Selenium sulfide; CASRN 7446-34-6

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 Selenium sulfide

File First On-Line 03/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	03/01/1991

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Selenium sulfide
CASRN — 7446-34-6

Not available at this time.

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

Substance Name — Selenium sulfide
CASRN — 7446-34-6

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Selenium sulfide
CASRN — 7446-34-6
Last Revised — 03/01/1991

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.

NOTE: This assessment is also for selenium disulfide (CASRN 7488-56-4).

II.A. Evidence for Human Carcinogenicity

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

Classification — B2; probable human carcinogen

Basis — Based on inadequate data from human studies and sufficient evidence in animals. When administered orally, selenium sulfide produced hepatocellular carcinomas in both sexes of F344 rats and female B6C3F1 mice and alveolar/bronchiolar carcinomas or adenomas in female B6C3F1 mice.

II.A.2. Human Carcinogenicity Data

Inadequate. Data on the possible carcinogenicity of selenium sulfide in humans are inadequate. Some human data for selenium and various selenium compounds are, however, available. Several investigators have studied the association between serum selenium and the risk of cancer through prospective, case-control and nested case-control studies. Analysis of blood serum levels indicated that patients with cancer, particularly gastrointestinal cancer, prostatic cancer, or Hodgkin's lymphoma, had significantly lower blood selenium levels than healthy patients (Shamberger et al., 1973; Salonen et al., 1984; Kok et al., 1987; Willet et al., 1983; Willet and Stampfer, 1986). The risk of cancer for men (Kok et al., 1987) or for all subjects (Willet et al., 1983) in the lowest quintile of serum selenium was twice that of subjects with higher levels.

Geographic correlational studies have compared cancer mortality in areas of high vs. low levels of naturally occurring selenium. Shamberger and Frost (1969) reported that an inverse relationship existed between cancer death rates and the selenium concentrations in foliage plants of several Canadian provinces. The human cancer death rate in provinces with selenium-containing plants was 122.2 +/- 7.8 (presumably per 100,000 population although this was not specified), while in the provinces devoid of these plants, the human death rate was 139.9 +/- 4.0.

In an ecological study Shamberger and Willis (1971) reported that there was a correlation between decreased cancer death rates in humans and an increase in the selenium in the forage crops in California. In high-selenium areas (selenium 0.11 ppm of forage crops) the cancer death rate per 100,000 was 141.2. In the medium-selenium areas (0.05-0.10 ppm) the cancer death rate was 190.1. In low-selenium areas (0.02-0.05 ppm) the cancer death rate was 233.0. Shamberger and Willis (1971) also investigated the ratio of observed to expected cancer death rates by anatomic site for men in 17 paired cities including high- and low-selenium areas. The anatomic sites that would come into contact with dietary selenium, such as pharynx, esophagus, stomach, bladder and intestine, showed a substantially lower rate ratio in the high- selenium cities than in the low-selenium cities. Other ecological and prospective studies have correlated an increased incidence of colon, breast and other forms of cancer in humans in geographic areas where selenium is deficient and a lowered cancer incidence with higher selenium concentrations (Schrauzer and Ishmael, 1974; Shamberger, 1976; Schrauzer et al., 1976; Jansson et al., 1978; Yang et al., 1983).

In a study of approximately 300 employees exposed to selenium (form not specified) in a rectifier (electronics) process over a 26-year period, only 17 deaths occurred, 6 of which were due to cancer (Glover, 1970). This number, however, is not statistically different from the 5.1 deaths expected based on national mortality rates. The source of the mortality rates was not specified. Several toxic effects including pulmonary irritation, epigastric pain and dermal

irritation and dermatitis were associated with selenium exposure in men, but no carcinogenic effect was reported.

II.A.3. Animal Carcinogenicity Data

Sufficient. NCI (1980a) conducted a bioassay of selenium sulfide on F344 rats and B6C3F1 mice. Selenium sulfide (a mixture of selenium monosulfide and selenium disulfide) in 0.5% aqueous carboxymethyl cellulose was administered by gavage at 3 or 15 mg/kg/day to F344 rats (50/sex/group) 7 days/week for 103 weeks. Survivors were sacrificed at 104-105 weeks. Controls (50/sex/group) consisted of an untreated group and a group receiving the vehicle only.

Body weights were slightly decreased relative to vehicle controls (approximately 10%) in high-dose male and female rats, suggesting an MTD had been achieved. Survival was comparable (approximately 78%) between treated groups and vehicle controls. A significant dose-related trend was seen in the incidence of hepatocellular carcinoma or neoplastic nodules in males and females. A statistically significant increase in the incidence of hepatocellular carcinomas and combined hepatocellular carcinoma or neoplastic nodules was observed in high-dose males and females relative to their respective vehicle controls. In males, incidence of hepatocellular carcinoma was 0/50, 0/50 and 14/49, and the incidence of hepatocellular carcinoma or neoplastic nodules was 1/50, 0/50 and 24/49 for the vehicle control, low-, and high-dose groups, respectively. In females, the incidence of hepatocellular carcinoma was 0/50, 0/50 and 21/50, and the incidence of hepatocellular carcinoma or neoplastic nodules was 1/50, 0/50 and 37/50 for vehicle control, low-, and high-dose groups, respectively.

