

Hazard Identification and Dose-response of Ingested Nickel Soluble Salts

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ABSTRACT

People can ingest soluble nickel compounds as a normal constituent of food or as a contaminant in drinking water. This paper presents an assessment of the noncancer and cancer human health risks from ingestion of soluble nickel compounds. A reference dose (RfD) of $8E-3$ mg Ni/kg/day *in addition to the amount in food* was calculated, based on albuminuria in female rats exposed to nickel sulfate in drinking water for 6 months (Vyskocil et al., 1994b). This RfD is comparable to the current RfD based on decreased body weight in a chronic feeding study in rats (Ambrose et al., 1976). The potential for nickel-induced reproductive toxicity was also taken into account in the derivation of the RfD. There are a number of negative animal bioassays with soluble nickel salts, but all of them have deficiencies that preclude a definitive conclusion. According to EPA's 1996 draft cancer guidelines, the carcinogenic potential of oral exposure to soluble nickel "*cannot be determined* because there are *inadequate data* to perform an assessment."

INTRODUCTION

Nickel and nickel compounds have many industrial and commercial uses. Nickel is extensively used in the plating industry, sometimes in combination with other metals. Nickel alloys and nickel compounds are also used in making a variety of materials, including coins, jewelry, and batteries (ATSDR, 1997). Nickel is a group VIII transition metal. Although it can exist in several different oxidation states, the only important oxidation state under environmental conditions is Ni(II), nickel in the +2 valence state. This paper presents an assessment that focuses on soluble nickel compounds, such as nickel sulfate, nickel acetate, and nickel chloride. All doses in the assessment were calculated in terms of the amount of nickel.

Oral exposure to nickel occurs through both water and food. Daily average intake from drinking water ingestion is approximately 2 µg Ni/day (or an intake of about 0.00003 mg Ni/kg-day for a 70 kg person). Average daily intake of nickel in food is much higher, approximately 170 µg Ni/day (or an intake of about 0.002 mg Ni/kg-day assuming a 70 kg person). It is difficult to compile all of these various intakes into a composite value, however, because humans absorb nearly 40 times as much nickel from water under fasting conditions as they do from food (Sunderman et al., 1989).

Several agencies have developed risk assessments for nickel compounds. Each of these agencies has a different focus on evaluating the toxicity of soluble and insoluble nickel compounds; the regulatory background for nickel compounds is summarized in Table 1. This paper presents the findings of a *Toxicological Review* of the human health effects of environmental exposure to ingested soluble nickel compounds, in particular for compounds such as nickel sulfate, nickel acetate, and nickel chloride (TERA, 1999). The document reviewed the

toxicity data on *soluble nickel salts* and presented a dose-response assessment for these compounds, in light of new studies that show differences in the toxicity of soluble and insoluble nickel compounds [e.g., National Toxicology Program (NTP), 1996a, 1996b, 1996c]. A reference dose (RfD) for noncancer toxicity of soluble nickel salts after chronic exposures via the oral route is discussed in this paper. The carcinogenic potential of soluble nickel salts via the oral route is also discussed. Assessment of soluble nickel following inhalation exposure is discussed in the companion paper (Haber et al., 2000). Development of these hazard identification and dose-response assessments for soluble nickel salts has followed the general guidelines for risk assessment as set forth by the National Research Council (1983), EPA guidelines (US EPA, 1986; 1995; 1996), Barnes and Dourson (1988), and Dourson (1994).

This work was performed under contract to the Metal Finishing Association of Southern California, Inc., the U.S. Environmental Protection Agency (U.S. EPA), and Health Canada. After U.S. EPA review of the *Toxicological Review*, the conclusions of the assessment will also be summarized for EPA's Integrated Risk Information System (<http://www.epa.gov/iris>), which will also make available the revised *Toxicological Review*. The conclusions of the *Toxicological Review* and opinions expressed in that document and this paper are those of the authors, and do not necessarily represent the views of the sponsors.

HAZARD IDENTIFICATION FOR NICKEL SOLUBLE SALTS

Toxicokinetics

Data from both animals and humans show that only a small proportion of ingested soluble nickel salts is absorbed; the rest is excreted in the feces (Diamond et al., 1998).

Absorption of ingested nickel is lower when nickel is administered in food, or in water with a

meal, than when it is administered in water to fasted subjects. Nickel absorption ranged from 12-33% of the dose when nickel was ingested after a fast, to 0.7-6% when nickel was administered either in food, in water, or in a capsule during (or in close proximity to) a meal (Diamond et al., 1998; Sunderman et al., 1989; Patriarca et al., 1997; Nielsen et al., 1999). The rate of absorption after ingestion is rapid. Ingestion of nickel sulfate led to increased nickel concentrations in serum within 1 hour, peaking 1-3 hours after ingestion (Christensen and Lagesson, 1981; Nielsen et al., 1999; Solomons et al., 1982; Sunderman et al., 1989).

