Nickel, soluble salts; CASRN Various

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Nickel, soluble salts

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	12/01/1991
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated; message	08/01/1994

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Nickel, soluble salts
CASRN — Various
Last Revised — 12/01/1991

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body and organ weights **Rat Chronic Oral Study** **Ambrose et al., 1976**	NOAEL: 100 ppm diet (5 mg/kg/day) LOAEL: 1000 ppm diet (50 mg/kg/day)	300	1	2E-2 mg/kg/day

*Conversion Factors -- 1 ppm = 0.05 mg/kg/day (assumed rat consumption)

I.A.2. Principal and Supporting Studies (Oral RfD)

Ambrose, A.M., D.S. Larson, J.R. Borzelleca and G.R. Hennigar, Jr. 1976. Long-term toxicologic assessment of nickel in rats and dogs. J. Food Sci. Technol. 13: 181-187.

Ambrose et al. (1976) reported the results of a 2-year feeding study using rats given 0, 100, 1000 or 2500 ppm nickel (estimated as 0, 5, 50 and 125 mg Ni/kg bw) in the diet. Body weights in the high-dose male and female rats were significantly decreased compared with controls. Body weight was also reduced at 1000 ppm. This reduction was significant for females at week 6 and from weeks 26 through 104, whereas males showed body weight reduction only at 52 weeks. Groups of female rats on the 1000 or 2500 ppm nickel diets (50 and 125 mg Ni/kg bw) had significantly higher heart-to-body weight ratios and lower liver-to-body weight ratios than controls. No significant effects were reported at 100 ppm (5 mg Ni/kg bw). The dose of 1000 ppm (50 mg Ni/kg bw) represents a LOAEL for this study, while the dose of 100 ppm (5 mg Ni/kg bw) is a NOAEL. In this study, 2-year survival was poor, particularly in control rats of both sexes (death: 44/50), raising some concern about the interpretation of the results of this study. A subchronic study conducted by American Biogenics Corp. (ABC, 1986) also found 5 mg/kg/day to be a NOAEL, which supports the Ambrose et al. (1976) chronic NOAEL of 5 mg/kg/day.

Dietary exposure of dogs to 2500 ppm Ni (about 63 mg/kg/day) resulted in depressed body weight gain; no effects were seen at either 100 ppm (about 2.5 mg/kg/day) or 1000 ppm Ni (about 25 mg/kg/day) in the diet (Ambrose et al., 1976). This study demonstrates that rats are the more sensitive of the two species.

ABC (1986) conducted the 90-day study with nickel chloride in water (0, 5, 35 and 100 mg/kg/day) administered by gavage to both male and female CD rats (30 animals/sex/group). The data generated in this study included clinical pathology, ophthalmological evaluations, serum biochemistry, body and organ weight changes and histopathological evaluations of selected organs (heart, kidney, liver).

The body weight and food consumption values were consistently lower than those of controls for the 35 and 100 mg/kg/day dosed males. Female rats in both high-dose groups had lower body weights than controls, but food consumption was unaffected by the test article. Clinical signs of toxicity, such as lethargy, ataxia, irregular breathing, cool body temperature, salivation and discolored extremities, were seen primarily in the 100 mg/kg/day group; these signs were less severe in the 35 mg/kg/day group. The 5 mg/kg/day group did not show any significant clinical signs of toxicity. There was 100% mortality in the high-dose group; 6/30 males and 8/30 females died in the mid-dose group (35 mg/kg/day). Histopathologic evaluation indicated that deaths of 3/6 males and 5/8 females in the mid-dose group were due to gavage errors. At sacrifice, kidney, liver and spleen weights for 35 mg/kg/day treated males and right kidney weights for 35 mg/kg/day treated females were significantly lower than controls. Based on the results obtained in this study, the 5 mg/kg/day nickel dose was a NOAEL, whereas 35 mg/kg/day was a LOAEL for decreased body and organ weights.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 10 is used for interspecies extrapolation and 10 to protect sensitive populations. An additional uncertainty factor of 3 is used to account for inadequacies in the reproductive studies (RTI, 1987; Ambrose et al., 1976; Smith et al., 1990) (see Additional Comments section). During the gestation and postnatal development of F1b litters in the RTI (1987) study, temperatures were about 10 degrees F higher than normal at certain times, which makes evaluation of this part of the reproductive study impossible. In the Ambrose et al. (1976) study, statistical design limitations included small sample size and use of pups rather than litters as the unit for comparison. There were also problems with the statistical analysis of the Smith et al. (1990) study.

