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Office of Research and Development
Office of Health and Environmental
Assessment
Environmental Criteria and
Assessment Office
Cincinnati OH 45268

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HEALTH EFFECTS ASSESSMENT FOR NICKEL

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with nickel. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Nickel, with Errata for Ambient Water Quality Criteria Documents dated June 9, 1981 (Updated: February 23, 1982). Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-060. NTIS PB 81-11715.

U.S. EPA. 1983a. Health Assessment Document for Nickel. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-83-012A. NTIS PB 83-213827.

U.S. EPA. 1983b. Reportable Quantity for Nickel (and Compounds). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Nickel. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. (Final draft)

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as

previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983c).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Human occupational data indicate that nickel refinery workers experience an elevated incidence of tumors of the nasal cavities and lungs. The specific compounds involved in the etiology of cancer in these workers have not been positively identified; however, nickel carbonyl, nickel sulfate, nitrate and chloride have been implicated. Animal inhalation data indicate an association between certain nickel compounds and lung neoplasms.

The human epidemiological data have been used to calculate a q_1^* of 1.2 $(mg/kg/day)^{-1}$ based on lung and laryngeal tumors in two epidemiological studies. This q_1^* is more conservative than that calculated from the incidence of lung tumors in animals or than that calculated from the incidence of total lung, laryngeal and nasal tumors in the two epidemiological studies.

Evidence is considered inadequate to consider nickel to be carcinogenic by the oral route. An oral AIS of 1.4 mg/day has been estimated based on a 6-week feeding study using rats. An oral AIC of 0.7 mg/day has been estimated based on a 2-year feeding study in rats. There are some uncertainties concerning absorption of nickel from the gastrointestinal tract which are reflected in an additional uncertainty factor. In addition, the toxicity data base is considered limited.

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ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
LOAEL	Lowest-observed-adverse-effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
RNA	Ribonucleic acid
SD	Standard deviation
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Nickel is a metal that belongs to the first transitional series of the periodic table. Elemental nickel has a CAS Registry number of 7440-02-0. In the environment, nickel almost always occurs in the 0 and +2 valence states (Cotton and Wilkinson, 1980). Besides a variety of inorganic compounds, nickel forms a number of complexes with organic ligands. Both inorganic and organic nickel compounds have a variety of uses (Antonses, 1981).

In the atmosphere, nickel is expected to be present as dusts and fumes from nickel smelting and processing facilities, coal burning and diesel oil combustion (Fishbein, 1981). The atmospheric fate of nickel has not been studied comprehensively. Any chemical interaction of nickel compounds in the atmosphere is likely to result in the conversion of nickel to nickel oxide and not its direct removal through decomposition, as frequently occurs with organic compounds. For example, nickel carbonyl is likely to be oxidatively converted to nickel oxide in the atmosphere (U.S. EPA, 1983a). The principal removal mechanisms for atmospheric nickel are wet and dry deposition (Fishbein, 1981). The atmospheric half-life for the physical removal mechanism is expected to depend on the particle size and particle density of atmospheric nickel or its compounds. In one study, enrichment of nickel from coal-fired power plants was found to occur in particulate fractions of diameter <1 μm (U.S. EPA, 1983a). Particulate nickel in such small sizes is expected to have a long lifetime in the atmosphere. No estimate of the atmospheric lifetime for nickel is available.

The aquatic fate of nickel has been studied extensively (Callahan et al., 1979). In most aerobic aquatic environments, nickel may exist in

solution as hydroxide, carbonate, sulfate and organic complexes (Callahan et al., 1979). Some of the nickel in solution may be coprecipitated with hydrous metal oxides or sorbed onto organic material, or it may undergo ion exchange with crystalline minerals. The ratio of the dissolved and precipitated nickel in an aquatic medium may be dependent upon the nature of the medium. In general, it appears that in pristine waters sorption to hydrous iron or manganese oxides controls dissolved nickel concentrations, while in polluted waters a higher concentration of dissolved nickel is expected (Callahan et al., 1979). No estimate of the aquatic half-life of nickel is available in the literature.

The fate of nickel in soil has been studied inadequately; however, the fate may be dependent upon the nature of soil. Soils containing relatively higher proportions of iron and manganese oxides may sorb nickel significantly. Soils rich in organic matter content may enhance the mobility of nickel through complexation. Although nickel has not been detected at appreciable concentration in most groundwaters (Fishbein, 1981), Page (1981) reported the detection of nickel in almost 100% groundwater at a median concentration of 3 ppb.