In male rats, there was a statistically significant dose-related increase in the incidence of lymphoma or leukemia. The incidence in the treated groups was significantly higher than the vehicle-control group; however, the untreated-control group was not included in the statistical analysis, and the incidence of lymphoma or leukemia in untreated controls was 21/49 (43%) compared with 7/50 (14%), 15/50 (30%), and 17/49 (35%) for the vehicle control, low-dose and high-dose groups, respectively. Because the incidence of these tumors was lower in the low- and high-dose groups than in the untreated controls, their occurrence in male rats cannot be clearly related to administration of selenium sulfide.

In male rats, incidence of testicular interstitial-cell tumors showed a statistically significant dose-related trend (41/50, 82% vehicle control; 45/50, 90% low dose; 47/49, 96% high dose) and the elevation in the high-dose group was statistically significant relative to vehicle controls. The untreated control incidence was 42/48 (88%). No historical records for this laboratory in which aqueous carboxymethyl cellulose was used as a vehicle are available for comparison. However, NCI reports that interstitial-cell tumors occur in 75-100% of aged control male F344 rats.

Female rats showed a statistically significant dose-related decrease in pituitary chromophobe adenoma (23/50, 14/49, 11/48).

Selenium sulfide (a mixture of selenium monosulfide and selenium disulfide) in 0.5% aqueous carboxymethyl cellulose was administered at 20 or 100 mg/kg/day by gavage to B6C3F1 mice (50/sex/group) 7 days/week for 103 weeks (NCI, 1980a). Survivors were sacrificed at 104-105 weeks. Controls (50/sex) consisted of an untreated group and a group receiving the vehicle. Body weights and survival of the treated mice were comparable with those of the vehicle control groups, suggesting an MTD may not have been reached. Survival at termination was approximately 60-70% for males and approximately 78-86% for females.

The incidence of alveolar/bronchiolar carcinoma in female mice (0/49, 1/50, 4/49 for control, low-dose and high-dose females, respectively) showed a statistically significant dose-related increase. The incidence of alveolar/bronchiolar carcinomas or adenomas in females also showed a statistically significant dose-related elevation. The incidence in the high- dose group was statistically significantly increased above vehicle controls and untreated controls. Incidence of alveolar/bronchiolar carcinomas or adenomas in the untreated controls, vehicle controls, low-dose, and high-dose groups was 2/50 (4%), 0/49, 3/50 (6%) and 12/49 (24%), respectively. The incidence of these tumors in other vehicle control groups maintained in the same room ranged from 2-12% (selenium sulfide untreated control females were 4%). NCI concluded the lung tumors in female mice were related to administration of selenium sulfide, but there was a high variability of these tumors.

In males, incidence of alveolar/bronchiolar carcinomas or adenomas (4/50, 10/50, 13/50 for control, low-dose and high-dose males, respectively) showed a statistically significant dose-related elevation and was significant in the high-dose group only when compared with the vehicle controls. When compared with the untreated control males (9/48, 18%), the incidence of alveolar/bronchiolar carcinomas or adenomas in treated male mice was not statistically significant. Because it uses a Bonferoni adjustment for pairwise comparisons, which has a more stringent significance criterion, NCI concluded that the incidence of lung tumors in male mice could not be clearly related to selenium sulfide administration.

In male mice, the incidence of lymphoma or leukemia (4/50, 12/50, 8/50 in the control, low- and high-dose groups, respectively) was statistically significantly elevated only in the low-dose group relative to vehicle controls. The incidence of hepatocellular carcinoma alone (15/50, 11/50, 23/50) and when combined with adenomas (15/50, 14/50, 23/50) showed a significant positive trend, but pairwise comparisons were not statistically significant.

Incidence of hepatocellular carcinomas alone or when combined with adenomas showed a statistically significant dose-related increase in female mice. Incidence of hepatocellular

carcinoma alone (0/49, 1/50, 22/49 in the control, low- and high-dose groups, respectively) and hepatocellular carcinoma or adenoma (0/49, 2/50, 25/49) was statistically significantly elevated in the high-dose females relative to vehicle control females.

Because selenium sulfide is used as an antidandruff agent in shampoos, NCI conducted two bioassays to assess possible carcinogenicity by the dermal route. In the first study, a suspension of selenium sulfide in 0.5% aqueous carboxymethyl cellulose was applied to the clipped backs of ICR Swiss mice (50/sex/group) at 0, 0.5 or 1.0 mg/animal three times weekly for 86 weeks (NCI, 1980b). The mice were housed individually. Body weights and mortality were comparable between treated and control mice, although mortality was high in all groups after 52 weeks and the study was terminated after 88 weeks. Survival at termination was approximately 10-20% for all groups. NCI attributed most of the deaths to multiple organ amyloidosis, especially that of the liver, kidney and spleen.