The Ni dietary study by Ambrose et al. (1976) identifying a NOAEL of 100 ppm (5 mg/kg/day) is supported by the subchronic gavage study in water (ABC, 1986), which indicated the same NOAEL (5 mg/kg/day).

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

In addition to the effects on organ weights described in the critical study, two other sensitive endpoints exist: neonatal mortality and dermatotoxicity. While no reproductive effects have been associated with nickel exposure to humans, several studies in laboratory animals have demonstrated fetotoxicity. These studies are described below.

Following the reproductive studies is a discussion of nickel-induced dermatotoxicity in hypersensitive humans. 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. A few representative studies and review articles are cited below.

While the systemic toxicity data (as manifested in organ weight changes) was used as the critical study for the RfD determination, the reproductive/fetotoxicity and the dermatotoxicity were both considered as possible endpoints upon which to base the quantitative risk assessment of nickel. The data for effects on the latter two endpoints do not demonstrate consistent dose-response relationships, and in both cases the available studies are sufficiently flawed so as to prevent their selection as the basis for the oral RfD. It is noted, however, that the RfD based on the Ambrose et al. (1976) study is considered to be protective of all endpoints with the possible exception of hypersensitive individuals as described below.

In addition to the 2-year feeding study used as the basis for the RfD, Ambrose et al. (1976) also reported reproductive toxicity of nickel. The study had some statistical design limitations including small sample size and use of pups rather than litters as the unit for comparison. Furthermore, the results were equivocal and did not clearly define a NOAEL or LOAEL. Because nickel was administered in a laboratory chow diet rather than drinking water, quantifying analogous nickel exposure via drinking water was problematic.

In a 2-generation study (RTI, 1987) nickel chloride was administered in drinking water to male and female CD rats (30/sex/dose) at dose levels of 0, 50, 250 and 500 ppm (0, 7.3, 30.8 and 51.6 mg/kg/day, estimated) for 90 days before breeding (10 rats/sex/group comprised a satellite subchronic nonbreeder group). At the 500 ppm dose level there was a significant decrease in the Po maternal body weight, along with absolute and relative liver weights. Thus, 250 ppm (30.8 mg/kg/day) was a NOAEL for Po breeders. Histopathology was performed for liver, kidney, lungs, heart, pituitary, adrenals and reproductive organs to make this assessment. This NOAEL is

higher than the NOAEL derived from the chronic Ambrose et al. (1976) and subchronic gavage (ABC, 1986) assays.

In the RTI (1987) F1a generation (postnatal days 1-4) at the 500 ppm dose level the number of live pups/litter was significantly decreased, pup mortality was significantly increased, and average pup body weight was significantly decreased in comparison with controls. Similar effects were seen with F1b litters of Po dams exposed to 500 ppm nickel. In the 50 and 250 ppm dose groups increased pup mortality and decreased live litter size was observed in the F1b litters. However, these effects seen with F1b litters are questionable because the room temperature tended to be 10 degrees F higher than normal at certain times (gestation-postnatal days) along with much lower levels of humidity. As evidenced in the literature, temperatures that are 10 degrees F above normal during fetal development cause adverse effects (Edwards, 1986). Therefore, the above results seen at 50 and 250 ppm cannot be considered to be genuine adverse effects.