The BCFs for nickel in aquatic organisms have been determined by several investigators and have been found to vary from <20 for marine plankton to 40,000 in an algae (Callahan et al., 1979). The bioaccumulation factor in edible fish, however, may not exceed 100 (Callahan et al., 1979).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

A number of studies indicate that in animals, 1-10% of the nickel ingested in the diet or in aqueous solution is absorbed by the gastrointestinal tract (Horak and Sunderman, 1973; Nodiya, 1972; Nomoto and Sunderman, 1970; Perry and Perry, 1959; Tedeschi and Sunderman, 1957).

2.2. INHALATION

Nickel can be inhaled either in gaseous form, as nickel carbonyl or in particulate form. Sunderman and Selin (1968) reported that nickel carbonyl was readily absorbed by rats exposed to 100 mg Ni/ℓ air for 15 minutes. Within 4 days after treatment, 26% of the administered dose was excreted in the urine.

On the other hand, particulate nickel in the form of nickel oxide is not readily absorbed by inhalation. Leslie et al. (1976) exposed rats to nickel in welding fumes (8.4 $\mu g/m^3$) and observed no clearance from the lungs or elevation of nickel levels in the blood within 24 hours of treatment.

Similarly, Wehner and Craig (1972) exposed hamsters to nickel oxide particles (2-160 $\mu g/\ell$; 1-2.5 μm mass median aerodynamic diameter) and measured the deposition of nickel in the lungs. Of the 20% of the administered dose deposited in the lungs, 50% remained at 45 days post-treatment. Furthermore, levels of nickel in the tissues did not increase, indicating that absorption was negligible.

In contrast, mice exposed to an aerosol of nickel chloride cleared 75% of the administered dose within 4 days of treatment (Graham et al., 1978), indicating appreciable absorption. The discrepancy between this and the previously mentioned studies can probably be accounted for in terms of the greater solubility of nickel chloride as compared with that of nickel oxide.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Studies pertaining to the subchronic toxicity of orally administered nickel are summarized in Table 3-1.

Whanger (1973) exposed weanling rats to 0, 100, 500 or 1000 ppm nickel (as nickel acetate) in the diet for 6 weeks. Assuming that a weanling rat consumes a quantity of food equivalent to 10% of its body weight/day, these dietary levels can be converted to doses of 0, 10, 50 and 100 mg/kg bw/day. No significant effects were reported at the 10 mg/kg bw/day level, while rats exposed to >50 mg/kg bw/day had hematological changes (decreased hematocrit and hemoglobin concentrations), decreased cytochrome oxidase activity and a reduction in the rate of gain of body weight. A NOEL of 10 mg/kg bw/day can thus be established from these data.

In the subchronic studies by Clary (1975) and Waltschewa et al. (1972), effects (see Table 3-1) were observed in rats exposed to drinking water containing 225 ppm nickel (22.5 mg Ni/kg bw/day, assuming that a rat consumes 0.035 ℓ water/day and weighs 0.35 kg), and in rats treated by gavage with 25 mg Ni/kg bw/day, respectively.

3.1.2. Inhalation. Studies pertaining to the subchronic toxicity of inhaled nickel are summarized in Table 3-2. The salient feature here is that adverse effects (particularly pulmonary effects) were seen at all the levels of exposure (0.04-0.594 mg/kg/day) employed in four different studies (Weischer et al., 1980; Ottolenghi et al., 1974; Bingham et al., 1972; Johansson et al., 1981). The lowest level of exposure that produced effects was reported for rats by Bingham et al. (1972). Unfortunately, these investigators do not report the numbers of animals treated nor the actual length of exposure ("up to several months").

TABLE 3-1

Subchronic Toxicity of Orally Administered Nickel

Species	Number	Vehicle	Compound	Dose	Duration	Effects	References
Weanling rats	24	diet	nickel acetate	100, 500, 1000 ppm Ni	6 weeks	100 ppm, no effects; 500 or 1000 ppm, decreased body weight gain, hematological changes,reduced cytochrome oxidase activity in heart, significantly reduced iron content in red blood cells	Whanger, 1973
Rats	10/group	drinking water	nickel chloride	225 ppm Ni	4 months	Reduced body weight and lower levels of serum lipid and cholesterol at the time of sacrifice	Clary, 1975
Rats	NR	gavage	nickel sulfate	0, 25 mg/Ni/kg bw/day	120 days	Degenerative cellular changes in the liver and kidney, and testicular changes	Waltschewa et al., 1972

