

Tungsten and Selected Tungsten Compounds

**Tungsten [7440-33-7]
Sodium Tungstate [13472-45-2]
Tungsten Trioxide [1314-35-8]**

Review of Toxicological Literature

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Prepared for

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Executive Summary

Basis for Nomination

Tungsten was nominated in 2002 by the Centers for Disease Control and Prevention's National Center for Environmental Health (NCEH) for toxicology and carcinogenesis studies based on recent data showing elevated tungsten body burdens in residents of Fallon, NV, and the limited data available to assess the potential long-term adverse health effects of tungsten exposure (<http://www.cdc.gov/nceh/clusters/Fallon>). Increased tungsten content in tree core samples in Sierra Vista, AZ, has also recently been reported. Both municipalities have a childhood leukemia cluster and also a nearby military base.

The source and pathways of exposure, and the form of tungsten to which Fallon, NV residents are exposed is currently unknown. This review includes available toxicological information for tungsten metal and selected tungsten compounds. While the major commercial use of tungsten is in the manufacture of cemented tungsten carbide, toxicological data for tungsten carbide is not included in this review.

Nontoxicological Data

Physical-Chemical Properties: Tungsten, also called Wolfram, is a steel-gray to tin-white metal with a high melting point and good electrical conductivity. At ordinary temperatures, tungsten is stable in dry air. At red heat, tungsten forms trioxide. At room temperature, it is attacked by fluorine; at 250-300 °C, it is attacked by chlorine, producing hexachloride in the absence of air and trioxide and oxychloride in the presence of air. Tungsten is oxidized to dioxide by steam but is very stable to acids. It strongly reacts with bromine trifluoride and chlorine trifluoride. With fluorine, the reaction may be luminescent.

Sodium tungstate effloresces in dry air and loses its water at 100 °C. As an aqueous solution, it is slightly alkaline (pH 8-9). When heated to decomposition, it emits toxic fumes of sodium oxide.

Tungsten trioxide reacts violently with chlorofluorine, lithium, and chlorine. With chlorine trifluoride, incandescence occurs.

Chemical Analysis: In air, tungsten can be determined by flame atomic absorption (FAA), inductively coupled plasma atomic emission spectrometry (ICP-AES), and flame atomic adsorption spectroscopy (AAS). In water and air, trace concentrations of tungsten can be estimated by instrumental neutron activation analysis (NAA) using automatic γ -ray spectroscopy. In biological samples, trace amounts of tungsten in the presence of molybdenum can quantitatively be determined using a spectrophotometric method. In urine, tungsten has been determined using inductively coupled plasma-mass spectrometry (ICP-MS).

Commercial Availability: Tungsten is available in technical, powder, single crystal, and ultrapure granule grades. Current U.S. suppliers include Alfa Aesar/Johnson Matthey; Atlantic Equipment Engineers, Division Micron Metals Inc.; Atomergic Chemetals Corporation; CERAC, inc.; GFS Chemicals Inc.; and Optella JSC. Several companies also produce various tungsten compounds. For example, Alfa Aesar/Johnson Matthey supplies tungsten acid, tungsten carbide, tungsten hexacarbonyl, tungsten hexachloride, tungsten hexafluoride, and tungsten trioxide. Corbin Manufacturing and Supply, Inc. provides powdered tungsten in 7000, 35,000, and 70,000 grain dispenser flasks for swaging powdered metal bullets.

Production Processes: Tungsten is produced commercially by the reduction of tungsten trioxide with hydrogen or carbon. It can also be prepared by the aluminothermic reduction of tungsten trioxide, the

hydrogen reduction of tungstic acid or its anhydride, or by the hydrogenation of tungsten trioxide or ammonium paratungstate. Large single crystals are grown by the arc-fusion process, and granules are obtained by the reduction of tungsten hexafluoride. Through the recycling of cemented carbide scrap, tungsten can be converted to the intermediate product ammonium paratungstate, which is then used to produce tungsten carbide powder, tungsten chemicals, or metal powder.

Sodium tungstate can be produced by the reaction of a mixture of soft and hard tungsten carbide with a mixture of sodium nitrate and sodium hydroxide in a fusion process. The dihydrate can be obtained by dissolving tungsten trioxide or the ground ore in sodium hydroxide.

Tungsten trioxide is prepared from sodium tungstate. It can also be produced by the treatment of scheelite ore with hydrochloric acid, yielding ammonium tungstate, which is then ignited to obtain the desired compound. The reaction of tungsten ore concentrates with sodium carbonate gives ammonium paratungstate, which is used to produce tungsten trioxide.

Production and Import Volumes: Production of tungsten has been steadily increasing. In the last five years, secondary production of the metal has been reported as follows (in metric tons): 2930 (1997), 3350 (1998), 4980 (1999), 5120 (2000), and 6000 (estimated; 2001). In contrast, import volumes for consumption have shown the opposite trend (in metric tons)—concentrate: 4850 (1997), 4750 (1998), 2870 (1999), 2370 (2000), and 2400 (estimated; 2001), respectively; import volumes for other forms were as follows: 7980, 8490, 8230, 7810, and 8000 (estimated), respectively.

Uses: Tungsten is used to increase the hardness, toughness, elasticity, and tensile strength of steel. It is used in the manufacture of alloys, in light filaments, in x-ray and electron tubes, in phonograph needles, and in contact points for vehicle, telegraph, radio, and television equipment. Other applications include its use in glass-to-metal seals, metal evaporative work, windings and heating elements, ferrous and nonferrous alloys (e.g., high-speed tool steel), welding electrodes, rocket nozzles and other aerospace applications, shell steel, chemical apparatuses, high-speed rotors (e.g., gyroscopes), solar energy devices, and plating material. Tungsten is also used to prepare green and blue pigments and to make cellulose non-flammable. A more recent use for tungsten is as a substitute for lead in military and recreational ammunition and in products of the sporting goods industry (e.g., golf clubs).

Sodium tungstate is used for fire- and waterproofing fabrics, in the preparation of complex compounds (e.g., phosphotungstate and silicotungstate), as a reagent for biological products, and as a precipitant for alkaloids. It is also used as a catalyst in the oxidation of maleic acid.

Tungsten trioxide is used as pigments in ceramics and as color-resistant mordants for textiles and fireproofing fabrics. It is used to form metals by reduction, in alloys, and in x-ray screens. With iron (iron:tungsten ratio of 1:0.005-0.8), it can reduce nitrogen oxides in exhausts or industrial waste gases.

Environmental Occurrence and Persistence: Tungsten is one of the rarer metals, comprising only about 1.5 ppm of the earth's crust. It occurs naturally as tungstate (WO_4^{2-}). The production and use of tungsten compounds (e.g., as catalysts and dyes) may result in the release of tungsten to the environment through waste streams. Very small amounts of tungsten ($<1.5 \text{ ng/m}^3$ [0.20 ppt]), primarily as tungsten trioxide, have been released into the atmosphere from industrial emissions and nuclear fallout. If released to the air, most tungsten compounds will exist exclusively in the particulate phase in the ambient atmosphere because of their low vapor pressures and can be removed by wet and dry deposition. In urban or suburban areas, the measured air concentrations of tungsten were $<1.5 \text{ } \mu\text{g/m}^3$ [0.20 ppb].

