

Methoxychlor, and Nickel – FINAL REPORT, December 2005 (hereinafter “chRD Development Document”) page 39.]

Springborn Laboratories (2000a) was a range-finding study, while Springborn Laboratories (2000b) was a 2-generation study performed in the same strain of rat from the same supplier. In the 2-generation study, as OEHHA notes, there were no adverse effects even at the highest dose, 2.2 mg Ni/kg-day – so in the 2-generation study, 2.2 mg Ni/kg-day was a NOAEL. See chRD Development Document page 39. The World Health Organization (“WHO”) agrees with that assessment.²⁷ In its earlier analyses, OEHHA interpreted the range-finding study as having a LOAEL of 2.2 mg Ni/kg-day. In fact, as stated in an independent reproductive toxicology Expert Review (see attached report by N.M. Leeming), there were “no conclusive indications of an adverse effect of treatment at 10 mg/kg/day [2.2 mg Ni/kg-day] in the range-finding study,” so that the NOAEL in that study, as in the 2-generation study, is 2.2 mg Ni/kg-day. Applying an Interspecies UF of 10 and an Intraspecies UF of 10 (as OEHHA did) to this NOAEL produces an Oral Chronic REL of 22 µg Ni/kg-day.

In deriving the PHG and chRD, OEHHA chose to use the 1.1 mg Ni/kg-day dose in the 2-generation Springborn study as the appropriate NOAEL, claiming that it “represents the highest NOAEL that is lower than the LOAEL from either the Smith, or Springborn range-finding study.” We question the logic of this because: (i) the purported LOAEL of 1.3 mg Ni/kg-day in Smith et al. (1993) is of questionable reliability; and (ii) the dose of 2.2 mg Ni/kg-day was the NOAEL in both the Springborn 2-generation study and the Springborn range-finding study. If OEHHA, nonetheless, chooses to treat 1.1 mg Ni/kg/day as the appropriate NOAEL, the Oral Chronic REL – after application of an Interspecies UF of 10 and an Intraspecies UF of 10 – would be 11 µg Ni/kg-day, which is the same as the chRD.

In sum, the Oral Chronic REL should be either 22 µg Ni/kg-day or, if OEHHA chooses to be unduly conservative, 11 µg Ni/kg-day. It should be noted that this value is based on exposure to nickel in water. This will be a conservative estimate when applied to ingestion of nickel from food, as the absorption of nickel from food or with food is lower (e.g., maximum of 23% absorption of Ni from water intake under fasting compared to 3% absorption of Ni from water ingested with food).³⁰ The value of 1.3 µg Ni/kg-day that OEHHA has proposed should be rejected because it does not reflect the latest and most comprehensive studies and is inconsistent with the PHG and chRD. Moreover, an Oral Chronic REL value of 1.3 µg Ni/kg-day implies that a 70 kg adult should limit his daily nickel intake to 91 µg of nickel (1.3 µg Ni/kg-day x 70 kg = 91 µg Ni/day). But, as OEHHA points out, our average daily intake of nickel from food alone is about twice that amount. So if the Oral Chronic REL value OEHHA has proposed were correct, we all would have to modify our diets in a way that simply is not possible.

Response

To quote from the PHG summary final on the OEHHA home page: “The PHG is based on three reproduction toxicity studies in rats (Smith et al., 1993, Springborn Laboratory, 2000a, 2000b). OEHHA identified the oral dose of 1.12 mg Ni/kg-d as the appropriate NOAEL value, from the lower range of the Springborn Laboratory (2000b) study. This NOAEL is lower than the doses at which early pup mortality was observed (a LOAEL of 2.23 mg/kg-d was identified in the preliminary study reported by Springborn Laboratory (2000a) and a LOAEL of 1.3 mg/kg-d was