NR = Not reported

TABLE 3-2

Subchronic Toxicity of Inhaled Nickel

Species	Number	Compound	Dose as Nickel*	Duration	Effects	References
Rat	NR	nickel oxide	200, 400, 800 μg/m³ (0.148, 0.297, 0.594 mg/kg bw/day)	continuously for 120 days	all levels, decreased kidney weights and growth rates; increased lung weight and urinary alkaline phosphatase activity; severe lung, liver and kidney lesions	Weischer et al., 1980
Rat	120 M and 104 F/group	nickel sulfide dust	0 or 0.97±0.18 mg/m³ (0 or 0.13 mg/kg bw/day)	6 hours/day, 5 days/week for 78 weeks	significantly increased mortality beyond 52 weeks; pulmonary lesions; 28/208 treated animals had tumors as compared with 2/115 controls	Ottolenghi et al., 1974
Rat	NR	nickel oxide	120 μg/m³ (~0.04 mg/kg bw/day)	12 hours/day up to several months	thickening of alveolar walls and respiratory bronchi	Bingham et al., 1972
Rat	NR	nickel chloride	109 μg/m³ (~0.04 mg/kg bw/day)	12 hours/day, 6 days/week up to several months	hyperplastic epithelia	Bingham et al., 1972
Rabbit	6/group	nickel dust	0 or 1.0 mg/m³ (0 or 0.25 mg/kg/day)	6 hours/day, 5 days/week for 6 months	changes in lung macrophage morphology; evidence of pneumonia in all 6 treated rabbits as compared with 1 control	Johansson et al., 1981

*The values in parentheses are calculated by the following equation:

$$\text{dose in mg/kg/day} = \frac{[\text{Concentration in mg/m}^3 \times (\text{hours exposed/24 hours}) \times (\text{days exposed/7 days}) \times (\text{inhalation rate in m}^3\text{/day})]}{\text{the body weight of the animal in kg}}$$

where: inhalation rate = 0.26 m³/day for rats and 1.6 m³/day for rabbits
body weight = 0.35 kg for rats and 1.13 kg for rabbits

NR = Not reported

3.2. CHRONIC

3.2.1. Oral. Two studies regarding the chronic toxicity of orally administered nickel are summarized in Table 3-3. Schroeder et al. (1974) exposed rats to 5 ppm nickel (unspecified compound) in drinking water for life and observed an ultimate reduction in mean body weight ($p<0.025$), compared to controls.

Ambrose et al. (1976) exposed rats to 0, 100, 1000 or 2500 ppm nickel (as nickel sulfate hexahydrate) in the diet (equivalent to 0, 5, 50 and 125 mg/kg bw/day) for 2 years. At levels >1000 ppm (>50 mg/kg/day), effects on body weight and on the ratio of organ-to-body weight were observed. A NOEL was established at 100 ppm (5 mg/kg bw/day). The U.S. EPA (1985) conducted an independent statistical analysis of these data and found the only significant effect to be a lower mean body weight in the 1000 ppm dietary dose group.

In a 3-generation reproductive study, Ambrose et al. (1976) exposed 20 female Wistar-derived rats to 0, 250, 500 or 1000 ppm nickel (as nickel sulfate hexahydrate) in the diet. Assuming that rats consume the equivalent of 5% of their body weight in food/day, these levels can be converted to doses of 0, 12.5, 25 or 50 mg/kg bw/day. At all levels of treatment, a higher incidence of fetal mortality compared with controls was observed in the F_{1a} generation, but not in the F_2 or F_3 generations. Furthermore, weanling body weight was reduced at the highest level of exposure for all generations.

The U.S. EPA (1985) has identified several design limitations including small sample size (17-20 females mated/generation) and use of pups rather than litters as the unit for comparison (the incidence of stillborn pups can be markedly elevated by a single stillborn litter). Furthermore, the

TABLE 3-3

Chronic Toxicity of Orally Administered Nickel

Species	Number	Vehicle	Compound	Dose*	Duration	Effects	References
Rat	52 M and 52 F/group	drinking water	NR	0, 5 ppm Ni (0, 0.5 mg/kg/day)	lifetime	at 18 months mean body weight of treated animals was significantly less ($p<0.025$) than controls; no increased incidence ($p<0.025$) of focal myocardial fibrosis compared with controls.	Schroeder et al., 1974
Rat	25 M and 25 F/group	diet	nickel sulfate hexahydrate	0, 100, 1000, 2500 ppm Ni (0, 5, 50, 125 mg/kg/day)	2 years	100 ppm, no significant effects; 1000 ppm, significant reduction in body weight for females at 6 weeks and >26 weeks ($p<0.05$); 1000-2500 ppm, females had significantly higher heart-to-body weight ratios and significantly lower liver-to-body weight ratios ($p<0.05$) than controls; both males and females had significantly reduced body weight at 2500 ppm.	Ambrose et al., 1976

*Dose values in parentheses were calculated by multiplying the dietary level (ppm) by the fraction of body weight consumed as food/day (0.05 for a rat) OR by multiplying the level in water by the fraction of body weight consumed as water/day (0.035 mL/day ÷ 0.35 kg).