If released to soil, tungsten compounds will have moderate to low mobility based upon sorption coefficients ranging from 10 to 50,000 at pHs 5 to 6.5. Expected to exist as ions or insoluble solids in the

environment, volatilization from moist soil surfaces is not an important fate process. Furthermore, the compounds are not expected to volatilize from dry soil surfaces because of their ionic character and low vapor pressures. In surface soils, tungsten concentrations ranged from 0.68 to 2.7 mg/kg [3.7 to 15 $\mu\text{mol/kg}$]. In plants, levels ranging from <0.001 to 100 mg/kg [5.4 to 544 nmol/kg] dry weight were reported.

If released into water, tungsten compounds will adsorb to suspended solids and sediment. As in soil, volatilization from water surfaces is not an important fate process.

Regulatory Status: The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values are 5 mg/m³ [0.7 ppm] as an eight-hour time-weighted average (TWA) and 10 mg/m³ [1.3 ppm] as a 15-minute short-term exposure limit (STEL) for tungsten metal and for insoluble compounds, as tungsten. For soluble compounds, as tungsten, the values are 1 and 3 mg/m³ [0.1 and 0.4 ppm], respectively. The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) (reported as ten-hour TWAs) is 5 mg/m³ [0.7 ppm] for tungsten and 1 mg/m³ [0.1 ppm] for soluble compounds, as tungsten. The 15-minute STEL is 3 mg/m³ [0.4 ppm] for soluble compounds, as tungsten.

Human Data

Human Exposure: Occupational exposure to tungsten compounds is possible from inhalation of dusts and dermal contact during the production or use of tungsten-containing compounds. In the manufacture of the metal, harmful exposures to related metals in the ore have been mainly to arsenic, antimony, bismuth, copper, lead, manganese, molybdenum, and tin. Although tungsten electrodes are widely used in welding, tungsten is generally not considered in the workers' exposure to heavy metals.

For the general population, exposure to tungsten is possible from ingestion of products containing tungsten or its compounds. For example, beverages such as wine, mineral water, beer, brewed tea, and instant coffee were found to significantly contribute to the total dietary intake of tungsten.

In healthy subjects, serum tungsten concentrations were 6 $\mu\text{g/L}$ [30 nM]; in 14 unexposed persons, the mean tungsten level in urine was 0.21 $\mu\text{g/L}$ [1.1 nM]. The geometric mean of urine concentrations for the U.S. population (n=2338 persons ≥ 6 years old) was 0.085 $\mu\text{g/L}$ (95% confidence interval: 0.077-0.093) (CDC, 2003). For adults, the following tungsten levels have been determined in human tissues and body fluids: 0.25 ppb [14 nmol/kg] in bone, 16 ppb [87 nmol/kg] in hair, 2 ppb [11 nmol/kg] in the heart, <0.7 mg/L [4 μM] in plasma, <0.07 mg/L [0.4 μM] in serum, 26 to 160 ppb [0.14 to 0.87 $\mu\text{mol/kg}$] in skin, 240 ppb [1.31 $\mu\text{mol/kg}$] in tooth enamel, 2600 ppb [14.14 $\mu\text{mol/kg}$] in tooth dentine, and up to 32 μg [0.17 μmol] in urine.

Chemical Disposition, Metabolism, and Toxicokinetics: The daily dietary intake of tungsten is about 0.01 mg [0.05 μmol], while the median for daily urinary excretion is 0.007 mg [0.04 μmol]. Tungsten(VI) is well-absorbed. About 75% of the amount ingested is excreted in the urine. In a limited study with no specific exposure, four healthy young adults eliminated trace quantities of tungsten in urine (2.0-13.0 μg [0.01-0.07 μmol]) and feces (1.6-5.7 μg [8.7-31 nmol]) over 24-hour periods.

Toxicity: No data on occupational exposure to tungsten compounds implicate them as toxic or hazardous. In a powder metallurgy operations plant using tungsten metal, workers chronically exposed to air concentrations of 5 mg/m³ [0.7 ppm] tungsten developed no pneumoconiosis. Tungsten poisoning, however, has occurred after continued exposure to dusts and vapors during the refining of tungsten.

One case of tungsten poisoning has been reported after the accidental ingestion of tungsten. A 19-year-old man who drank 250 mL of a mixture of beer and wine that he had rinsed in a hot gun barrel

experienced nausea, followed by seizures, and then became comatose for 24 hours, showing signs of encephalopathy. Moderate renal failure became an extensive tubular necrosis with anuria by day two. High concentrations of tungsten were found in the drink (1540 mg/L [8.376 mM]), gastric content (8 mg/L [44 μ M]), blood (5 mg/L [27 μ M]), and urine (101 mg/L [549 μ M]). The high levels in blood (>0.005 mg/L [0.03 μ M]) were observed until day 13 despite six hemodialyses, and in urine until day 33. Hair and nails also contained tungsten. The individual fully recovered after five months.

Carcinogenicity: Lung cancer mortality in tungsten metal miners has been associated with silicosis. A more recent study, however, found that the risk of lung cancer decreased inversely to the dust-exposed level, while the rate was not in proportion with the stage of silicosis. The results, therefore, did not support the etiological relationship between silicosis and lung cancer.

Toxicological Data

In 1977, NIOSH published a Criteria Document for tungsten and cemented tungsten carbide (available at URL <http://www.cdc.gov/niosh/77-127.html>; last accessed on September 27, 2002). Toxicity studies (e.g., acute exposure and carcinogenicity) for metallic tungsten and various tungsten compounds, including tungsten trioxide, sodium tungstate, and tungsten chloride, dating as early as 1924, are summarized. Epidemiological studies of workers exposed to dusts of the metal and its products in the cemented tungsten carbide industry are also reported. In 1977, the Permanent Commission and International Association of Occupational Health Subcommittee on the Toxicology of Metals also published a review that included the toxicology of tungsten (Kazantzis, 1977). In this ILS report, studies cited in recent reviews (e.g., Domingo, 2002) are presented.

Elemental tungsten is basically insoluble and as a result is considered to be of low toxicity. Soluble compounds are more toxic than the insoluble forms.

Chemical Disposition, Metabolism, and Toxicokinetics: *Absorption:* When rats were orally administered diets containing tungsten as finely ground metal, sodium tungstate, tungsten trioxide, or ammonium paratungstate (doses not provided) for 100 days, tungsten mainly accumulated in bone and in spleen; trace quantities (<1.0 mg%) were found in the kidney, liver, blood, lung, muscle, and testes.

When beagle dogs were exposed to radioactive 181 tungsten trioxide ($^{181}\text{WO}_3$) mist (98 mCi/mL specific activity for six hours) by inhalation, 60% of the inhaled activity was rapidly deposited in the respiratory tract. During the first ten days, about 33% of the deposited activity entered the systemic circulation; the remaining activity was cleared from the lung via the ciliary escalatory system. In the lung, 69% of the activity was lost, with a biological half-life (BHL) of 4 hours. When given a weak acidic aqueous solution of tungsten trioxide, absorption was 25% in the animals.

In dogs and rats orally administered a solution of sodium tungstate (25 or 50 mg/kg [0.085 or 0.17 mmol/kg]), absorption of tungsten occurred between one and two hours. In beagle dogs, uptake of tungsten was from 57 to 74%. As in dogs, absorption in rats was 40 to 92% when tungsten was administered as tungstate and only 1% when administered as tungstic acid.

Distribution and Retention: *In vivo* experiments using various species, routes of administrations, and compounds showed that a majority of the administered tungsten is rapidly removed from blood. Injection, inhalation, or ingestion of tungsten generally produced higher tungsten levels in the liver compared to other soft tissues, which may be explained by the ability of tungsten to replace molybdenum in certain liver enzymes. The other soft tissues, which accumulate a significant amount of deposited tungsten immediately after entering the blood, eliminate it within a few hours.