identified in the study reported by Smith et al. (1993)).” As noted above OEHHA previously identified a NOAEL of 1.12 mg Ni/kg-d (the penultimate dose in the 2-generation reproduction study) which appears in conflict with the 1.3 mg Ni/kg-d LOAEL from Smith et al. (1993) since it’s unlikely that 1.1 and 1.3 are toxicologically distinct doses. NiPERA’s expert review of both 1- and 2-generation studies (Springborn Laboratory cited as NiPERA 2000a, b in the RELs draft) by N.M.Leeming (2002, submitted with these comments) supports a NOAEL of 2.24 mg Ni/kg-d in the 2-generation study. There are many operational differences between the studies that could factor into the LOAEL vs. NOAEL difference. Smith et al.(1993) used Long-Evans Rats vs. Sprague-Dawley for NiPERA; 2 consecutive breedings of a single generation vs. 2 generations, one breeding of each generation; drinking water administration vs. aqueous gavage; dose range 1.3 to 32.5 vs. 0.22 to 2.23 mg Ni/kg-d; NiCl hydrate vs. NiSO₄ hydrate; females only dosed vs. both males and females dosed; perinatal lethality vs. post-implantation loss endpoint, respectively. These studies have been extensively evaluated by OEHHA staff and the Smith et al. (1993) study and the LOAEL of 1.3 mg Ni/kg-d are considered valid. In our view the Smith study has the advantage of being a peer-reviewed study available in the open literature. However, the commenter makes a compelling argument for consistency among OEHHA program oral values for nickel. Therefore, we will adjust our oral REL calculation and base it upon the NOAEL of 1.12 mg Ni/kg-d identified in the NiPERA (2000b) study. This adjustment results in an oral cREL of 11µg Ni/kg-d consistent with the chRD and PHG basis.

Comment 13.

Additional Studies Relevant to OEHHA’s Review of Nickel

Although not directly relevant to OEHHA’s derivation of RELs for nickel, there are several recent studies that OEHHA should be aware of (and should reference) in its discussion of the reproductive toxicity and genetic toxicity of nickel. Given the objective of setting RELs to protect the general population against health risks of nickel in the ambient air (the bulk of which consists of soluble nickel species), OEHHA should call attention to the fact that a reproductive study of female nickel refinery workers has not demonstrated an association between relatively high soluble nickel exposures (a worst case scenario resulting in elevated blood and urinary nickel levels) and the following reproductive outcomes: genital malformations (hypospadias and cryptorchidism), spontaneous abortions, small-for-gestational-age newborns, and skeletal malformations (Vaktskjold et al., 2006, 2007, 2008a&b). Genital malformations are considered to be one of the most sensitive endpoints for human developmental toxicity, while spontaneous abortions may be the closest human equivalent outcome to the effects seen in animals. The geometric means of the workers’ exposures in this study ranged from 0.03-0.084 mg Ni/m³ in the low exposure group to 0.15-0.33 mg Ni/m³ in the high exposure group.

These data demonstrate that a weight-of-evidence approach to the evaluation of reproductive toxicity of nickel substances is needed. While a reproductive “hazard” from nickel exposure can be demonstrated in animals, there is no demonstrable “risk” of reproductive impairment in the single female occupational cohort that can be confirmed to have been consistently exposed to high levels of nickel. Consequently, the risk of reproductive impairment from occupational nickel exposure is exceedingly small, and the risk for the general population is almost non-existent. The Vaktskjold study (and its associated papers) is the definitive epidemiology study that resulted from the same cohort (and the somewhat anecdotal report) by Chashschin et al.

(1994), which purported to find an apparent association of nickel exposure and reproductive toxicity in this Russian refinery based on preliminary data. OEHHA references Chashschin et al. (1994) and relies on it in its summary of reproductive and developmental toxicity in section 7.3 (page 41) of the Draft Nickel REL Document. The preliminary findings of Chashschin et al. (1994) have now been rejected by the most recent study. Consequently, section 7.3 (page 41) of the Draft Nickel REL Document needs to be revised to reflect the Vaktskjold study, its failure to find an association between nickel exposure and observed reproductive effects, and its status as superseding the Chashschin et al. study.

*In addition, in its discussion of mutagenicity and other genotoxic effects, OEHHA should reference an oral repeated dose study with nickel sulfate hexahydrate looking at the induction of micronuclei in bone marrow. (Oller AR, Erexson G. 2007. Lack of micronuclei formation in bone marrow of rats after repeated oral exposure to nickel sulfate hexahydrate. *Mutat. Res.* 626:102-110.) Although blood and bone marrow nickel levels were several-fold higher than controls, repeated gavage exposure to up to 112 mg Ni/kg/day did not increase the frequency of micronuclei in bone marrow of exposed animals.*

Response

All of the Vaktskjold et al. studies noted except the 2007 are reviewed in the text of the draft Nickel RELs document (p 31). We will add a description of Vaktskjold et al. 2007 to the discussion although we could find no reference to the geometric mean of the workers' exposures in this study. We disagree that our summary of human reproductive and developmental nickel toxicity is based solely on Chashschin et al. (1994). We view the findings of Vaktskjold et al. (2008b) as indicating a weakly positive SA effect (their Table 3).

We will also add Oller & Erexson (2007) to our discussion of nickel genotoxicity.