NR = Not reported

results are equivocal and do not clearly define a NOAEL or LOAEL. The incidence of stillborn pups did not exhibit a consistent dose-response relationship, the incidence of stillborn pups in the 250 ppm (12.5 mg Ni/kg bw) groups was increased in the F_{1a} but not the F_{1b} generation and the elevated incidences of stillborn pups observed in the first generation did not occur in the subsequent two generations.

In another 3-generation study, Schroeder and Mitchener (1971) exposed five pairs of Long-Evans BLV(LE) rats to either 0 or 5 ppm nickel (unspecified salt) in drinking water. Assuming that rats consume the equivalent of 10% of their body weight in drinking water/day (0.035 mℓ/day ÷ 0.35 kg), these levels are equivalent to doses of 0 or 0.50 mg/kg bw/day. In all three generations, neonatal mortality was significantly increased compared with controls. Furthermore, the number of runts was significantly increased in the first and third generations. In their review of this study, U.S. EPA (1985) states:

> The ambient water criteria was originally based on this study (U.S. EPA, 1980) but the criterion was subsequently revised because a number of design problems precluded the use of the Schroeder and Mitchener (1971) study for risk assessment purposes (U.S. EPA, 1982). Design problems included small sample size (five females were mated to produce the F_1 generation), use of diets low in trace metals (deficient in chromium) and use of animals rather than litters as the unit for statistical analysis. An attempt was made to duplicate these results, however, the investigators were unsuccessful.

3.2.2. Inhalation. Chronic inhalation data for nickel are summarized in Table 3-4. In both studies (Hueper, 1958; Wehner et al., 1975), severe effects, including death and pathological changes in the respiratory system, were seen at the levels of exposure employed (15 mg/m³ in the Hueper study, 53.2 mg/m³ in the Wehner et al. study). It should be noted that

TABLE 3-4

Chronic Toxicity of Inhaled Nickel

Species	Number	Compound	Dose as Nickel (mg/m^3)	Duration	Effects	References
Guinea pig	32 M, 10 F	nickel (metallic dust)	15	6 hours/day, 5 days/ week for 21 months	early death, pulmonary edema, hyperemia, hemorrhage, liver necrosis	Hueper, 1958
Rat	50 M, 110 F	nickel (metallic dust)	15	6 hours/day, 5 days/ week for 21 months	early death, pleurisy, pneumonia, congestion, edema, bronchiectasis	
Mouse	20 F	nickel (metallic dust)	15	6 hours/day, 5 days/ week for 15 months	early death, hemorrhagic lungs, congested liver	
Hamster	102	nickel oxide	53.2	7 hours/day, 5 days/ week for life	lung lesions (pneumoconiosis), emphysema, early death, bronchial hyperplasia	Wehner et al., 1975

these levels are well above the TLVs recommended by the ACGIH (1983) for metallic nickel (1 mg/m³) or soluble compounds of nickel (0.1 mg/m³) in the workplace.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity of orally administered nickel could not be located in the available literature; however, other reproductive effects associated with oral exposure to nickel have been discussed in Section 3.2.1.

3.3.2. Inhalation. Sunderman et al. (1959) investigated the teratogenicity of nickel carbonyl vapors in Fischer-344 rats. Pregnant rats were exposed to 0.08, 0.16 or 0.30 mg/ℓ nickel carbonyl for 15 minutes on days 7, 8 or 9 of gestation. Pups were either removed from dams on day 20 of gestation or were born naturally. Of those pups born to mothers exposed to 0.30 mg/ℓ nickel carbonyl on day 7 of gestation, 25% had eye malformations. Of the pups delivered by Caesarian section, 64 of 433 had eye malformations. Furthermore, the highest incidence of eye malformations was found in pups removed from dams exposed to 0.30 mg/mℓ on day 7 of gestation. A significant number of anomalies was also seen in fetuses delivered from mothers exposed to 0.16 mg/ℓ on day 7 of gestation. Furthermore, two fetuses of dams exposed to 0.08 mg/ℓ had anomalies (the total number of fetuses was not specified in the secondary source). There were no malformations in fetuses delivered from sham-treated dams or from dams exposed to carbon monoxide. Thus, inhalation of nickel carbonyl produced dose-related teratogenic effects in rats.

3.4. TOXICANT INTERACTIONS

Nickel appears to antagonize the arrhythmias induced by cardiac glycosides such as digitoxin, presumably by competing with calcium at the membrane binding site (Prasad et al., 1980).

Nickel also seems to have a synergistic effect on the carcinogenicity of polycyclic aromatic hydrocarbons (Maenza et al., 1971; Kasprzak et al., 1973), and may also play a role in the carcinogenicity associated with asbestos (NAS, 1975; Morgan et al., 1973) and cigarette smoke (Kreyberg, 1978).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Data pertaining to the carcinogenicity of orally ingested nickel could not be located in the available literature.