Animal studies show that the absorption of nickel compounds administered orally is closely related to the solubility of the compound. Nickel absorption was much higher for the soluble nickel compounds nickel sulfate, nickel chloride, and nickel nitrate (11%, 9.8%, and 34%, respectively), compared to 0.47% for slightly soluble nickel subsulfide and 0.01% for insoluble green nickel oxide (Ishimatsu et al., 1995). These values for percent absorption correlate with the relative solubility of the different compounds.

Very little information exists on the tissue distribution of nickel after oral exposure, but the available data generally indicate that the highest nickel level following oral exposure is observed in the kidney (Jasim and Tjalve, 1986; Ishimatsu et al., 1995; Borg and Tjalve, 1989; Whanger, 1973; Dieter et al., 1988). In studies where the lung was examined, the second highest nickel concentration was usually observed in this tissue (Jasim and Tjalve, 1986; Ishimatsu et al., 1995; Borg and Tjalve, 1989; Whanger, 1973; Dieter et al., 1988; Ambrose et al., 1976). The absorbed nickel can also cross the placenta and accumulate in fetal tissues (Jasim and Tjalve, 1986; Schroeder et al., 1964).

Absorbed nickel is excreted primarily through the urinary route in both humans and animals. Maximal rates of urinary excretion occur during the first 10 hours after ingestion in

humans and excretion is essentially complete within 96 hours (Nielsen et al., 1999; Sunderman et al., 1989).

Noncancer Effects

The weight of evidence in both humans and animals suggests that oral exposure to soluble nickel salts results in systemic effects on the kidney, on neonatal mortality, and on the immune system. Table 2 summarizes key studies and endpoints. Both animal and human studies provide weak support for the kidney as a target organ of nickel toxicity. The most sensitive effect of oral exposure to nickel was decreased glomerular function in rats exposed via drinking water for 6 months (Vyskocil et al., 1994b). Increased levels of albumin in urine were observed in female rats exposed for 6 months; the increase observed in males was not statistically significant, due to two outliers in the control males (see Table 3). No effect was seen at the 3-month sacrifice. No statistically significant effects on urinary levels of β 2-microglobulin (β 2m) levels or on total protein were observed. One animal study provides some limited support for the kidney as a target organ. Dieter et al. (1988) reported mild tubular nephrosis in B6C3F1 mice treated with 108 or 150 mg Ni/kg-day as nickel sulfate in drinking water; no effect was seen at 44 mg Ni/kg-day (no effect at 25 mg Ni/kg-day if the doses were reported as nickel sulfate hexahydrate instead of anhydrous nickel sulfate). It is possible, however, that the nephrosis reported by Dieter et al. (1988) was related to decreased water consumption, rather than nickel exposure.

Available human data show weak support for effects on the kidney. Among workers who accidentally drank water contaminated with nickel sulfate, nickel chloride, and boric acid, a transient increase in urine albumin was observed in 3/21 exposed workers (Sunderman et al.,

1988). It is unclear whether the boric acid would have contributed to the kidney effect. This study suggests that a high bolus dose of nickel can lead to glomerular effects, although it is not clear whether similar effects would be seen at lower doses. Among nickel refinery workers, urinary β_2 microglobulin (β_2m) levels correlated with nickel levels in urine (a measure of exposure) (Sunderman and Horack, 1981). Urinary β_2m levels were not elevated in electroplating workers, but the urinary nickel levels were also lower. Vyskocil et al. (1994a) found statistically significant effects on markers of tubular function (urinary N-acetyl- β -D-glucosaminidase [NAG] levels in both sexes, and β_2m and retinol binding protein [RBP] in females) in workers exposed to soluble nickel compounds at a chemical plant. Correlations between levels of these proteins and urinary nickel levels were also observed. Urinary albumin was increased in both males and females, but the increase was not statistically significant. It is unclear why tubular damage (i.e., increased urinary excretion of low molecular weight proteins without albuminuria) was reported in most of these studies (Sunderman and Horack, 1981; Vyskocil et al., 1994a), while Vyskocil et al. (1994b) reported glomerular damage (i.e., albuminuria in the absence of an increase in urinary excretion of low molecular weight proteins) in rats. It should also be noted that the human studies with positive results were based on spot samples (i.e., urine was not sampled over a specified time duration), which can lead to false positives or false negatives in comparison with 24-hour samples. Indeed, Sanford and Nieboer (1992) found elevated levels of β_2m in spot urine samples from two subjects, but the total β_2m excretion in the 24-hour void from these subjects was normal.

Nickel can cross the placenta, and several oral studies in laboratory animals have reported increased neonatal mortality at doses below those resulting in maternal toxicity. Several oral multigeneration reproduction studies are available (Research Triangle Institute, 1988; Smith et

al., 1993; Ambrose et al., 1976; Schroeder and Mitchener, 1971), and one (Research Triangle Institute, 1988) included teratological evaluation of the F2 generation rats. No standard developmental studies with soluble nickel species via either the oral or inhalation routes were located. There is an inhalation developmental toxicity study in rats exposed to nickel oxide (Weischer et al., 1980), but there was only minimal evaluation of the pups. Although nickel oxide is an insoluble form of nickel, any observed systemic effects would be attributable to absorbed nickel, which presumably would be in a soluble form. Overall, these data indicate that ingested nickel can cause increased neonatal deaths at relatively low doses, but no reliable NOAEL (no observed adverse effect level) for this endpoint has been identified, as described in the next paragraph.