When male and pregnant female mice were injected with ^{185}W -tungstate, an increase in tungsten levels was found in the skeleton, kidneys, liver, and spleen; tungsten was then rapidly excreted in urine and feces. Transfer of tungsten from mother to fetus, particularly in late gestation, was also observed. Significant retention of the compound was found in the maternal skeleton, kidneys, and spleen and in the visceral yolk sac epithelium and skeleton of the fetus.

In guinea pigs orally or subcutaneously (s.c.) given sodium tungstate (500 mg [1.70 mmol]), tungsten was detected in the blood and urine, as well as the liver, kidneys, lungs, stomach, and intestines. The lungs and kidneys had maximal radioactivity, whereas other tissues contained only about 10% of the administered dose.

Elimination: Injection or oral administration of tungstate is rapidly eliminated via urine or feces; the former appears to be the major excretion pathway. In rats and dogs, 80-95% is excreted within 24 hours after administration.

Acute Exposure: The intraperitoneal (i.p.) LD₅₀ value of tungsten metal powder in rats is 5 g/kg [0.03 mol/kg]. For tungsten trioxide, an oral LD₅₀ value of 1059 mg/kg [4.568 mmol/kg] has been reported in the animals. Acute toxicity values for sodium tungstate for various routes (oral, intramuscular [i.m.], i.p., intravenous [i.v.], and s.c.) have been calculated for the mouse, rat, guinea pig, and rabbit.

Tungsten: In rats, an i.p. injection of tungsten (5 g/kg [0.03 mol/kg]) caused regional or general vascular dilation, liver damage (not otherwise specified [n.o.s.]), and blood changes (n.o.s.). White rats given a single intratracheal (i.t.) dose of metallic tungsten (50 mg [0.27 mmol]) and sacrificed four, six, or eight months later exhibited a proliferative reaction of the lymphoid and mild fibrosis. In guinea pigs receiving an i.t. suspension of tungsten metal dust (150 mg [0.816 mmol]) as three equal doses and observed for up to one year, focal interstitial pneumonitis and bronchiolitis, focal interstitial infiltration, atrophic emphysema, peribronchial and periarterial fibrocellular reaction, and endarteritis obliteration were observed. When applied to the skin and eyes of rabbits for 24 hours, tungsten (500 mg [2.72 mmol]) was a mild irritant.

Sodium Tungstate: When administered orally or i.v., mice and rats exhibited decreased motor activity and muscle tone, ataxia, palpebral ptosis, hunched back, pallor, prostration, and dyspnea. In both species, i.p. injection of sodium tungstate produced asthenia, adynamia, prostration, coma, and ultimately death. When given s.c. to rats, a severe drop in rectal temperature occurred. When given parenterally, sodium tungstate caused enlargement of the kidneys and adrenals.

In guinea pigs, oral administration or injection of sodium tungstate produced anorexia, colic, confusion, tremors, and dyspnea. When applied directly to the corneal stroma of rabbits, it produced toxic effects in the pH range of 7 to 9. Administered i.m., the compound (105 mg/kg [0.357 mmol/kg]) affected food intake and caused convulsions, hypermotility, and diarrhea in the rabbits.

Tungsten Trioxide: Oral administration of tungsten trioxide (1059 mg/kg [4.568 mmol/kg]) affected the behavior of rats; they exhibited somnolence, excitement, and muscle weakness. A single i.t. injection of tungsten trioxide (50 mg [0.22 mmol]) in white rats produced histological changes in the lung, consisting of proliferative reaction of the lymphoid and histiocytic element and eventually mild fibrosis. The walls of small vessels became thick, while their endothelium became swollen.

Short-term and Subchronic Exposure: *Tungsten:* In weanling rats fed tungsten metal powder at concentrations of 2, 5, and 10% of the diet for 70 days, no effect on the growth rate was observed in male rats. In females, however, a 15% reduction in weight gain was reported.

Sodium Tungstate: Sodium tungstate (equivalent to 2% tungsten) orally administered to young rats caused the deaths of all animals within ten days. When diets were reduced to contain an equivalent of 0.5% tungsten, death occurred in 75% of rats by the end of the 70-day exposure period. When given by gavage or in drinking water to young rats, sodium tungstate (15-1000 mg/kg [0.051-3.403 mmol/kg] per day) for four or 13 weeks produced emesis, anorexia, cachexia, pallor, and dyspnea. At the high dose, levels of urea, creatinine, and total cholesterol were increased, while erythrocyte count and glucose, AST/ALT, protein, hematocrit, and hemoglobin levels were decreased; all parameters returned to normal after a recovery period of six weeks.

Tungsten Trioxide: Inhalation of tungsten trioxide (490 $\mu\text{g}/\text{m}^3$ [51.7 ppb]) for 24 hours a day for 15 continuous weeks produced impairment in liver function tests, changes in true cholinesterase, and changes in leukocyte count. Oral administration of tungsten trioxide (equivalent to 3.96% tungsten) was significantly toxic, causing initial weight loss and then death in all animals within ten days. In diets having an equivalency of 0.5% tungsten, the compound caused deaths in 75% of rats by the end of the 70-day exposure period.

Chronic Exposure:

Sodium Tungstate: In Long Evans rats, sodium tungstate (5 ppm [0.02 mmol/kg]) in the drinking water for a lifetime significantly reduced longevity in males. In male Wistar rats, daily oral administration of the compound (<150 mg/kg [0.511 mmol/kg] body weight [bw]) for up to 300 days produced no significant effects on body and organ weights, nor on survival. When administered orally for 30 weeks intermittently, sodium tungstate (106 mg/kg [0.361 mmol/kg]) caused alterations of classical conditioning in the animals. Inhalation of the compound (504 $\mu\text{g}/\text{m}^3$ [41.9 ppb]) for 24 hours per day for 17 continuous weeks resulted in changes in blood (n.o.s.), true cholinesterase, and other protein levels.

In rabbits, oral administration of sodium tungstate (1214 mg/kg [4.132 mmol/kg]) for 35 weeks intermittently caused biochemical changes in true cholinesterase and phosphatases.

Synergistic/Antagonistic Effects: In mammals, tungsten has been found capable of serving as a substitute for molybdenum in enzymes. In studies with rats, chickens, goats, and cows, tungsten was an antagonist toward molybdenum; it decreased sulfite and xanthine oxidase activities and hepatic molybdenum levels. Its ability to activate brain glutaminase and inactivate liver glutaminase shows that it can act at more than one enzyme site. Tungstate, like molybdate, can also replace phosphate in bone. At 5 ppm [0.02 mmol/kg], it can reduce the toxic effects of selenium.

Small doses of the metals tungsten, molybdenum, nickel, lead, and copper in drinking water can cause nonspecific changes in metabolic processes. When rats were given tungsten in drinking water at an effective dose (ED) for six months, molybdenum and copper decreased in bone tissue and kidneys; at a threshold dose (TD), both elements increased in bone tissue. With molybdenum at ED, tungsten decreased in the liver, kidneys, and blood.

Cytotoxicity: In *in vitro* assays using murine embryonic cells, tungstate inhibited cartilage production in limb bud mesenchymal cultures at concentrations similar to those found *in vivo*.