Incidence of alveolar/bronchiolar carcinoma or adenoma in female mice (2/50, 4% control; 4/49, 8% low dose; 8/49, 16% high dose) showed a statistically significant dose-related increase and was elevated in the high- dose animals when compared with vehicle controls. However, the incidence of these tumors in untreated controls (9/49, 18%) was greater than the vehicle control group or the dosed groups. The time-to-tumor onset in the high-dose group was 25 weeks, whereas in the vehicle controls the first tumor was observed at 86 weeks. In female mice a statistically significant dose-related increase was reported in the total hemangiomas or hemangiosarcomas incidence for all sites combined. The incidence was 1/50, 0/50, 1/50 and 4/50 for the untreated, vehicle, low-dose and high-dose groups, respectively. No tumors were found in male mice. While an MTD did not appear to be reached, skin irritation (hyperkeratosis and acanthosis) at the application site suggests higher doses might not have been tolerated. Under the conditions of this bioassay, dermal application of selenium sulfide produced an equivocal carcinogenic effect in ICR Swiss mice, but the study was limited by the relatively short lifespan of this strain of mouse.

In the second bioassay (NCI, 1980c), Selsun shampoo, which contains 2.5% selenium sulfide, was applied to the clipped backs of ICR Swiss mice (50/sex/group). Doses of 0.05 mL of 25% or 50% Selsun in distilled water (0.313 or 0.625 mg selenium sulfide/animal) were applied three times weekly for 86 weeks. Vehicle controls were clipped and treated with distilled water; untreated controls were clipped only. The mice were housed individually. Mean body weights and mortality were comparable between groups, although mortality was high in all groups after 52 weeks and the study was terminated after 88 weeks. Survival at termination was approximately 10-20% for all groups. NCI attributed most of the deaths to multiple organ amyloidosis, especially that of the liver, kidney and spleen.

In male mice, alveolar/bronchiolar carcinomas or adenomas occurred with a significant dose-related trend. Incidences in the high-dose group (9/48, two of which were carcinomas) and in the low-dose group (7/50, all adenomas) were statistically significantly higher than the incidence in the vehicle control group (1/49). The time to observation of the first tumor was 49, 68, 87 and 53 weeks for the high-dose, low-dose, vehicle control and untreated control groups, respectively. NCI concluded that comparison of matched vehicle- control groups with the high-dose group indicates the possibility of an association of the administration of Selsun with the occurrence of lung tumors. However, since alveolar/bronchiolar adenomas have been reported as common tumors in aged Swiss mice, the incidences of these tumors observed among male mice could not be clearly related to dermally-applied Selsun. Tumor incidences in treated female mice were comparable to controls. While an MTD did not appear to be reached, skin irritation (hyperkeratosis and acanthosis) at the application site suggests higher doses might not have been tolerated. The study is limited by the short lifespan of the animals.

II.A.4. Supporting Data for Carcinogenicity

Although selenium sulfide has not been assayed for genotoxicity, other selenium compounds have given conflicting results in genotoxicity assays. These results have been reviewed in U.S. EPA (1989a,b) and in the Selenium and Compounds IRIS assessment.

Selenium is an essential micronutrient for several species, including humans, and is part of several enzymes, such as glutathione peroxidase, an enzyme involved in cellular defense against oxidative damage, and heme oxidase. While low doses of selenium are essential, high doses of selenium or a deficiency of dietary selenium may produce toxicity, such as a carcinogenic response. Under some conditions selenium may be protective against tumor development.

Bioavailability of selenium is dependent on numerous factors, including the intake levels, chemical form and nutritional status. Organic forms of selenium are more bioavailable than inorganic forms; selenates and selenites are the inorganic forms more readily absorbed. Selenium sulfide is less soluble in water than sodium selenate and selenite, but the extent to which selenium sulfide is absorbed dermally or through the gastrointestinal tract has not been fully elucidated (U.S. EPA, 1989b).

Exposure to selenium sulfide is primarily through the use of antidandruff shampoos and pharmaceuticals. The greatest daily exposure to selenium is via food (U.S. EPA, 1989b).

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

Not available.

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

Not available.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1989a,b

The 1989 Health and Environmental Effects Document on Selenium and Compounds has received OHEA review.

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

Agency Work Group Review — 11/09/1989, 03/07/1990, 05/03/1990

Verification Date — 05/03/1990

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 Selenium sulfide conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to 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 — Selenium sulfide
CASRN — 7446-34-6

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 — Selenium sulfide
CASRN — 7446-34-6

Date	Section	Description
03/01/1991	II.	Carcinogenicity assessment on-line
12/03/2002	II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Selenium sulfide
CASRN — 7446-34-6
Last Revised — 03/01/1991

- 7446-34-6
- Selenium sulfide
- HSDB 679
- NCI-C50033
- Selenium monosulfide
- Selenium sulphide
- Selensulfid [German]
- SULFUR SELENIDE
- 7488-56-4
- Selenium sulfide
- Caswell No. 732A
- Disulfure de selenium [French]
- Disulfuro de selenio [Spanish]
- EPA Pesticide Chemical Code 072003
- Exsel
- Seleen
- Selenium disulfide
- Selenium disulphide

- Selsun
- Selsun Blue
- Sulfur selenide
- UN 2657