An equivocal LOAEL (lowest observed adverse effect level) of 1.33 mg Ni/kg-day was observed in a 2-generation study with Long-Evans rats administered nickel chloride in drinking water (Smith et al., 1993). This LOAEL is based on statistically significant increases in the total number of dead pups and the percentage of dead pups per litter in the second generation. The only reproductive effect in the first generation was increased numbers of litters with dead pups (but no effect on other indices of pup mortality) at a dose 24-fold higher. Inconsistency in response between generations and the absence of a clear dose-response make it difficult to identify a NOAEL or LOAEL. In a 2-generation study of nickel chloride in drinking water with CD rats, Research Triangle Institute (1988) also observed increased neonatal mortality at doses below those causing maternal toxicity. However, a reliable reproductive NOAEL could not be identified for that study, due to a lack of a dose response. Other problems with the study include potential confounding due to high room temperature, as well as decreased maternal water consumption and possible dehydration. The Research Triangle Institute (1988) study was the

only oral study that included teratological evaluations; no nickel-related developmental effects were observed. In a 3-generation study of Wistar rats administered nickel sulfate in feed, a clear and consistent decrease in live pups/litter was observed on postnatal day 5, and mean weanling body weight was decreased at the high dose in all generations (Ambrose et al., 1976). However, a NOAEL or LOAEL could not be clearly defined in this study, because there was no statistical analysis, and the reporting used pups, rather than litters, as the unit of analysis. Increased neonatal mortality was also observed by Schroeder and Mitchener (1971) in a 3-generation drinking water study in rats, but a reliable LOAEL could not be identified in this study, due to methodological inadequacies.

While nickel has long been recognized as a contact irritant, many studies have also demonstrated dermal effects in sensitive humans resulting from ingested nickel. The weight-of-evidence from these studies indicates that ingested nickel may invoke an eruption or worsening of eczema; however, a dose-response relationship is difficult to establish. The research regarding sensitization effects of oral exposures to nickel addresses three issues:

- 1) whether oral exposures to nickel can elicit responses in sensitized individuals, a reaction called systemic contact dermatitis;
- 2) whether low level of exposure to nickel can induce tolerance in those not previously sensitized; and
- 3) whether long-term exposure to low levels of nickel can reduce sensitivity in those previously sensitized.

Many studies have been published regarding nickel sensitivity in humans. Of the general population, approximately 8-10% of women and 1-2% of men demonstrate a sensitivity to nickel as determined by a patch test (North American Contact Dermatitis Group, 1973; Prystowsky et

al., 1979). The higher occurrence in women than in men is attributed to the fact that women more commonly wear nickel-containing jewelry. Initial sensitization to nickel is believed to result from dermal contact, but recurring flares of eczema, particularly of the hands, may be triggered by ingestion. Burrows (1992) reviewed 11 trials of oral challenges of nickel-sensitized subjects, including several double blind, placebo-controlled trials, usually of single doses. Three of these studies (Gawkrodger et al., 1986; Cronin et al., 1980; Kaaber et al., 1979, as cited in Burrows, 1992) provide the best dose-response information available on doses that cause a flare-up of eczema in previously-sensitized individuals. In all three studies, previously-sensitized individuals were administered single doses of nickel as nickel sulfate hexahydrate at doses ranging from 0.4 to 5.6 mg (approximately 0.006 to 0.08 mg Ni/kg). In all three studies all or most of the subjects reacted to the highest nickel dose tested (either 2.5 or 5.6 mg). A few subjects responded to doses of 1.2 mg nickel. Several other studies of sensitized individuals have reported systemic contact dermatitis, typically with single doses of 2.5 mg (approximately 0.035 mg Ni/kg) via the oral route (Veien et al., 1987; Veien and Menne, 1990; Christensen et al., 1981).

The human sensitivity studies are difficult to interpret for several reasons. Very small numbers of subjects (mostly women already determined to be sensitive to nickel by a patch test) were used in the studies, and many investigators reported a placebo effect. Many of the studies were not conducted in a double-blind manner, thereby introducing investigator bias, and it was often not specified whether subjects had fasted overnight or whether there were other dietary restrictions. There is a 40-fold difference between the absorption of nickel in drinking water by fasted healthy humans, and their absorption of nickel in food (Sunderman et al. 1989). It is also difficult to take into account dietary intake of nickel. Finally, the subjects in the studies of

sensitized women were generally given a bolus dose of nickel. The absorption and biokinetics following such an exposure may be quite different from an exposure that is given incrementally throughout the day. Therefore, it is difficult to establish a clear NOAEL for oral challenge. The data are consistent, however, with the conclusion that most sensitized individuals respond to a single capsule or gavage dose of 5 mg nickel (about 0.08 mg Ni/kg), and few respond to doses of 1.2 mg nickel (about 0.02 mg Ni/kg). These doses are in addition to normal dietary nickel intake.