Reproductive and Teratological Effects: *Tungsten:* In female rats, oral administration of tungsten (1210 $\mu\text{g}/\text{kg}$ [6.581 $\mu\text{mol}/\text{kg}$; TL_{Lo}]) for 35 weeks before pregnancy resulted in post-implantation mortality (e.g., dead and/or resorbed implants per total number of implants) and developmental abnormalities in the musculoskeletal system. When tungsten (1150 $\mu\text{g}/\text{kg}$ [6.255 $\mu\text{mol}/\text{kg}$; TL_{Lo}]) was administered 30 weeks before pregnancy and on days 1 through 20 of pregnancy, only the latter effects were seen.

Sodium Tungstate: In mice, a single dose of sodium tungstate (concentration not specified) given at early organogenesis produced a high frequency of resorptions but did not induce any fetal malformations.

In male rats, inhalation of sodium tungstate ($504 \mu\text{g}/\text{m}^3$ [41.9 ppb]) for 24 hours a day for 17 weeks affected spermatogenesis. In pregnant rats, tungstate inhibited the production of xanthine oxidase, and high doses (not specified) caused death in fetuses. When administered to pregnant rats at doses that did not produce maternal toxicity (not specified), sodium tungstate increased embryonal lethality and inhibited bone ossification in fetuses. In embryonic rat calvaria, sodium tungstate (0.1 mM [29 $\mu\text{g}/\text{mL}$]) had no effect on collagen synthesis.

Carcinogenicity: When administered in the drinking water for a lifetime, sodium tungstate (5 ppm [0.02 mmol/kg]) produced tumors in four of 25 (16%) male rats and in 13 of 20 (65%) female rats. The numbers of malignant tumors were two and five, respectively.

Initiation/Promotion Studies: *Tungsten*: When male Sprague-Dawley rats were administered benzo[*a*]pyrene (BaP) simultaneously with systemic sulfite (drinking solution containing tungsten [0, 100, or 400 ppm; 0, 0.544, or 2.18 mmol/kg] plus sodium molybdate), deaths from pulmonary squamous cell carcinoma was not significantly different from controls. A slight nonsignificant increase in mammary tumors occurred in rats treated with tungsten; however, the data did not support a co-carcinogenic role for sulfite with BaP-induced cancer.

In another study, rats given tungsten (200 ppm [1.99 mmol/kg]) in the drinking water for 19 weeks with *N*-nitrososarcosine ethyl ester (NSEE) had more hyperplastic and precancerous lesions than animals not receiving tungsten.

Sodium Tungstate: In Sprague-Dawley female rats administered *N*-methyl-*N*-nitrosourea (MNU), oral pretreatment with sodium tungstate [13472-45-2] (150 ppm [0.511 mmol/kg] in drinking water daily for 140 or 213 days beginning 15 days before carcinogen treatment) did not cause significant multiplicity in papillary carcinomas in mammary glands. At 140 days, a significant incidence of carcinomas was observed. In a similar study, sodium tungstate [11120-01-7] (150 ppm [0.511 mmol/kg] in drinking water daily for 198 days beginning at 35-days-old) produced a significant incidence of MNU-induced mammary carcinomas at 125 days.

In Sprague-Dawley male rats administered NSEE, oral pretreatment with sodium tungstate (100 ppm [0.340 mmol/kg] in drinking water daily for 19 or 30 weeks beginning 21 days before carcinogen treatment) did not induce a significant incidence of carcinoma in the esophagus or the forestomach.

Genotoxicity: *Sodium Tungstate*: In *Saccharomyces cerevisiae*, sodium tungstate (100 mmol/L [29.4 mg/mL]) produced gene conversion, mitotic recombination, and sex chromosome loss and nondisjunction. In *Escherichia coli*, the compound (5 mmol/L [1 mg/mL]) caused phage inhibition capacity. In Syrian hamster embryo cells, sodium tungstate did not induce morphological transformation, sister chromatid exchange (SCE), or chromosome aberration (CA); the latter two were also not seen in human lymphocytes.

In *S. cerevisiae*, sodium tungstate dihydrate [10213-10-2] (dose[s] not provided) induced disomic and diploid meiotic products. In a test for SCE in human lymphocytes, no conclusion could be made regarding its mutagenicity.

Tungsten Alloys: Tungsten alloys used in military projectiles were genotoxic in SCE, micronuclei, and alkaline filter elution assays. Like depleted uranium (DU) compounds, they were neoplastic transforming

agents but at a lower frequency, suggesting a possible relationship between long-term exposure and the development of neoplastic disease.

Other Data: When orally administered to streptozotocin (STZ)-induced diabetic rats, sodium tungstate (0.7 mg/mL [2 mM] for the first three weeks and then 2 mg/mL [7 mM] for the remainder of the eight-month treatment period) in the drinking water decreased serum glucose levels, restored pyruvate kinase activity and fructose 2,6-bisphosphate concentrations, prevented diabetes-induced morphological changes in the kidney and ocular lens, and reduced mortality. Additionally, because no hypoglycemic episodes or undesirable side effects were noted in both the treated diabetic or healthy rats, the results support the possible use of tungstate as a long-term treatment of diabetes mellitus. When administered to Zucker diabetic fatty (ZDF) rats with moderate hyperglycemia, sodium tungstate (dose[s] not provided) caused the animals to become normoglycemic for about ten days before glycemia began to rise again, stabilizing at ~200 mg/dL.

Additionally, sodium tungstate may be useful in the treatment of diet-induced obesity. When diet-induced obese Wistar rats were given sodium tungstate (2 g/L [7 mM]) in the drinking water for 32 days, body weight gain was significantly decreased, as was triglyceride, free fatty acid, and insulin plasma levels. No toxic effects were observed. The animals quickly gained body weight during a recovery period of 35 days.

In male Wistar rats, sodium tungstate exerted radioprotective effects on hematopoietic injury caused by exposure to ⁶⁰cobalt γ -rays.

When rats were exposed to tungsten trioxide (0.25 mg/m³ [0.026 ppm] [5 km from nonferrous-metal works] or 0.46 mg/m³ [0.049 ppm] [500 m from the works]) for 135 days, the number of reticulocytes was increased, blood histamine was decreased, fluctuations in the urinary elimination of hippuric acid were seen, and porphyrin metabolism was disturbed in a dose-dependent manner. At 500 m from the works, the numbers of leukocytes and segmented-nucleus neutrophils were increased, while the numbers of lymphocytes and thrombocytes were decreased. Additionally, the relative weights of the kidneys and spleen were decreased, blood cholinesterase was inhibited, and coproporphyrin elimination was lowered.

Structure-Activity Relationships

Tungsten Hexachloride [13283-01-7]

In Syrian hamster embryo (SA7/SHE) cells, tungsten hexachloride was not mutagenic.

Tungstoantimonic acid, ammonium salt [59372-48-4]

In Syrian hamster embryo (SA7/SHE) cells, tungstoantimonic acid, ammonium salt induced cell transformation and viral enhancement.

Ammonium 21-tungsto-9-antimonate (Antimoniotungstate; HPA-23) [89899-81-0]

The antiviral activity of HPA-23 has been demonstrated in mice; administered via the i.p. route, the LD₅₀ value is 750 mg/kg. It has also exhibited *in vitro* inhibition of the rabies virus. The drug has been proposed for use as an AIDS vaccine. After i.v. injection of various doses of the drug in the rat, high amounts were found in the lysosomes and localized in the macrophages of different tissues—thymus, spleen, and bone marrow. The tungsten to antimony ratio was identical in each macrophage.