4.1.2. Inhalation. A number of studies provide evidence that nickel refinery workers have an increased risk of contracting cancer of the nasal cavities and lungs by inhalation. The nickel compounds implicated in carcinogenesis include nickel subsulfide and nickel oxide dusts; vapors of nickel carbonyl; and soluble aerosols of nickel sulfate, nickel nitrate and nickel chloride (Sunderman, 1977). These cases have been reviewed extensively by numerous authors (NIOSH, 1977; IARC, 1976; NAS, 1975; Sunderman, 1977). Two of these studies (Doll et al., 1977; Pedersen et al., 1973), summarized below, were used by the U.S. EPA Carcinogen Assessment Group in the quantitative assessment of carcinogenic risk (U.S. EPA, 1983a).

An epidemiological study of the increased risk of cancer in a nickel refinery at Clydach, Wales, was reviewed and updated by Doll et al. (1977). At this plant, the Mond refining process for nickel had been used since 1900, and the mortality of the workers was monitored continuously. Between 1900 and about 1930, the concentration of airborne nickel was 20-25 mg Ni/m^3 in areas of high exposure (International Nickel Co., 1976). Workers employed during this period of time had a higher incidence of cancer of the nasal cavities and lungs than would be expected in the general population. After 1925, however, the Clydach plant made basic changes in the refinery process, which resulted in pollution control and a subsequent decrease in exposure to nickel. Concomitantly, a reduction in the number of observed vs. expected cancers of the nasal cavity and lungs was observed among

workers employed in or after 1930. These results are summarized in Table 4-1. As a further note on this study, there has been some speculation that arsenic, a component of the nickel matte feed material, was the causal agent in carcinogenesis. Evidence from a Norwegian study of occupational exposure, however, implicates nickel as the causal agent (Pedersen et al., 1973, 1978; Andersen et al., 1980; Kreyberg, 1978; Torjussen et al., 1979), as does a study by Sutherland (1959), who observed a high incidence of lung cancer in an Ontario nickel refinery where arsenic was not a component of the feed material.

Pedersen et al. (1973) reported on the incidence of lung and nasal cavity cancers among workers employed at a Norwegian nickel refinery. The cohort analyzed (1916 men) had started working at the plant at least 3 years prior to 1961 and were followed through 1971 . The results were similar to those reported for the Clydach workers prior to 1930; the risks of lung cancer and nasal cavity cancer were increased 3.75- and 27-fold, respectively. In a 1980 update (Andersen et al., 1980), 2247 persons were followed from 1953-1979. Among these, there were 21 cancers of the nasal cavities as opposed to the 0.88 expected, and 82 lung cancers as opposed to the 22 expected. In a further analysis of these same data, Kreyberg (1978) reported that exposed workers still had a higher incidence of lung cancer even if cigarette smoking was taken into account. In addition, Torjussen and Andersen (1979) reported finding a higher mean concentration of nickel in the nasal mucosa of nickel workers (279.9$\pm$ SD 412.1) than in controls (12.9$\pm$ SD 20.3). Unfortunately, the variance about the mean is large.

4.2. BIOASSAYS

4.2.1. Oral. Data specifically pertaining to the carcinogenicity of orally administered nickel could not be located in the available literature.

TABLE 4-1

Mortality by Cause and Year of First Employment, Clydach Nickel Refinery, Wales[a]

Year of First Employment	No. of Men	Man-Years of Risk	No. of Deaths From Nasal Sinus Cancer[b]			No. of Deaths From Lung Cancer			No. of Deaths From Other malignant neoplasma			No. of Deaths From Other Diseases		
			O[c]	E[d]	O/E	O[c]	E[d]	O/E	O[c]	E[d]	O/E	O[c]	E[d]	O/E
Before 1910	119	1980.0	14	0.036	389	24	2.389	10.0	10	14.637	0.68	69	84.95	0.81
1910-1914	150	2665.5	24	0.137	649	34	3.267	10.4	10	13.549	0.74	69	75.99	0.91
1915-1919	105	2204.0	11	0.025	440	20	3.070	6.5	10	8.064	1.24	48	44.28	1.08
1920-1924	285	7126.5	7 (1)	0.071	99	50	9.642	5.2	27	20.902	1.29	25	15.63	1.08
1925-1929	103	2678.0	0 (1)	0.026	0	9	3.615	2.5	7	7.247	0.97	44	41.02	1.07
All periods before 1930	762	6655.0	56 (2)	0.195	287	37	1.983	6.2	64	64.399	0.99	55	61.87	0.98
1930-1944	205	4538.5	0	0.034	0	8	5.463	1.5	11	8.786	1.25	58	46.14	1.25

[a]Source: Doll et al., 1977

[b]Number of cases of nasal sinus cancer referred to as an associated cause of death