Animal studies have been reported to show that low doses of allergens, including nickel, administered for long periods of time can induce tolerance. In a study of 2176 male and female patients in nine European dermatology clinics who had positive skin patch tests, Van Hoogstraten et al. (1991) found that nickel sensitivity occurred less often among individuals who had their ears pierced after wearing braces than in those who had the ear piercing before they wore the dental braces. These results provide indirect evidence of induction of increased tolerance from oral exposure to low levels of nickel among people who had dental braces for at least 6 months prior to ear piercing. The large numbers of patients and the information on age and timing of exposure are important measures of quality. However, the group sizes differ, and no measure of the statistical variability of the estimates (i.e., no confidence interval or standard error) was reported.

Two studies in humans were designed to determine whether low levels of oral nickel intake reduce the frequency or intensity of existing allergy (Sjovall et al., 1987; Panzani et al., 1995). The former study found some evidence of reduced sensitization, although some flare-ups were observed. Panzani et al. (1995) reported an overall increase in tolerance, based on remission of dermal symptoms and results of provocation tests. However, the conclusions of this study are limited, since several patients stopped treatment because symptoms were aggravated; patch tests showed no significant difference; and the numbers are small, inconsistent across trials and difficult to interpret. These small studies in humans provide some limited support that sensitivity can be reduced by long-term, low-level exposure. These data also suggest no adverse effects on sensitized individuals, and possibly a beneficial effect, from short-term oral exposures to nickel at levels below about 0.5 mg per day (approximately 0.007 mg Ni/kg-day).

Cancer

Standard animal bioassays of soluble nickel compounds administered to rats or mice by the oral route (Ambrose et al., 1976; Schroeder et al., 1964, 1974; Schroeder and Mitchener, 1975) were negative, but deficiencies in all of these studies preclude a definitive conclusion (See Table 4). The Ambrose et al. (1976) study was limited by high mortality in all groups, resulting in a relatively small number of animals that were exposed for a full 2 years. The studies by Schroeder and colleagues tested only a single dose and exposed the animals until all of the animals died, decreasing the study sensitivity, due to the potential for age-related neoplasms. It is unclear if a maximum tolerated dose was achieved in any of those studies (Schroeder et al., 1964, 1974; Schroeder and Mitchener, 1975), because the decreases in body weights (~10%) were not clearly adverse. In addition, the studies by Schroeder et al. (1964, 1974) are limited by

high (>30%) autolysis and incomplete documentation, and it is unclear whether non-neoplastic lesions which were not considered to have caused death were evaluated. Similarly, less than half of the animals in the remaining two studies (Ambrose et al., 1976; Schroeder and Mitchener, 1975) were necropsied, and even fewer were sectioned. Therefore, nonneoplastic lesions and any small tumors could have been missed. Together, these study limitations preclude a definitive assessment of the carcinogenic potential of ingested soluble nickel compounds.

Based on these findings, the carcinogenicity of soluble nickel compounds for oral exposures *cannot be determined* at this time. According to EPA's 1996 draft cancer guidelines, the following subdescriptor applies: The carcinogenic potential of oral exposure to soluble nickel "*cannot be determined* because there are *inadequate data* to perform an assessment." Several negative oral experimental animal studies exist, but each of them has a deficiency that makes conclusive statements difficult. The available parenteral and initiation and promotion studies (summarized in Haber et al., 2000), which have indirect relevance to tumor formation after oral (or inhalation) exposure, suggest some tumorigenic activity for some soluble nickel compounds in some assays.

DOSE-RESPONSE ASSESSMENT

The studies considered as the basis for the RfD for soluble nickel salts are summarized in Table 2. Although the most sensitive endpoint appears to be increased albuminuria in the absence of indications of tubular injury (indicating renal glomerular dysfunction) in rats exposed to nickel in drinking water, none of the available oral studies (e.g., Vyskocil et al., 1994b; Ambrose et al., 1976) are ideally suited for selection as the principal study for the development of the RfD. The study by Vyskocil et al. (1994b) has been selected as the most appropriate study

to serve as the principal study. In this study, nickel sulfate was administered to rats in drinking water for 6 months. Effects were seen following 6 months of exposure at the only dose tested (6.9 mg Ni/kg/day for males and 7.6 mg Ni/kg/day for females), but not after 3 months of exposure. The study evaluated sensitive indicators of kidney damage (β_2 m, NAG, and lactate dehydrogenase), and included both group-level and some individual animal data.

The limitations of Vyskocil et al. (1994b) include the fact that the study was conducted for only 6 months, tested only one dose, did not provide a comparison to baseline values, and evaluated only 10 rats/sex/time point. Only one measure of renal function was clearly affected (although the increases were not large for that endpoint), and the interpretation of the results was complicated by considerable variability in response in both the control and exposed groups. The supporting data indicate that it is biologically plausible that the kidney is *a target organ*, but these data are weak and it is not clear whether the kidney is the *most sensitive* target organ. Studies reporting kidney damage following parenteral exposure to nickel (Foulkes and Blanck, 1984; Gitlitz et al., 1975) also support the plausibility of the kidney as a target organ. Kidney histopathology has not been observed in chronic studies testing to lethal doses (Ambrose et al., 1976; American Biogenics Corporation, 1988) although no other study included evaluation of sensitive measures of kidney function (i.e., individual protein markers of glomerular and tubular function). Mild tubular nephrosis was reported in mice consuming 108 mg Ni/kg-day for 180 days in a drinking water study (Dieter et al., 1988), but it was not clear if this was secondary to decreased water consumption. Finally, although occupational studies have reported elevated levels of urinary protein markers, these elevations have been observed only in spot urine samples (Sunderman and Horak, 1981; Vyskocil et al., 1994a), which are subject to much more variability than 24-hour multi-void samples (Sanford and Nieboer, 1992).