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1.0 Basis for Nomination

Tungsten was nominated in 2002 by the Centers for Disease Control and Prevention's National Center for Environmental Health (NCEH) for toxicology and carcinogenesis studies based on recent data showing elevated tungsten body burdens in residents of Fallon, NV, and the limited data available to assess the potential long-term adverse health effects of tungsten exposure (<http://www.cdc.gov/nceh/clusters/Fallon/>). Increased tungsten content in tree core samples in Sierra Vista, AZ, has also recently been reported. Both municipalities have a childhood leukemia cluster and also a nearby military base (AP, 2002).

The source and pathways of exposure, and the form of tungsten to which Fallon, NV residents are exposed is not currently known. This review includes available toxicological information for tungsten metal and selected tungsten compounds. While the major commercial use of tungsten is in the manufacture of cemented tungsten carbide, toxicological data for tungsten carbide is not included in this review.

2.0 Introduction

Few toxicological studies have been conducted on tungsten and tungsten compounds. While epidemiological surveys and other studies have been conducted on tungsten-carbide, which usually contains cobalt in cemented form, these are not presented in this report. A brief summary, however, is available in "Cobalt Dust [7440-48-4]—Review of Toxicological Literature," prepared by ILS, Inc. in February 2002 (available at Internet address: http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPdf/cobaltdust.pdf).

The majority of toxicological data included in this report are studies with tungsten metal powder, sodium tungstate, and tungsten trioxide. Limited data for tungsten hexachloride, the ammonium salt of tungstoantimonic acid, and antimoniotungstate are presented in Section 10.0.

2.1 Chemical Identification and Analysis

2.1.1 Tungsten [7440-33-7]

Tungsten ([W]; mol. wt. = 183.85) is also called Wolfram (Budavari, 1996). In air, tungsten can be determined by flame atomic absorption (FAA; NIOSH Method 7074); the detection limit is 0.050 mg/m³ (soluble). Inductively coupled plasma atomic emission spectrometry (ICP-AES) analysis can also be used (Environmental Protection Agency equivalent air depth [EPA EAD] Method 1620-D); the range is from 5 to 2000 µg/m³ and the detection limit is 1.0 mg/L. Flame atomic adsorption spectroscopy (AAS) analysis can be used for the determination for soluble tungsten (range 0.14-6.8 mg/m³) and insoluble tungsten (0.35-17.4 mg/m³) in air. A membrane filter is used for the collection of soluble tungsten, while acid ash is used for the insoluble form (HSDB, 2002c). Using the epiphytic lichen *Hypogymnia physodes* (L.) Nyl., information about element levels in the atmosphere, including tungsten, and identification of significant pollution sources have been obtained (Jeran et al., 1996).

In water and air, trace concentrations of tungsten can be estimated by instrumental neutron activation analysis (NAA) using automatic γ -ray spectroscopy. In biological samples, trace amounts of tungsten in the presence of molybdenum can quantitatively be determined using a spectrophotometric method (HSDB, 2002c). In urine, tungsten has been determined using inductively coupled plasma-mass spectrometry (ICP-MS) (Schramel et al., 1997).

2.1.2 Sodium Tungstate [13472-45-2]

Sodium tungstate ($[\text{Na}_2\text{WO}_4]$; mol. wt. = 293.82) is also called:

Tungstate (WO_4^{2-}), disodium, (T-4) (9CI)
 Disodium tetraoxatungstate (2-)
 Disodium tetraoxotungstate (2-)
 Disodium tungstate
 Sodium tungstate(VI)
 Sodium tungsten oxide
 Sodium wolframate
 Tungstic acid, disodium salt

Sources: HSDB (2002a); RTECS (2002d)

2.1.3 Tungsten Trioxide [1314-35-8]

Tungsten trioxide ($[\text{WO}_3]$; mol. wt. = 231.85) is also called:

C.I. 77901
 Tungsten blue
 Tungsten oxide
 Tungsten(VI) oxide
 Tungstic acid
 Tungstic acid anhydride
 Tungstic anhydride
 Tungstic oxide
 Wolframic acid, anhydride

Sources: HSDB (2002d); RTECS (2002c)

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
<i>Tungsten</i>		
Physical State	steel-gray to tin-white metal; gray-black crystalline form	Budavari (1996); HSDB (2002b)
Boiling Point ($^{\circ}\text{C}$) @760 mm Hg	5900	Budavari (1996)
Melting Point ($^{\circ}\text{C}$)	3410	Budavari (1996)
Density (g/cm^3 at $20^{\circ}\text{C}/4^{\circ}\text{C}$)	18.7-19.3	Budavari (1996)
Vapor Pressure (mm Hg @2327 $^{\circ}\text{C}$)	1.97×10^{-7}	Budavari (1996)
Heat of Vaporization (cal/g)	1150	HSDB (2002b)
Soluble in:	mixture of hydrofluoric acid and nitric acid; fused potassium hydroxide in air; fused sodium carbonate in air; fused mixture of sodium hydroxide and nitrate	Budavari (1996); HSDB (2002b)
Insoluble in:	water, potassium hydroxide, and hydrofluoric acid	Langård (2001)
<i>Sodium Tungstate</i>		
Physical State	colorless crystals; white, crystalline powder	Budavari (1996)
Melting Point ($^{\circ}\text{C}$)	698	HSDB (2002a)
Specific Gravity (g/cm^3)	4.179	HSDB (2002a)

Water Solubility	1.1 parts water	Budavari (1996)
Insoluble in:	alcohol and acid (dihydrate)	Budavari (1996); HSDB (2002a)
Property	Information	Reference(s)
<i>Tungsten Trioxide</i>		
Physical State	canary yellow, heavy powder; dark orange, when heated	Budavari (1996)
Melting Point (°C)	1473	Langård (2001)
Specific Gravity (g/cm ³)	7.16	Langård (2001)
Soluble in:	hydrofluoric acid and hot alkalies	Budavari (1996); Langård (2001)
Insoluble in:	water and acids	Budavari 91996); Langård (2001)

Tungsten

The naturally occurring isotopes of tungsten are 180 (0.135%), 182 (26.4%), 183 (14.4%), 184 (30.6%), and 186 (28.4%). The artificial radioactive isotopes are 173-179, 181, 185, and 187-189 (Budavari, 1996). Elemental tungsten is a good electrical conductor (HSDB, 2002b).

At ordinary temperatures, tungsten is stable in dry air. At red heat, tungsten forms trioxide. At room temperature, it is attacked by fluorine; at 250-300 °C, it is attacked by chlorine, producing hexachloride in the absence of air and trioxide and oxychloride in the presence of air. Although not attacked by water, tungsten is oxidized to dioxide by steam. It is very stable to acids but is attacked superficially by concentrated nitric acid or aqua regia (Budavari, 1996).

Tungsten strongly reacts with bromine trifluoride and chlorine trifluoride. With fluorine, the reaction may be luminescent. Additionally, tungsten is corroded by seawater (HSDB, 2002b). Under certain conditions, powdered tungsten can be pyrophoric (Budavari, 1996).

Sodium Tungstate

Sodium tungstate effloresces in dry air and loses its water at 100 °C. As an aqueous solution, it is slightly alkaline (pH 8-9) (Budavari, 1996). When heated to decomposition, it emits toxic fumes of sodium oxide (HSDB, 2002a).

Tungsten Trioxide

Tungsten trioxide reacts violently with chlorofluorine, lithium, and chlorine. With chlorine trifluoride, incandescence occurs (HSDB, 2002d).