[c]Observed

[d]Expected

The following discussion of the issue is excerpted from U.S. EPA (1985):

> A number of reviews have discussed the carcinogenicity of nickel compounds (U.S. EPA, 1980; NIOSH, 1977; IARC, 1976; NAS, 1975; Sunderman, 1981, 1979, 1977a, 1976, 1973). It is apparent from these reviews that the chemical form and route of exposure are important factors in determining the carcinogenic potential of nickel. The soluble nickel salts do not generally appear to be carcinogenic, although repeated i.p. injections of nickel acetate at a dose of 360 mg/kg induced lung carcinomas in mice (Stoner et al., 1976).
>
> The results of several oral studies suggest that 5 ppm nickel in drinking water is not carcinogenic to rats and mice (Schroeder et al., 1974; 1964; Schroeder and Mitchener, 1975). Schroeder et al. (1974) exposed a group of 52 male and 52 female weanling Long-Evans rats to 0 or 5 ppm nickel in drinking water for life. The diet for both control and treated groups contained an estimated 0.44 μg Ni/g of food. Assuming the average daily food and water consumption of the rats was ~5% and 7.8% bw, respectively, average daily doses can be calculated as 0.02 and 0.41 mg Ni/kg bw for control and exposed rats, respectively. Tumor incidences were determined after natural death of the experimental animals. Longevity of control and exposed rats was similar. There were no significant differences in tumor incidences (sarcomas, lymphomas or carcinomas) between the exposed and control groups.
>
> In an earlier study with mice, Schroeder et al. (1964) exposed 50 male and 54 female Charles River mice to 5 ppm nickel in drinking water. This is a daily dose of ~0.85 mg Ni/kg bw assuming mice consume water at a rate equivalent to 17% of their bw/day. No estimate of dietary nickel intake was provided, although the investigators stated that it was low. Causes of death were determined at autopsy in 33 and 41 treated females and males, respectively, and 60 female and 44 male controls. The number of deaths from all tumor types was significantly ($p<0.01$) lower in treated females compared with controls. No other statistically significant differences in causes of death or longevity were observed. Early mortality was observed in both the exposed and control groups.

U.S. EPA (1985) concluded that there is insufficient evidence to support the carcinogenicity of nickel via the oral route.

4.2.2. Inhalation. Four carcinogenicity studies involving chronic exposure to nickel compounds via inhalation are summarized in Table 4-2. Hueper (1958) reported that nickel powder was tumorigenic in rats and guinea pigs.

TABLE 4-2

Carcinogenicity Studies Involving Chronic Inhalation Exposure to Nickel

Species/ Strain	Number	Compound	Dose	Duration	Effects	References
Rats/Wistar Rats/ NIH black	50 M, 50 F 60 F	nickel powder (<4 μm in diameter)	15 mg/m³	6 hours/day, 4-5 days/week for up to 21 months	128/160 died within 15 months; 15/50 rats of both strains were found to have adenomatoid lung lesions (benign neoplasms) but no excess of neoplasms in other organs.	Hueper, 1958
Guinea pigs/ NR	32 M, 10 F	nickel powder (<4 μm in diameter)	15 mg/m³	6 hours/day, 4-5 days/week for up to 21 months	23 animals survived >12 months, 2 survived >18 months; At death nearly all animals had abnormal adenomatoid formations in the alveolar and broncheolar epithelia.	
Rats/Wistar	64 M 32 M 41 controls	nickel carbonyl nickel carbonyl	0.03 mg/ℓ 0.06 mg/ℓ	30 minutes, 3 times/ week for 12 months 30 minutes, 3 times/ week for 12 months	All animals were dead within 30 months of the first exposure; 4/9 rats surviving 2 years had lung neoplasms; none of the controls had pulmonary tumors.	Sunderman et al., 1957, 1959
Rats/Wistar	285 M 70 M controls	nickel carbonyl	0.03 mg/ℓ	30 minutes, 3 times/ week until death	8 treated rats survived ≥2 years, of these 1 had a pulmonary adenocarcinomas with metastases; 44 controls survived ≥2 years, none had pulmonary carcinomas.	Sunderman and Donnelly, 1965
Rats/ Fischer 344	226 M and F 241 controls	nickel subsulfide (70% <1 μm in diameter, 25% 1-1.5 μm in diameter)	1 mg/m³ average	6 hours/day, 5 days/week for 78 weeks	Significantly higher number of benign and malignant lung tumors ($p<0.01$) in treated animals (14%) than in controls (1%); treated animals, 10 adenocarcinomas, 3 squamous cell carcinomas, 1 fibrosarcoma; Control animals, 1 adenocarcinoma.	Ottolenghi et al., 1974

NR = Not reported

In studies by Sunderman et al. (1957, 1959) and Sunderman and Donnelly (1965), animals exposed to nickel carbonyl had lung neoplasms, but the numbers of animals examined were small (due to excessive mortality). The study by Ottolenghi et al. (1974) conclusively demonstrated that Fischer rats chronically exposed to 1 mg nickel subsulfide/m^3 developed a significantly higher number of lung tumors ($p<0.01$) than did controls.