A possible alternative would be use of one of the reproductive toxicity studies. A continuing issue related to the assessment of a RfD for soluble nickel compounds is the inconsistent results in the reproductive studies. Soluble nickel compounds can cause reproductive toxicity, but the doses at which such effects occur generally fall above those that cause kidney toxicity. The equivocal LOAEL of 1.3 mg Ni/kg-day for increased postnatal deaths in the study of Smith et al. (1993) was considered as a potential principal study. This equivocal LOAEL is approximately a factor of 5 below the LOAEL for kidney effects in the study by Vyskocil et al. (1994b). This study was not chosen as the principal study, due to the equivocal nature of the response (in the absence of a clear dose-response) and the absence of reproductive effects in other reproductive toxicity studies at this dose. The results of Smith et al. (1993) were, however, taken into consideration in the choice of uncertainty factors. The critical effect, increased albuminuria in rats, should be protective of the reproductive endpoints as well. The Metals Subcommittee of the U.S. EPA Science Advisory Board reviewed the reproductive toxicity data in 1991, and concluded that the “most cogent” of the reproductive toxicity studies “failed to yield an RfD that was substantially different” from that derived from the Ambrose et al. (1976) study (SAB, 1991). Similarly, the RfD derived from the Vyskocil et al. study would also be protective from reproductive effects.

A second alternative for the choice of principal study is the chronic feeding study of Ambrose et al. (1976). Ambrose et al. (1976) identified a NOAEL of 8 mg Ni/kg-day, based on decreased body weight, in a study of rats administered nickel sulfate in feed for 2 years. The corresponding BMDL₁₀ was estimated as 6.8-36 mg Ni/kg-day, depending on whether the benchmark response (BMR) was defined as a 10% increased risk of low body weight (lower value) or a 10% decrease in the mean body weight (higher value). This study, however, is

limited by minimal reporting and high mortality in both the control and exposed groups. Because Ambrose et al. (1976) identified a NOAEL in a chronic study, but Vyskocil et al. (1994b) identified only a LOAEL in a subchronic study (without a NOAEL), the Ambrose et al. (1976) is a less conservative choice as the basis for the RfD. A third alternative principal study is American Biogenics Corporation (1988), in which nickel was administered by gavage in water to male and female rats. Decreased body weight in males was the most sensitive endpoint, along with pneumonitis in both sexes. The NOAEL in that study was 5 mg Ni/kg-day (assuming that the doses were reported as nickel amounts, or 2.7 mg Ni/kg-day, assuming the doses were reported as amounts of nickel chloride hexahydrate). The utility of this study for risk assessment is limited, however, by uncertainties regarding the dose (i.e., whether the doses were reported as nickel or as nickel chloride hexahydrate).

Following U.S. EPA methods, the minimal LOAEL from Vyskocil et al. (1994b) of 7.6 mg Ni/kg-day was divided by a composite uncertainty factor of 1000 to derive a RfD of 0.008 mg Ni/kg-day. The composite uncertainty factor (UF) to use with a given database for developing RfDs is a case-by-case judgment by experts (Dourson et al., 1996). Factors were selected to address uncertainty in the areas of human variability (H), interspecies variability (A), extrapolation from a subchronic study (S), insufficiencies in the database (D), and use of a minimal LOAEL (L).

The critical effect for the soluble nickel RfD is increased urinary albumin levels, a marker of decreased glomerular function of the kidney. Other than people who have been dermally sensitized, sensitive populations have not been specifically identified for nickel. However, based on the critical effect and the observed concentration of nickel in the kidney of animals and humans, it is reasonable to expect that people with kidney dysfunction would be

more sensitive to ingested nickel. In addition, such individuals would likely have decreased urinary excretion of nickel, and thus might have higher nickel levels in the kidney. Particular groups with decreased kidney function include dialysis patients and diabetics. The default UF_H of 10 is considered appropriate for protecting these populations with decreased kidney function, in the absence of data to address the variability of individuals in toxicokinetics and toxicodynamics of soluble nickel.

Although some data on absorption and excretion of ingested soluble nickel compounds are available for both humans and rats, the data are not detailed enough to quantitatively compare the rate of nickel absorption or excretion. It does appear that the absorption of ingested soluble nickel is higher in rats than in humans, although the rat data are limited. Ishimatsu et al (1995) found that nonfasted male Wistar rats absorbed 9.8-34% of a single gavage dose of soluble nickel salts administered in a 5% starch saline solution. By contrast, absorption by nonfasted human subjects of soluble nickel salts was only 5.7% (Christensen and Lagesson, 1981, as calculated by Diamond et al., 1998). It is not clear if this difference is due to interspecies differences or to the differences in dosing vehicles. Thus, the default UF_A of 10 for interspecies extrapolation is appropriate in the absence of data to specifically address the extrapolation from experimental animals to humans on toxicokinetics and toxicodynamics.