2.3 Commercial Availability

Tungsten

Tungsten is available in technical, powder, single crystal, and ultrapure (50-600 U) granule grades (HSDB, 2002b). In 2000, major U.S. processors of tungsten materials were Allegheny Technologies Inc.'s Metalworking Products business (Huntsville, AL), General Electric Co. (Euclid, OH), Kennametal Inc. (Latrobe, PA, and Fallon, NV), OM Group, Inc. (Midland, MI, and St. George, UT), and Osram Sylvania Inc. (Towanda, PA) (Shedd, 2000). Suppliers listed for the 2002 year in *Chemyclopedia* include Alfa Aesar/Johnson Matthey; Atlantic Equipment Engineers, Division Micron Metals Inc.; Atomergic Chemetals Corporation; CERAC, inc.; GFS Chemicals Inc.; and Optella JSC (Block, 2001).

Corbin supplies powdered tungsten in 7000, 35,000, and 70,000 grain dispenser flasks for swaging powdered metal bullets (Corbin Manufacturing and Supply, Inc., 1999).

Tungsten Compounds

Sodium tungstate dihydrate is commercially available in technical, CP (chemically pure), or crystalline grades (HSDB, 2002a).

Alfa Aesar/Johnson Matthey supplies tungsten acid, tungsten carbide, tungsten hexacarbonyl, tungsten hexachloride, tungsten hexafluoride, and tungsten trioxide. Other suppliers of tungsten acid include Pechiney World Trade. Other suppliers of tungsten carbide are CERAC, inc. and OMG, Americas (OH). OMG, Americas (NC) produces tungsten carbide powders. ATMI, Inc., Gelest Inc., and Strem Chemicals Inc. make available tungsten hexacarbonyl. Suppliers of tungsten hexachloride include Noah Technologies Corporation and Strem Chemicals Inc. Suppliers of tungsten hexafluoride are Air Products and Chemicals Inc., Central Glass International Inc., and CERAC, inc. Other producers of tungsten trioxide are CERAC, inc. and Pechiney World Trade (Block, 2001).

A search on the Thomas Register found 148 industries using or producing tungsten products [Noted: The list is not all-inclusive.] (Thomas Register, 2002).

3.0 Production Processes

Tungsten

Tungsten is produced commercially by the reduction of tungsten trioxide with hydrogen or carbon. It can also be prepared by the aluminothermic reduction of tungsten trioxide, the hydrogen reduction of tungstic acid or its anhydride, or by the hydrogenation of tungsten trioxide or ammonium paratungstate. Large single crystals are grown by the arc-fusion process, and granules are obtained by the reduction of tungsten hexafluoride (HSDB, 2002b).

Through the recycling of cemented carbide scrap, tungsten can be converted to the intermediate product ammonium paratungstate, which is then used to produce tungsten carbide powder, chemicals, or metal powder. Cobalt is recovered separately (USGS, 2000).

Sodium Tungstate

Sodium tungstate can be produced by the reaction of a mixture of soft and hard tungsten carbide with a mixture of sodium nitrate and sodium hydroxide in a fusion process. The dihydrate can be obtained by dissolving tungsten trioxide or the ground ore in sodium hydroxide (HSDB, 2002a).

Tungsten Trioxide

Tungsten trioxide is prepared from sodium tungstate. It can also be produced by the treatment of scheelite ore with hydrochloric acid, yielding ammonium tungstate, which is then ignited to obtain the desired compound. The reaction of tungsten ore concentrates with sodium carbonate gives ammonium paratungstate, which is used to produce tungsten trioxide (HSDB, 2002d).

4.0 Production and Import Volumes

Tungsten

Production of tungsten has been steadily increasing. In the last five years, secondary production of the metal has been reported as follows (in metric tons): 2930 (1997), 3350 (1998), 4980 (1999), 5120 (2000), and 6000 (estimated; 2001). In contrast, import volumes for consumption

have shown the opposite trend (in metric tons)—concentrate: 4850 (1997), 4750 (1998), 2870 (1999), 2370 (2000), and 2400 (estimated; 2001), respectively; import volumes for other forms were as follows: 7980, 8490, 8230, 7810, and 8000 (estimated), respectively. Last year, eight U.S. companies were reported as processing tungsten concentrates, ammonium paratungstate, tungsten trioxide, and/or scrap to make tungsten powder, tungsten carbide powder, and/or tungsten chemicals (Shedd, 2002).

From 1999 to 2000, total tungsten content of U.S. imports decreased by 8%. China continued to be the largest supplier of imported tungsten with 36% ammonium paratungstate, 25% tungsten oxides, 14% concentrates, 8% ferrotungsten, 5% tungsten metal powders, 5% tungsten waste and scrap, 3% tungsten carbide powder, and the rest being calcium tungstate, other tungstate, unwrought tungsten, and wrought tungsten. Imports of calcium tungstate, other tungsten chemicals, tungsten carbide powder, tungsten metal powders, unwrought tungsten, and wrought tungsten increased from the previous year, while those of ferrotungsten, other tungstates, tungsten chloride, and tungsten waste and scrap decreased; oxides remained moderately unchanged (Shedd, 2000).

Sodium Tungstate

The only data available for sodium tungstate was the amount imported to the United States in 1976, which was 1.59×10^7 g (35,060 pounds) (HSDB, 2002a).

5.0 Uses

Tungsten

Tungsten is used to increase the hardness, toughness, elasticity, and tensile strength of steel. It is used in the manufacture of alloys, in light filaments, in x-ray and electron tubes, in phonograph needles, and in contact points for vehicle, telegraph, radio, and television equipment (Budavari, 1996). Other applications include its use in glass-to-metal seals, metal evaporative work, windings and heating elements (in furnaces and vacuum-metallizing equipment), ferrous and nonferrous alloys (e.g., high-speed tool steel), welding electrodes, rocket nozzles and other aerospace applications, shell steel, chemical apparatuses, high-speed rotors (e.g., gyroscopes), solar energy devices, and plating material. Tungsten is also used to prepare green and blue pigments and to make cellulose non-flammable (HSDB, 2002b).

A more recent use for tungsten is as a substitute for lead in military and recreational ammunition and in products of the sporting goods industry (e.g., golf clubs). It is predicted that the use of tungsten to produce 5.56 mm "green ammunition" will grow from nearly zero in 2000 to between 450 and 800 metric tons in 2005 (Shedd, 2000). In 1989, the U.S. Navy switched from depleted-uranium (DU) bullets to tungsten munitions in its Phalanx weapons system. Tungsten's costliness and reduced effectiveness compared to DU, however, keep it from completely replacing the latter in the military (Peterson, 1999, 2001). Currently, 200 million tungsten bullets are produced annually, using an ounce of tungsten each (> 5500 tons) (ITIA, 2001). The U.S. Fish and Wildlife Service has proposed to approve tungsten (65%)-iron-nickel-tin (TINT) shot as nontoxic for hunting waterfowl and coots; currently, tungsten-iron, tungsten-polymer, tungsten-matrix, and tungsten-nickel-iron shot are approved for use (U.S. EPA, 2002a).

Sodium Tungstate

Sodium tungstate is used for fire- and waterproofing fabrics, in the preparation of complex compounds (e.g., phosphotungstate and silicotungstate), as a reagent for biological products, and as a precipitant for alkaloids (Budavari, 1996). It is also used as a catalyst in the oxidation of maleic acid (HSDB, 2002a).

Tungsten Trioxide

Tungsten trioxide is used as pigments in ceramics and as color-resistant mordants for textiles and fireproofing fabrics (Langård, 2001). It is used to form metals by reduction, in alloys, and in x-ray screens. With iron (iron:tungsten ratio of 1:0.005-0.8), it can reduce nitrogen oxides in exhausts or industrial waste gases (HSDB, 2002d).