Other studies regarding the carcinogenicity of inhaled nickel have been summarized by IARC (1976). These studies either were inconclusive because of confounding factors (Hueper and Payne, 1962), gave negative results (52 µg/NiO/ℓ to hamsters for life) (Wehner, 1974; Wehner et al., 1975) or failed to employ controls (Kasprzak et al., 1973).

These animal bioassays studies indicate that nickel subsulfide, and possibly nickel carbonyl, are carcinogenic to animals (IARC, 1982).

4.3. OTHER RELEVANT DATA

Nickel chloride and nickel sulfate (soluble in water) have been shown to be mutagenic in eukaryotic systems (Miyaki et al., 1979; Amacher and Paillet, 1980; Wulf, 1980). Nickel chloride was not mutagenic in Escherichia coli (Green et al., 1976) or Bacillus subtilis (Kanematsu et al., 1980; Nishioka, 1975).

Nickel compounds have also been shown to inhibit DNA or RNA synthesis (Beach and Sunderman, 1970; Leonard et al., 1981) and have induced DNA breakage and repair in hamster cells in vitro (Robison and Costa, 1982; Robison et al., 1982).

4.4. WEIGHT OF EVIDENCE

IARC (1982) concluded that the evidence for carcinogenicity to humans is limited for nickel and certain nickel compounds, but sufficient for nickel refining.

According to the IARC criteria for evaluating the overall weight of evidence of carcinogenicity to humans, nickel and nickel compounds are classified as Group 2A chemicals, while nickel refining is classified as Group 1 (IARC, 1982). The corresponding classifications using the criteria for evaluating weight of evidence proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) are Group A for nickel refining and Group B2 for nickel and compounds. These classifications are based on occupational and hence inhalation exposure.

The lack of data concerning the oral carcinogenicity of nickel would correspond to an IARC group 3 or a CAG group D.

5. REGULATORY STANDARDS AND CRITERIA

In the June 1981 Errata for Ambient Water Quality Criteria Documents (U.S. EPA, 1980b), a criterion of 632 μg nickel/ℓ water was recommended, based on the study of Ambrose et al. (1976).

The ACGIH (1983) has recommended TLVs for inhalation exposure to nickel and nickel compounds in the workplace. These include a TWA-TLV of 0.35 mg Ni/m³ for nickel carbonyl (to protect from chronic and acute intoxication and to minimize potential carcinogenic effects), a TWA-TLV of 1 mg Ni/m³ for nickel sulfide roasting fumes and dust (with the cautionary note that cancer may be caused at levels below this value), a TWA-TLV of 1 mg/m³ for nickel metal and a TWA-TLV of 0.1 mg/m³ with an STEL of 0.3 mg/m³ for soluble compounds of nickel (based on the observation that soluble compounds of nickel may be carcinogenic while insoluble compounds are not).

NIOSH (1977) has adopted a TLV of 0.007 mg/m³ for nickel carbonyl, based upon its carcinogenic potential.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. As discussed in Section 4.2.1., evidence is currently inadequate to consider nickel carcinogenic by the oral route. Therefore, it is appropriate to develop an AIS. The only subchronic study available which demonstrates a NOEL is a 6-week study in which weanling rats were administered nickel acetate in the diet. The low dose, estimated to be equivalent to 10 mg/kg bw/day, was a NOEL while the mid-dose, estimated to be 50 mg/kg bw/day, resulted in depressed weight gain and hematological changes (Whanger, 1973).

Two other subchronic studies defined effect, but not no-effect levels. Clary (1975) administered 225 ppm nickel in the drinking water to rats for 4 months (estimated 22.5 mg/kg/day). These animals showed reduced body weights as well as lower serum lipid and cholesterol levels. Waltschewa et al. (1972) administered 25 mg Ni/kg bw/day by gavage for 120 days. These animals exhibited degenerative cellular changes in the liver, kidneys and testes.

U.S. EPA (1985) has postulated that various dietary components may retard nickel absorption by the gastronintestinal tract. They have pointed out that this may be a particular concern for human exposures by nickel in drinking water. Since the comparability of nickel absorption by laboratory animals of nickel in feed to human absorption of nickel from water or the human diet is uncertain, they have suggested an additional uncertainty factor of 0.2 be applied when extrapolating from animal dietary exposures.

An AIS can be estimated from the rat NOEL of 10 mg/kg bw/day established in a 6-week feeding study (Whanger, 1973). Multiplying by an assumed human body weight of 70 kg, by 0.2 to account for possible absorption differences

and dividing by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for interindividual variability) results in an AIS of 1.4 mg/day.