A combined factor of 10 is appropriate for subchronic-to-chronic extrapolation, use of a minimal LOAEL, and for an incomplete database, based on four points

- The severity of the adverse effect is minimal.
- The available chronic studies do not identify a lower LOAEL than the critical study.
- Although soluble nickel did have an effect in reproductive studies, the studies do not collectively indicate that reproductive effects occur at a lower dose than the critical

effect. As noted above, if the RfD were based on the equivocal LOAEL of 1.3 mg Ni/kg-day for reproductive effects in Smith et al. (1993), it would change by only a factor of approximately 2-6, depending on a potential different choice of UFs).

- The toxicokinetic data suggest that absorption of ingested soluble nickel is higher in rats (9.8-34% of a gavage dose; Ishimatsu et al., 1995) than in humans (5.7% for soluble nickel salts with nonfasted subjects; Christensen and Lagesson, 1981, as calculated by Diamond et al., 1998). It is not clear if this difference is due to interspecies differences or to the differences in dosing vehicles, but lower absorption by humans would mean a lower human tissue dose for a given ingested amount, and therefore that the use of the rat LOAEL as the basis of the RfD is conservative.

Therefore, for soluble nickel salts, two full factors of 10 (for intrahuman variability and for interspecies extrapolation) and a combined factor of 10 (for subchronic-to-chronic extrapolation, an insufficient database, and use of a minimal LOAEL) were used. A composite factor of 1000 results. It is of note that standard EPA practice is to condense four full UFs of 10 to a composite UF of 3000 (due to overlap of UFs) (Dourson, 1994). Thus, if three partial UFs were used rather than the combined 10, the composite UF could be 1000 or 3000, depending on the overall judgement of the database.

A modifying factor is not considered necessary with this database because the outstanding uncertainties are adequately addressed with the standard uncertainty factors above

Based on these considerations, a composite UF of 1000 is considered sufficient. Thus, the RfD is derived as:

$$7.6 \text{ mg Ni/kg-day} \div 1000 = 0.0076 \text{ mg Ni/kg-day}$$

Rounded to one significant figure, the resulting RfD is 8×10^{-3} mg Ni/kg-day. The nickel doses in the animal studies did not include the nickel in the diet. Therefore, the RfD presented here represents the dose of nickel *in addition* to the amount in food.

PEER REVIEW

The draft assessment document was independently peer reviewed by a panel of ten experts from the fields of risk assessment, epidemiology, occupational medicine, and toxicology in a two-day meeting. The peer review was organized by Toxicology Excellence for Risk Assessment (*TERA*) with selection of panel members made by a group of *TERA* trustees to avoid a conflict of interest. All panel members disclosed any potential conflicts of interest and the panel discussed these, agreeing that three of the panel members should participate in the discussion, but not be polled for consensus. Two of the three were from federal agencies that have assessed nickel and the third had performed work for a nickel trade group. A complete description of the peer review process and a summary of the discussions and conclusions of the nickel soluble salts review can be found at <http://www.tera.org/peer>.

The panel reviewed the draft document and focused their discussion on the conclusions regarding cancer and non-cancer risk in the draft document. For the RfD, the panel members were asked to comment on the principal study, critical effect, LOAEL, and uncertainty factors; on whether the issue of nickel-related contact dermatitis was appropriately addressed; and whether background exposure levels were appropriately addressed. Additional information about the issues discussed by the peer review panel are presented in the accompanying paper

(Haber et al., 2000). The authors of the assessment considered the comments of the peer review panel and revised the assessment document accordingly. Significant revisions included expanding the discussion of the strengths and limitations of the Vyskocil et al. (1994b) and Ambrose et al. (1976) studies; expanding the discussion of the issue of nickel-related contact dermatitis and sensitization; and addressing levels of nickel in the diet of the experimental animals.

A brief summary of the nickel assessment and conclusions regarding cancer and non-cancer risk can also be found on the International Toxicity Estimates for Risk (*ITER*) database at <http://www.tera.org/iter>. This database compares risk values derived by U.S. EPA, ATSDR and Health Canada, alongside independently derived values (such as those for nickel described here) which have been approved by an independent peer review.

DISCUSSION AND CONCLUSIONS

The RfD of 0.008 mg/kg-day based on the minimal LOAEL from Vyskocil et al. (1994b) can be seen as consistent with the soluble nickel RfD described on IRIS (U.S. EPA, 1999). EPA derived its RfD in 1987 and reviewed it in 1991. The EPA RfD of 0.02 mg Ni/kg-day is based on a chronic NOAEL of 5 mg Ni/kg-day for body weight decrease seen in the Ambrose et al. (1976) study, and a 300-fold UF. The composite uncertainty factor includes 10-fold for within-human variability, 10-fold for animal to human extrapolation, and 3-fold for uncertainties in the database on reproductive endpoints. The EPA RfD is within a factor of 2-3 of the RfD presented here, a difference well within the inherent uncertainty of the RfD. The EPA RfD is based on

total nickel, while the RfD described here is based on nickel in addition to dietary contributions, and so would be expected to be lower than a RfD based on total nickel.

