Nickel subsulfide; CASRN 12035-72-2

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 subsulfide

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	09/30/1987

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Nickel subsulfide
CASRN — 12035-72-2

Not available at this time.

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

Substance Name — Nickel subsulfide
CASRN — 12035-72-2

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Nickel subsulfide
CASRN — 12035-72-2
Last Revised — 09/30/1987

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — A; human carcinogen

Basis — Increased risks of lung and nasal cancer in humans exposed to nickel refinery dust, most of which was believed to have been nickel subsulfide; increased tumor incidences in animals by several routes of administration in several animal species and strains; and positive results in genotoxicity assays form the basis for this classification.

II.A.2. Human Carcinogenicity Data

Sufficient. The lung and nasal cancer risk seen for nickel subsulfide, a major constituent of nickel refinery dust, is attributable to the formerly high dust and nickel subsulfide levels at sulfide nickel matte refineries. At Copper Cliff and Port Colborne, Ontario, populations showing

elevated lung and nasal cancer worked in what were considered the dustier areas of the refineries. Greatest exposures were to nickel subsulfide, nickel sulfide, nickel oxide, coke particles, and polycyclic aromatic hydrocarbons at Copper Cliff (INCO, Ltd., 1976) and nickel subsulfide, nickel sulfate, and nickel oxide at Port Colborne (Roberts et al., 1982).

Roberts et al. (1982) reported that the calcining/sintering process at Port Colborne was dusty (SMR for lung cancer = 298 and for nasal cancer = 9412) and caused similar exposures to those at the Clydach, Wales calcining sheds (SMR for lung cancer = 510 and for nasal cancer = 26,667) (Peto et al., 1984). Roasting/smelting workers at Kristiansand, Norway were exposed to "dry dust" containing nickel subsulfide and nickel oxide and had the highest risk of nasal cancer (SMR = 4000) and an elevated risk of lung cancer (SMR = 360) (Magnus et al., 1982). The high cancer response in the electrolytic tankhouse workers of this plant (SMR for lung and nasal cancer are 550 and 2600, respectively) is the one apparent contradiction to the hypothesis that the pyrometallurgical process and nickel subsulfide exposures are responsible for the observed cancer increases. In the electrolytic tankhouse, workers are exposed primarily to nickel sulfate, nickel metal, copper and nickel oxides, and nickel chloride. These increases were not observed in the electrolysis operations at Port Colborne (Roberts et al., 1984). In the study of refinery and nonrefinery workers at a nickel refinery in West Virginia, nasal cancer was exclusive to the refinery workers, with an SMR of 2443 (Enterline and Marsh, 1982). No large excess of lung cancer was observed in either refinery (SMR = 118) or nonrefinery (SMR = 107.6) employees. The data do show a dose- response relationship between cumulative nickel exposure and lung cancer response (allowing for a 20-year latent period).

II.A.3. Animal Carcinogenicity Data

Although nickel subsulfide is the most studied nickel compound, only one study has used inhalation as the route of exposure. Ottolenghi et al. (1974) exposed Fischer 344 rats to an airborne nickel subsulfide concentration. The design of the experiment included two sub-treatments in a 2**4 factorial arrangement: a total of 467 rats of both sexes (factor 1) were pre-exposed to nickel subsulfide, 0.97 mg Ni/cu.m, 6 hours/day, 5 days/week, for 1 month (factor 2), and then followed by a second treatment of an intravenous injection with hexachlorotetrafluorobutane (HTFB), an agent used to induce pulmonary infarction (factor 3). The fourth factor was the actual treatment (after the injection factor) with nickel subsulfide for 78 to 80 weeks, followed by 30 weeks of observation before terminal sacrifice. Fewer than 5% of the nickel subsulfide group were alive at the end of 108 weeks, as compared with 31% of the controls. The lungs were the major organ affected by the nickel subsulfide treatment. No differences in response were attributed to sex differences or the injections of HTFB. The lung effects included hyperplasia, metaplasia, adenomas, and adenocarcinomas equally in both males and females. These changes and tumors occurred in both the bronchiolar and alveolar regions of the lung.

Studies comparing species and strain, route of administration, organ sensitivity, and dose-response characteristics of nickel subsulfide carcinogenesis have been performed and reviewed by Sunderman (1984) and Gilman and Yamashiro (1985). While there are definite differences in tumor response between species/strain and route of administration, different experimental conditions among laboratories make cross-comparison difficult. Sunderman (1984) reported a dose-response relationship for tumor induction by nickel subsulfide following intrarenal and intramuscular injections. Numerous studies have shown nickel subsulfide to be a potent carcinogen by injection. All routes of administration have led to positive tumor induction except three: buccal brushing of Syrian golden hamsters, submaxillary implantation into Fischer 344 rats (Sunderman et al., 1978), and intrahepatic injection of Sprague-Dawley rats (Jasmin and Solymoss, 1978) and Fischer 344 rats (Sunderman et al., 1978). Although Kasprzak et al. (1973) reported no pulmonary tumors in Wistar rats given 5 mg nickel subsulfide intratracheally, bronchial metaplasia was increased from 31% to 62% when 5 mg nickel subsulfide was administered with benzpyrene (2 mg). Nickel subsulfide pellets implanted into heterotopic tracheas which were grafted in Fischer 344 rats produced mainly sarcomas with a low yield of carcinomas (Yarita and Nettesheim, 1978).