6.0 Environmental Occurrence and Persistence

Tungsten is one of the rarer metals, comprising only about 1.5 ppm of the earth's crust (Budavari, 1996). It occurs naturally as tungstate (WO_4^{2-}). In the lithosphere, tungsten levels ranged from 0.1 to 2.4 mg/kg [0.5 to 13 $\mu\text{mol/kg}$]. Concentrations in rocks have also been reported (e.g., 20 to 270 mg/kg [0.11 to 1.14 mmol/kg] in rock phosphates and phosphorites and 1.7 to 4.0 mg/kg [9.2 to 22 $\mu\text{mol/kg}$] in alkaline rocks) (HSDB, 2002c).

The production and use of tungsten compounds (e.g., as catalysts and dyes) may result in the release of tungsten to the environment through waste streams. Very small amounts of tungsten (<1.5 ng/m^3 [0.20 ppt]), primarily as tungsten trioxide, have been released into the atmosphere from industrial emissions and nuclear fallout. If released to the air, most tungsten compounds will exist exclusively in the particulate phase in the ambient atmosphere because of their low vapor pressures and can be removed by wet and dry deposition (HSDB, 2002b,c). In 1976, two coal-burning units at a western state power plant released an average of 2.0 to 23.3 $\mu\text{g/m}^3$ [0.27 to 3.10 ppb] of particle-born tungsten in stack gases; average concentrations in the power plant plume ranged from 0.0050 to 0.019 $\mu\text{g/m}^3$ [0.66 to 2.5 ppt]. In urban or suburban areas, the measured air concentrations of tungsten were <1.5 $\mu\text{g/m}^3$ [0.20 ppb] (HSDB, 2002c). In landfill gas, volatile tungsten compounds (carbonyl) were found in the range of 0.005 to 0.01 $\mu\text{g/m}^3$ [0.7 to 1 ppt] tungsten (Feldmann and Cullen, 1997).

If released to soil, tungsten compounds will have moderate to low mobility based upon sorption coefficients ranging from 10 to 50,000 at pHs 5 to 6.5 (coefficients increase with decreasing pH). Expected to exist as ions or insoluble solids in the environment, volatilization from moist soil surfaces is not an important fate process. Furthermore, the compounds are not expected to volatilize from dry soil surfaces because of their ionic character and low vapor pressures (HSDB, 2002b,c). In surface soils, tungsten concentrations ranged from 0.68 to 2.7 mg/kg [3.7 to 15 $\mu\text{mol/kg}$]. In Iowa, agricultural soils contained a mean of 0.89 mg/kg [4.8 $\mu\text{mol/kg}$] tungsten. In plants, levels ranging from <0.001 to 100 mg/kg [5.4 to 544 nmol/kg] dry weight were reported (HSDB, 2002c).

Elemental tungsten is basically insoluble in water (U.S. EPA, 2002a). If released into water, tungsten compounds will adsorb to suspended solids and sediment. As in soil, volatilization from water surfaces is not an important fate process (HSDB, 2002b,c). In a study of the river waters in Japan, tungsten was mainly present in the dissolved phase, ranging from 27.6 to 107

ng/L [0.15 to 0.58 nM]. The element may be present not only as tungstate but also as species associated with the small inorganic colloids (Tanizaki et al., 1992).

In ash samples from hospital and municipal incinerators, 12.4 and 16 ppm [67.4 and 87 $\mu\text{mol/kg}$] tungsten, respectively, were found (Ko and Jervis, 1992). In 1980, municipal sewage sludges from 23 U.S. cities had tungsten levels ranging from 0.65 to 140 mg/kg [35 to 761 $\mu\text{mol/kg}$] dry weight. In a separate study, 16 cities had a mean tungsten concentration of 19.4 mg/kg [0.106 mmol/kg] dry weight in sewage sludges (HSDB, 2002c). Tungsten content of soils, plants, and sewage sludges in Iowa ranged from 0 to 2, 0 to 0.35, and 0.5 to 62 mg/kg [0 to 11, 0 to 1.9, and 2.7 to 340 $\mu\text{mol/kg}$], respectively (Fu and Tabatabai, 1988). Tungsten concentrations have also been determined in fertilizers (e.g., 1.47 to 7.04 mg/kg [8.00 to 38.3 $\mu\text{mol/kg}$] were in superphosphate). In manure, tungsten levels ranged from 8 to 2800 mg/kg [0.04 to 15.23 mmol/kg] (HSDB, 2002c).

Fallon, NV, and Sierra Vista, AZ

In Fallon, NV, there are six archived U.S. EPA Superfund sites: Don Wooten Metal and Recycling, Fallon Naval Air Station, Fallon Pest Container DSPL Site, Kennametal Inc., Sand Spring Silver-Lorraine Leac, and T & K Mobile (U.S. EPA, 2002c).

In both Fallon, NV, and Sierra Vista, AZ, the level of tungsten found in trees has risen during the past 20 years. The increase is 45 and 72%, respectively (McCain, 2002).

7.0 Human Exposure

Occupational exposure to tungsten compounds is possible from inhalation of dusts and dermal contact during the production or use of tungsten-containing compounds (HSDB, 2002b). Large amounts of tungsten dust are released from the crushing and milling of ores, in the loading and emptying from furnaces of graphite boats, during the mixing of components, and in the shaping and grinding of products (HSDB, 2002d). In the manufacture of the metal, harmful exposures to related metals in the ore have been mainly to arsenic, antimony, bismuth, copper, lead, manganese, molybdenum, and tin (Langård, 2001). In an assessment of metal dust exposures from the process of sharpening saw blades and tools at the Eccles Saw and Tool Company (Cincinnati, OH), tungsten concentrations for two personal air samples were 365 and 925 mg/m³ [47.3 and 123 ppm] (Hunninen and Rondinelli, 1987). Although tungsten electrodes are widely used in welding, tungsten is generally not considered in the workers' exposure to heavy metals (Sampara, 1985). Airborne tungsten trioxide fibers, however, have been detected in static and personal samples from hard metal manufacturing industries (Sahle et al., 1996).

For the general population, exposure to tungsten is possible from ingestion of products containing tungsten or its compounds. In a study of trace element reference values in tissues of residents of the European Community (specifically, Italians), beverages were found to significantly contribute to the total dietary intake of tungsten. Mean tungsten content (in $\mu\text{g/L}$ [nM]) were found for the following: 1.7 \pm 1.4 [9.2] in wine, 1.1 \pm 1.2 [6.0] in mineral water, 7.4 \pm 6.5 [40] in beer, 0.31 \pm 0.51 [1.7] in tea infusion (brewed tea), and 1.8 \pm 0.3 [9.8] in instant coffee. The total estimated contributions of the drinks on the dietary weekly intake of tungsten were 3.4, 5.5, 2.24, 0.15, and 0.36 μg [18, 30, 12.2, 0.82, and 1.9 nmol], respectively, for a total weekly dietary intake of >100% (Minoia et al., 1994).