Health Canada under the evaluation of priority substances under the Canadian Environmental Protection Act (CEPA) has evaluated soluble nickel compounds and has derived tolerable intakes (TIs) for nickel sulfate and nickel chloride, based on data identified prior to August, 1993 (Health Canada, 1996). Health Canada's nickel sulfate TI of 0.05 mg Ni/kg-day is based on the same NOAEL from the Ambrose et al. (1976) study used by EPA for its soluble nickel salts RfD. The values developed by the U.S. EPA and Health Canada are slightly different, because Health Canada used an uncertainty factor of 100, while EPA used 300, with the extra 3-fold factor for inadequacies in the reproductive studies. For nickel chloride, Health Canada derived a TI of 0.0013 mg Ni/kg-day based on Smith et al. (1993). EPA discussed this study in its RfD documentation, and determined that a NOAEL or LOAEL could not be defined for this study because of the absence of a clear dose-response trend at the lower dose.

The Vyskocil et al. (1994b) study was not available when either EPA or Health Canada derived their estimates. However, the RfD presented in this paper falls among the other two organization's values.

ATSDR did not derive any oral minimal risk levels (MRLs) for nickel because nickel can cause dermal reactions in sensitive people (those who have been sensitized and have nickel-contact allergy) (ATSDR, 1997). ATSDR considered deriving an MRL based on dermatitis in sensitive individuals, but the application of uncertainty factors to the effect level would bring the dose below normal dietary intake.

Both the RfD discussed here and EPA's RfD are calculated to be protective of all endpoints with the possible exception of hypersensitive individuals. Sensitivity to nickel

(contact dermatitis) results from dermal contact with nickel, and oral exposure of sensitized individuals may also elicit dermatitis reactions (systemic contact dermatitis). However, the data also suggest that low levels of oral exposure may induce tolerance, either preventing or reducing dermal contact sensitivity. Either way, there is no evidence regarding whether oral exposure to nickel can cause the initial sensitization. This RfD is designed to protect people from sensitization, but may not necessarily be protective for sensitized individuals.

The uncertainties regarding the derivation of the noncancer RfD have been described above. Confidence in the critical study is considered low. The critical study was of 6 months duration and measured multiple sensitive endpoints for kidney function. However, the study only tested one dose and only tested ten animals/sex/exposure duration. Confidence in the supporting database is considered medium. Although the critical study was the only one that reported kidney effects at such low doses, kidney effects have been seen in some human studies, but not in another well-conducted human study at lower exposures. Uncertainties in the developmental and reproductive toxicity studies also preclude a higher rating for database confidence. Overall confidence in the RfD is considered low; meaning that additional data may more likely change the value of this RfD when compared to a high confidence RfD (for another chemical).

There are numerous areas of uncertainty surrounding this assessment of soluble nickel compounds. There are uncertainties relating to the potential reproductive effects, and to the carcinogenic potential of orally-administered soluble nickel compounds. Although multiple oral studies of soluble nickel compounds in different experimental animal species did not indicate any cancer-causing potential, each of these studies had design flaws that preclude a definitive conclusion that soluble nickel is not carcinogenic after oral exposure. According to EPA's 1996

draft cancer guidelines (U.S. EPA, 1996), the carcinogenic potential of oral exposure to soluble nickel “*cannot be determined*” because there are *inadequate data* to perform an assessment.” The complete assessment document is available on the Internet at <http://www.tera.org/vera>.

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Table 1. U.S. and Canadian Risk Values for Oral Exposure to Soluble Nickel Compounds

Agency	Nickel Compound Evaluated	Critical Effect	Risk Value	Study	Comments
U.S. EPA	Soluble salts	Decreased body and organ weights	RfD, 0.02 mg/kg-day 1987	Ambrose et al., 1976	The RfD for soluble nickel salts is based on a NOAEL of 5 mg/kg-day and an uncertainty factor of 300. EPA has not evaluated the carcinogenicity of nickel soluble salts as a class of compounds; however EPA has classified nickel refinery dust and certain insoluble nickel compounds as group A – known human carcinogens.
ATSDR	Multiple	---	---	---	ATSDR did not derive any oral values for nickel because nickel can cause dermal reactions in people who have been sensitized and have nickel contact allergy. ATSDR considered deriving a value based on dermatitis in sensitive people, but the application of uncertainty factors to the effect level would bring the dose below normal dietary intake.
Health Canada	Nickel chloride	Reproductive toxicity	Tolerable Intake, 0.0013 mg/kg-day 1993	Smith et al., 1993	The TI is based on a NOAEL of 1.3 mg/kg-day and an uncertainty factor of 1000. Health Canada classifies soluble nickel salts as Group I, carcinogenic to humans, but does not estimate cancer potency by the oral route.
Health Canada	Nickel sulfate	Liver and heart relative weights	Tolerable Intake, 0.05 mg/kg-day 1993	Ambrose et al., 1976	The TI is based on a NOAEL of 5 mg/kg-day and an uncertainty factor of 100.