II.A.4. Supporting Data for Carcinogenicity

Nickel subsulfide induces morphologic transformation in Syrian hamster embryo (Casto et al., 1979) and baby hamster kidney (BHK-21) cell cultures (Hansen and Stern, 1983), sister chromatid exchange in human lymphocytes (Saxholm et al., 1981), and DNA strand breaks (Robison and Costa, 1982). Nickel as nickel subsulfide has been observed to concentrate in the cell nucleus in in vitro assays (Sunderman, 1984).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 4.8E-4 per (ug/cu.m)

Extrapolation Method — Additive and multiplicative

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E-1 ug/cu.m
E-5 (1 in 100,000)	2E-2 ug/cu.m
E-6 (1 in 1,000,000)	2E-3 ug/cu.m

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Estimates of Incremental Unit Risks for Lung Cancer due to Exposure to 1 ug Ni/cu.m for a Lifetime Based on Extrapolations from Epidemiologic Data Sets

Study	Relative Risk Mode
Huntington, WV (Enterline and Marsh, 1982) (maximum likelihood estimates only)	
Refinery workers	1.5E-5 - 3.1E-5
Nonrefinery workers	9.5E-6 - 2.1E-5
Copper Cliff, Ontario (Chovil et al., 1981)	1.1E-5 - 8.9E-5
Clydach, Wales (Peto et al., 1984)	8.1E-5 - 4.6E-4
Kristiansand, Norway (Magnus et al., 1982)	1.9E-5 - 1.9E-4
Midpoint of range for refinery workers	2.4E-4

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

Since nickel subsulfide is a major component of nickel refinery dust and has been shown to produce the highest incidence of tumors for nickel compounds in animals (supported by in vitro studies), the incremental unit risk estimate of nickel refinery dust [2.4E-4 per (ug/cu.m)] may be used with a multiplication factor of 2 to account for the roughly 50% nickel subsulfide composition. If the two observed nasal cancer deaths and expected nasal cancer deaths are included for refinery workers in Huntington, WV, the incremental unit risk increases to 1.3E-4. The average relative risk model was applied to the Huntington, WV and Copper Cliff, Ontario data sets. Data sets from nickel refineries in Huntington, WV (Enterline and Marsh, 1982); Copper Cliff, Ontario (Chovil et al., 1981); Clydach, Wales (Peto et al., 1984); and Kristiansand, Norway (Magnus et al., 1982) provide information available either for choice of model or for separation of risk by the type of nickel exposure. The dose-response data for nasal cancer were not used for risk estimation since nasal cancer risk from nickel is thought to be an occupational hazard associated only with the pyrometallurgical process and is not found in the general public to the same extent as lung tumors.

For the four data sets analyzed, both the additive and multiplicative excess risk models were fitted whenever possible. The relative risk or multiplicative model follows the assumption that the background cause-age- specific rate at any time is increased by an amount proportional to the cumulative dose up to that time. The model assumes the SMR is linearly related to dose and is constant for a set cumulative exposure. Excess mortality for a set cumulative exposure is constant over time, and excess risk remains constant once exposure ceases. The relative risk model differs from the additive risk model in that the latter model assumes that the excess cause-age-specific rate is increased by an amount proportional to the cumulative exposure up to that time.

The unit risk estimates ranged from 2.2E-5 to 9.2E-4 per (ug/cu.m). This is 2 times the incremental unit risk for nickel refinery dust: 1.1E-5 to 4.6E-4 per (ug/cu.m). The midpoint of the range, 4.8E-4 per (ug/cu.m), is taken as the incremental unit risk due to a lifetime exposure to nickel subsulfide.

The unit risk should not be used if the air concentration exceeds 20 ug/cu.m, since above this concentration the unit risk may not be appropriate.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Four data sets, all from human exposure, offer a range of incremental unit risk estimates that are consistent with each other. Upper-limit incremental unit risks for nickel subsulfide exposure

have been estimated from a rat inhalation study (Ottolenghi et al., 1974). They range from 2.7E-3 to 6.1E-3 per (ug/cu.m), with the maximum likelihood estimates ranging from 1.8E-3 to 4.1E-3 per (ug/cu.m). This range is the consequence of a variety of assumptions for species differences using pooled treated animals vs. pooled controls. These estimates are approximately one order of magnitude greater than those obtained from the human studies.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1986

The 1986 Health Assessment Document has received both Agency and external review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 04/01/1987

Verification Date — 04/01/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Nickel subsulfide conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

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).

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

VI. Bibliography

Substance Name — Nickel subsulfide
CASRN — 12035-72-2

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Nickel subsulfide
CASRN — 12035-72-2

Date	Section	Description
12/03/2002	II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Nickel subsulfide
CASRN — 12035-72-2
Last Revised — 09/30/1987

- 12035-72-2
- HEAZLEWOODITE
- Nickel Subsulfide
- NICKEL SUBSULPHIDE
- NICKEL SULFIDE
- alpha-NICKEL SULFIDE (3:2) CRYSTALLINE
- NICKEL SULPHIDE
- NICKEL TRITADISULPHIDE