6.1.2. Inhalation. Nickel and compounds have been shown to be carcinogenic to humans and data are sufficient for computation of a q_1^*. It is inappropriate, therefore, to calculate an AIS for these chemicals.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. As discussed in Section 4.2.1., evidence is inadequate to consider nickel carcinogenic by the oral route. Therefore, it is appropriate to develop an AIC for oral exposure. As a result of design and statistical deficiencies in the Schroeder and Mitchener (1971) study and the 3-generation portion of the Ambrose et al. (1976) study as discussed in Section 3.2.1., U.S. EPA (1985) has determined that the study of Ambrose et al. (1976) in which rats were administered nickel in the feed for a period of 2 years provides the soundest basis for an AIC estimate. In this study, rats were fed diets containing 0, 100, 1000 or 2500 ppm nickel (estimated to provide doses of 0, 5, 50 and 125 mg/kg bw/day). A reanalysis of the data from this study indicated a significantly lower body weight in the 1000 ppm group (U.S. EPA, 1985). U.S. EPA (1985) considered the reduced body weight to be an adverse effect and chose the 100 ppm dietary dose (5 mg/kg bw/day), designated a NOAEL, as the basis for ADI calculation. Following this precedent, assuming a 70 kg human body weight, multiplying by 0.2 to account for possible absorption differences (see Section 6.1.1.), and dividing by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for interindividual variability) results in an AIC of 0.7 mg/day. This estimate should be reevaluated when more complete data concerning both toxicity and absorption are available.

6.2.2. Inhalation. Nickel and compounds have been shown to be carcinogenic to humans and data are sufficient for computation of a q_1^*. It is inappropriate, therefore, to calculate an AIC for these chemicals.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The lack of data pertaining to the carcinogenicity of orally ingested nickel precludes assessment of carcinogenic risk.

6.3.2. Inhalation. The U.S. EPA (1983a) derived cancer-based risk assessment for human exposure to nickel, based on the animal study of Ottolenghi et al. (1974) and the human epidemiological studies by Doll et al. (1977) and Pedersen et al. (1973).

Based on lifetime exposure to 1 μg nickel sulfide/m³, the upper limit risk calculated from the Ottolenghi et al. (1974) data is 4.8×10^{-3} $(\mu g/m^3)^{-1}$. From the Pedersen et al. (1973) study and the Doll et al. (1977) study, the upper limit lifetime unit carcinogenic risks for lung and nasal cancers were calculated as 6.3×10^{-4} and 8.1×10^{-4} $(\mu g/m^3)^{-1}$, respectively. Taking the geometric mean of these values gives a lifetime unit carcinogenic risk of 7.1×10^{-4} $(\mu g/m^3)^{-1}$ for total lung, larynx and nasal cancers. This is only slightly less than the unit risk calculated from the animal studies (4.8×10^{-3}).

U.S. EPA (1983a) also derived a value for lifetime unit carcinogenic risk, based only on lung and larynx cancers rather than on total lung, larynx and nasal cancers. This was established by taking the midpoint of the range of the geometric mean of the lifetime unit risks from the studies of Pedersen et al. (1973) and Doll et al. (1977) (7.5×10^{-5}, 5.8×10^{-4}).

Assuming a 70 kg man and a human inhalation rate of 20 m^3/day, the mid-point, 3.3×10^{-4} $(\mu g/m^3)^{-1}$, is adjusted to 1.2 $(mg/kg/day)^{-1}$ by the following formula:

$$3.3 \times 10^{-4} (\mu g/m^3)^{-1} \times 70 \text{ kg} \div (20 \text{ m}^3) \times 10^{-3} \text{ mg}/\mu g.$$

A complete discussion of the derivation of q_1^*s from various data bases has been reported in U.S. EPA (1983a).

7. REFERENCES

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APPENDIX

Summary Table for Nickel

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1*	Reference
Inhalation	human	20-25 mg/m³ occupational	nasal, laryngeal and lung tumors	1.2 $(mg/kg/day)^{-1}$	Doll et al., 1977; Pederson et al., 1975; U.S. EPA, 1983a
Oral				ND	

Route	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Oral					
AIS	rat	0, 100, 500, 1000 ppm diet/ 6 weeks (0, 10, 50, 100 mg/kg bw/day)	>50 mg/kg decreased body weight, hematological changes	1.4 mg/day	Whanger, 1973
AIC	rat	0, 100, 1000, 2500 ppm diet/ 2 years (0, 5, 50, 125 mg/kg bw/day)	decreased body weight at 50 mg/kg	0.7 mg/day	Ambrose et al., 1976
Inhalation				ND	

ND = Not derived