Table 2. Studies and Endpoints Considered as the Basis for the Soluble Nickel Compound RfD

Study/ Nickel Species	Strain, Species and Number	Route/Doses (mg Ni/kg- day)	Duration	Critical Effect	NOAEL/ LOAEL (mg/kg-day)	BMDL ₁₀ (mg/kg-day)
Vyskocil et al., 1994b/ NiSO ₄	Wistar Rat 20/sex/group	Drinking water 0, 6.9 (males) or 7.6 (females)	6 months	Increased urinary albumin levels	None/ 7.6 (females)	— ¹
Ambrose et al., 1976/ NiSO ₄	Wistar Rat 25/sex/group	Feed 0, 8, 80, and 200	2 years	Decreased body weight	8 ² / 80	11 – 58 ³
American Biogenics Corporation, 1988/ NiCl ₂	Sprague Dawley Rat 30/sex/group	Gavage in water 0, 5, 35, and 100	92 days	Decreased body weight in males, pneumonitis in both sexes	5 ⁴ (2.7) 35 (19)	1.5-17 ³ (Based on decreased BW)
Dieter et al., 1988/ NiSO ₄	B6C3F1 Mouse 10 females/group	Drinking water 0, 44, 108, and 150	180 days	Thymic atrophy, decreased thymus weight	None/ 44	— ¹
Smith et al., 1993/ NiCl ₂	Long-Evans Rat 34 females/group	Drinking water 0, 1.3, 6.8, and 31.6	2-gen repro	Increased pup death	None/ 1.3 (equivocal)	— ¹

¹The data for this study were not appropriate for calculating a BMD.

²The NOAEL and LOAEL were reported as 5 mg/kg-day and 50 mg/kg-day by EPA (on IRIS, 1999), due to the use of a generic food factor of 0.05, rather than the strain-specific value used for this assessment.

³The calculated BMDL₁₀ varies with the model used and the definition of BMR (see text).

⁴Assuming doses were reported in terms of nickel dose. Values in parentheses are the nickel doses if the doses were reported in terms of nickel chloride hexahydrate

Table 3. Effect of Exposure to 100 mg/L Nickel in Drinking Water Measures of Kidney Effects in Male and Female Rats¹

Sex	Exposure Duration	Condition	Albumin ² (µg/24 hr)	β2m ² (µg/24hr)	Relative Kidney Weight ³ (g/kg)
Males	3 months	Control	622 (216-2970)	5.15 (2.1-15.4)	5.93 ± 0.08
		Nickel	720 (132-2406)	4.59 (1.7-15.1)	6.08 ± 0.13
	6 months	Control	989 (194-11200)	3.02 (0.2-24.7)	5.43 ± 0.10
		Nickel	2065 (448-5600)	4.91 (0.6-17.4)	5.91 ± 0.16*
Females	3 months	Control	202 (88-326)	0.52 (0.05-14.4)	6.12 ± 0.23
		Nickel	329 (115-1162)	1.11 (0.23-6.60)	6.47 ± 0.12
	6 months	Control	354 (114-1575)	0.55 (0.05-1.93)	6.52 ± 0.12
		Nickel	1319* (209-9600)	0.87 (0.06-3.90)	6.78 ± 0.11

¹ Adapted from Vyskocil et al., 1994b; data were evaluated by two-way variance analysis and Bonferroni test

² Geometric mean (range) of ten animals

³ Arithmetic mean ± SEM of ten animals

*Statistically significant at p<0.05 with respect to the matched controls

Table 4. Summary of Studies that Evaluated Carcinogenicity of Ingested Soluble Nickel Compounds

Study/ Nickel Species	Strain, Species and Number	Route/Doses (mg Ni/kg-day)	Duration	Results
Ambrose et al., 1976 NiSO ₄	Wistar Rat 25/sex/group	Feed 0, 8, 80, and 200	2 years	No exposure related neoplastic lesions in either sex. However, high mortality limits study.
Schroeder et al., 1964 Ni(CH ₃ CO ₂) ₂	Swiss Mouse 50-54 male and 52-54 female/group	Drinking water 0 and 0.45 to 0.51 (estimated)	Until all animals died (36 months)	No exposure related neoplastic lesions in either sex. However, poor ascertainment and study design limit study conclusions
Schroeder et al., 1974 Ni(CH ₃ CO ₂) ₂	Long-Evans Rat 50-54 male and 52-54 female/group	Drinking water 0, 0.012 (males), 0.17 (females) (estimated, based on nickel and water and feed)	Lifetime (maximum, >3 years)	No exposure related neoplastic lesions in either sex. However, poor ascertainment and study design limit study conclusions
Schroeder and Mitchener, 1975 Ni(CH ₃ CO ₂) ₂	Swiss Mouse 54/sex/group	Drinking water 0, 0.95 (estimated)	Lifetime (maximum - 2 years, 7 months)	No exposure related neoplastic lesions in either sex. However, poor ascertainment and study design limit study conclusions