F1b males and females of the RTI (1987) study were randomly mated on postnatal day 70 and their offspring (F2a and F2b) were evaluated through postnatal day 21. This phase included teratological evaluations of F2b fetuses. Evaluation of the data indicated that the 500 ppm dose caused significant body weight depression of both mothers and pups, and increased neonatal mortality during the postnatal development period. The intermediate dose, 250 ppm nickel, produced transient depression of maternal weight gain and water intake during gestation of the F2b litters. The 50 ppm nickel exposure caused a significant increase in short ribs (11%). However, since this effect was not seen in both the higher dose groups, the reported incidence of short ribs in the 50 ppm group is not considered to be biologically significant.

Schroeder and Mitchener (1971) conducted a 3-generation study in which 5 mating pairs of rats were provided drinking water containing 5 mg Ni/L (estimated as 0.43 mg/kg bw). Results of this study indicated significant increases in neonatal mortality and in the number of runts born to exposed rats compared with controls. The major weakness of this study, however, is that the end result is based on a total of five matings. The matings were not randomized and the males were not rotated. The Schroeder and Mitchener (1971) study was conducted in an environmentally controlled facility where rats had access to food and water containing minimal levels of essential trace metals. Because of the interactions of nickel with other trace metals, the restricted exposure to trace metals (chromium was estimated as inadequate) may have contributed to the toxicity of nickel.

Smith et al. (1990) also studied the reproductive and fetotoxic effects of nickel. Four groups of 34 female Long-Evans rats were given drinking water containing nickel chloride in the following concentrations of nickel: 0, 10, 50 or 250 ppm (0, 1.3, 6.8 or 31.6 mg/kg/day) for 11 weeks prior to mating and during two successive gestation periods (G1, G2) and lactation periods (L1, L2).

Maternal body weight gain was reduced during G1 in mid- and high-dose females. The reproductive performance of the exposed rats was not affected. Pup birth weight was unaltered by treatment, and weight gain was reduced only in male pups exposed to 50 ppm nickel during L1. The most significant toxicological finding was the increased incidence of perinatal mortality. The proportion of dead pups per litter was elevated at the high dose in L1 and at 10 and 250 ppm in L2. While the perinatal mortality reported in this study is consistent with other reproductive studies on nickel, it is hard to define a NOAEL and LOAEL because of the absence of a clear dose-response trend at the lower doses.

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). 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.

The human studies described below 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; many investigators reported a placebo effect; many studies were not conducted in a double-blind manner, thereby introducing investigator bias; and it was often not specified whether subjects had been fasted overnight or whether there were other dietary restrictions. It is important to note that the way in which nickel is consumed may greatly affect its bioavailability. Sunderman et al. (1989) demonstrated that 27+/-17% of the nickel in drinking water was absorbed by healthy humans whereas only 0.7+/-0.4% of the same dose of nickel ingested in food was absorbed (a 40-fold difference). One final point to bear in mind in interpreting these studies is that the subjects were generally given a bolus dose of nickel. The absorption and biokinetics following such an exposure may be quite different from an exposure which is given incrementally throughout the day.

Following an overnight fast, groups of 5 nickel-sensitive women were given 100 mL of water along with one oral dose of nickel sulfate containing 0.6, 1.25 or 2.5 mg nickel (Cronin et al., 1980). The clinical response was observed for the next 24 hours. Worsening of hand eczema was reported in 2/5 female subjects that received 0.6 mg, 3/5 at 1.25 mg and 5/5 at 2.5 mg. Erythema was observed in 1/5 (0.6 mg), 4/5 (1.25 mg) and 4/5 (2.5 mg) women. While there appears to be a good dose-response relationship, this study did not report controls. The response observed at the lowest dose may well be within background levels.

Numerous other studies have been conducted to attempt to establish the relationships between nickel exposure and dermal irritation. Kaaber et al. (1978, 1979) reported worsening of eczema following an oral challenge with 2.5 mg nickel. In the 1978 study, 17/28 subjects experienced aggravation of dermatitis following nickel ingestion. Nine of the 17 that experienced adverse

effects from the nickel found that their condition improved when they adopted a low nickel diet. In the 1979 study 9/14 subjects responded negatively to nickel treatment.

Studies conducted by Gawrodger et al. (1986), Burrows et al. (1981) and Jordan and King (1979) offer different results. Jordan and King's double blind, placebo controlled investigation suggested that 0.5 mg supplement to a normal diet was safe with the possible exception of extremely sensitive individuals. Gawrodger et al. (1986) reported that 5/10 women responded to both the 0.4 and 2.5 mg doses of nickel, but 10/26 also reacted to a placebo. They determined the LOAEL of their experiment to be 5.6 mg of nickel, a dose at which 100% of the women responded. Burrows et al. (1981) administered 0.5 mg nickel twice a day on two consecutive days to 22 patients, each of whom served as her own control. There was no significant difference between the number of individuals responding to a placebo as compared to nickel. However, the placebo response was high (12/22). The authors concluded that there is probably no connection between nickel in an ordinary diet and exacerbation of dermatitis but that a higher level may aggravate dermatitis in some individuals.

Nielsen (1989) describes a study in which 12 nickel-sensitive women were challenged for a 4-day period with a diet providing 490 ug Ni/day. No changes were observed before the start of the nickel challenge to day 0 (start of challenge). On day 4, the eczema of 6 patients was considered to be worse according to both the patients' impressions and a dermatologist's evaluation. The delayed reaction in this study may be attributed to the fact that the dose of nickel was ingested in the diet throughout the day as opposed to studies which employed a bolus dose. This difference may greatly affect the pharmacokinetics of ingested nickel.

While the previous studies on humans with a hypersensitivity to nickel were considered in developing the RfD, none of them were adequate to serve as the basis for the quantitative risk assessment. The RfD is believed to be set at a level which would not cause individuals to become sensitized to nickel; however, those who have already developed a hypersensitivity (e.g., from a dermal exposure) may not be fully protected.

One final point to bear in mind in establishing an RfD for nickel is that nickel has been shown to be an essential trace element for several animal species. Rats deprived of nickel exhibit retarded growth and low hemoglobin levels (Schnegg and Kirchgessner, 1977). A requirement for nickel has not been conclusively demonstrated in humans, but nickel is considered to be a normal constituent of the diet. Typical daily intake of nickel ranges from 100-300 ug/day.

I.A.5. Confidence in the Oral RfD

Study — Low
Database — Medium
RfD — Medium

The chronic study (Ambrose et al., 1976) was properly designed and provided adequate toxicological endpoints; however, high mortality occurred in the controls (44/50). Therefore, a low confidence is recommended for the study. The database provided adequate supporting subchronic studies, one by gavage and the other in drinking water (Po animals of the RTI subchronic study, 1986). A medium confidence level in the database is recommended since there are inadequacies in the remaining reproduction data.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 1986, 1991

The information contained in the Quantification of Toxicologic Effects for Nickel was reviewed by the Science Advisory Board in August 1990.

Other EPA Documentation — None

Agency Work Group Review — 04/16/1987, 05/20/1987, 07/16/1987, 05/17/1990, 08/14/1991

Verification Date — 07/16/1987

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Nickel, soluble salts
CASRN — Various

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Nickel, soluble salts
CASRN — Various

The U.S. EPA has not evaluated soluble salts of nickel, as a class of compounds, for potential human carcinogenicity. However, nickel refinery dust and specific nickel compounds - nickel carbonyl and nickel subsulfide - have been evaluated. Summaries of these evaluations are on IRIS.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Nickel, soluble salts
CASRN — Various

VI.A. Oral RfD References

Ambrose, A.M., P.S. Larson, J.R. Borzelleca and G.R. Hennigar, Jr. 1976. Long-term toxicologic assessment of nickel in rats and dogs. J. Food Sci. Technol. 13: 181-187.

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VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Nickel, soluble salts
CASRN — Various

Date	Section	Description
12/01/1991	I.A.4.	Text significantly revised; additional studies added
08/01/1994	II.	Message added
12/10/1998	I., II.	This chemical is being reassessed under the IRIS Program.

VIII. Synonyms

Substance Name — Nickel, soluble salts
CASRN — Various
Last Revised — 09/30/1987

- 7440-02-0
- C.I. 77775
- NICHEL
- Nickel
- Nickel, soluble salts