In healthy subjects, serum tungsten concentrations were 6 µg/L [30 nM]; in 14 unexposed persons, the mean tungsten level in urine was 0.21 µg/L [1.1 nM] (HSDB, 2002c). The geometric mean of urine concentrations for the U.S. population (n=2338 persons ≥6 years old) was 0.085 µg/L (95% confidence interval: 0.077-0.093) (CDC, 2003). For adults, the following tungsten levels have been determined in human tissues and body fluids: 0.25 ppb [1.4 nmol/kg] in bone, 16 ppb [87 nmol/kg] in hair, 2 ppb [11 nmol/kg] in the heart, <0.7 mg/L [4 µM] in plasma, <0.07 mg/L [0.4 µM] in serum, 26 to 160 ppb [0.14 to 0.87 µmol/kg] in skin, 240 ppb [1.31 µmol/kg] in tooth enamel, 2600 ppb [14.14 µmol/kg] in tooth dentine, and up to 32 µg [0.17 µmol] in urine (Iyengar et al., 1978).

8.0 Regulatory Status

The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values are 5 mg/m³ [0.7 ppm] as an eight-hour time-weighted average (TWA) and 10 mg/m³ [1.3 ppm] as a 15-minute short-term exposure limit (STEL) for tungsten metal and for insoluble compounds, as tungsten. For soluble compounds, as tungsten, the values are 1 and 3 mg/m³ [0.1 and 0.4 ppm], respectively. The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) (reported as ten-hour TWAs) is 5 mg/m³ [0.7 ppm] for tungsten and 1 mg/m³ [0.1 ppm] for soluble compounds, as tungsten. The 15-minute STEL is 3 mg/m³ [0.4 ppm] for soluble compounds, as tungsten. The Occupational Safety and Health Administration (OSHA) has not established a permissible exposure limit (PEL) for tungsten or any of its compounds (HSDB, 2002b,c; NIOSH Pocket Guide online).

Under section 5(a)(2) of the Toxic Substances Control Act (TSCA), EPA promulgated significant new use rules (SNURs) for 163 chemical substances that were the focus of TSCA section 5(e) consent orders and premanufacture notices (PMNs). Sodium metatungstate is listed among these substances. An unreasonable risk could not be established with its use in "an open non-dispersive use" in the PMN due to the lack of significant inhalation exposures. A two-year, two-species oral bioassay and a 90-day subchronic inhalation study in rats were recommended (40 CFR Part 721, Section 721.9840) (U.S. EPA, 1998).

9.0 Toxicological Data

9.1 General Toxicology

In 1977, NIOSH published a Criteria Document for tungsten and cemented tungsten carbide (available at URL <http://www.cdc.gov/niosh/77-127.html>; last accessed on September 27, 2002). Toxicity studies (e.g., acute exposure and carcinogenicity) for metallic tungsten and various tungsten compounds, including tungsten trioxide, sodium tungstate, and tungsten chloride, dating as early as 1924, are summarized. Epidemiological studies of workers exposed to dusts of the metal and its products in the cemented tungsten carbide industry are summarized. In 1977, the Permanent Commission and International Association of Occupational Health Subcommittee on the Toxicology of Metals also published a review that included the toxicology of tungsten (see Kazantzis, 1977). In this ILS report, studies cited in recent reviews (e.g., Domingo, 2002) are presented. Additionally, current toxicological studies not mentioned in the reviews were also incorporated. Those in domestic animals, including cows, sheep, swine, and hens are not included.

Elemental tungsten is basically insoluble and as a result is "essentially nontoxic" (U.S. EPA, 2002a). Soluble compounds are more toxic than the insoluble forms (Langård, 2001).

9.1.1 Human Data

Chemical Disposition, Metabolism, and Toxicokinetics: The daily dietary intake of tungsten is about 0.01 mg [0.05 μmol], while the median for daily urinary excretion is 0.007 mg [0.04 μmol]. Tungsten(VI) is well-absorbed. About 75% of the amount ingested is excreted in the urine (Bowen, 1982). In a limited study with no specific exposure, four "normal" young adults eliminated trace quantities of tungsten in urine (2.0-13.0 μg [0.01-0.07 μmol]) and feces (1.6-5.7 μg [8.7-31 nmol]) over 24-hour periods; excretion was balanced with tungsten intake (Friberg et al., 1979; cited by HSDB, 2002b).

Toxicity: "There are no data available on occupational exposures to compounds of tungsten which incriminate these as toxic or hazardous agents" (Friberg et al., 1979; cited by HSDB, 2002b). In a powder metallurgy operations plant using tungsten metal, workers chronically exposed to air concentrations of 5 mg/m³ [0.7 ppm] tungsten developed no pneumoconiosis (ACGIH, 1991; cited by HSDB, 2002b).

Tungsten poisoning has occurred after continued exposure to dusts and vapors during the refining of tungsten. Tungsten and its salts are considered "moderately toxic." The probable oral lethal dose for a person weighing 150 pounds is between 0.5 to 5 g/kg [3 to 27 mmol/kg]. The element is a skin and eye irritant (HSDB, 2002a,b,c).

One case of tungsten poisoning has been reported after the accidental ingestion of tungsten. A 19-year-old man who drank 250 mL of a mixture of beer and wine that he had rinsed in a hot gun barrel experienced nausea, followed by seizures, and then became comatose for 24 hours, showing signs of encephalopathy. Moderate renal failure became an extensive tubular necrosis with anuria by day two. High concentrations of tungsten were found in the drink (1540 mg/L [8.376 mM]), gastric content (8 mg/L [44 μM]), blood (5 mg/L [27 μM]), and urine (101 mg/L [549 μM]). The high levels in blood (>0.005 mg/L [0.03 μM]) were observed until day 13 despite six hemodialyses, and in urine until day 33. Hair and nails also contained tungsten. The individual fully recovered after five months (Marquet et al., 1997; cited by Langård, 2001).

Carcinogenicity: Lung cancer mortality in tungsten metal miners has been associated with silicosis (Amandus and Costello, 1991). A more recent study, which reported the incidence of silicosis among tungsten miners to be higher than other mines and factories, found that the risk of lung cancer decreased inversely to the dust-exposed level, while the rate was not in proportion with the stage of silicosis. The results, therefore, did not support the etiological relationship between silicosis and lung cancer (Chen et al., 1994).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

When rats were orally administered diets containing tungsten as finely ground metal, sodium tungstate, tungsten trioxide, or ammonium paratungstate (doses not provided) for 100 days, tungsten mainly accumulated in bone and in spleen; trace quantities (<1.0 mg%) were found in the kidney, liver, blood, lung, muscle, and testes. In another rat study, ingestion of ¹⁸⁵tungsten resulted in 40% of the dose being excreted in the urine after 24 hours, about 58% being excreted

in the feces or remaining unabsorbed in the gut, and 2% remaining in tissues (Friberg, 1979; cited by HSDB, 2002b,d).

The data below were extracted from the recent reviews by Langård (2001) and Lagarde and Leroy (2002). When provided, dose(s) and routes were recorded.

Absorption: When beagle dogs were exposed to radioactive ^{181}W -tungsten trioxide ($^{181}\text{WO}_3$) mist (98 mCi/mL specific activity for six hours) by inhalation, 60% of the inhaled activity was rapidly deposited in the respiratory tract. Half of it was in the lower portion of the tracheobronchial compartment and in the pulmonary compartment. During the first ten days, about 33% of the deposited activity entered the systemic circulation; the remaining activity was cleared from the lung via the ciliary escalatory system. In the lung, 69% of the activity was lost, with a biological half-life (BHL) of 4 hours. Twenty-three percent was removed with a BHL of 20 hours, 4.6% with a BHL of 6.3 days, and 3% with a BHL of 100 days. When given a weak acidic aqueous solution of tungsten trioxide, absorption was 25% in the animals (Aamodt, 1975). In a separate dog study, instillation of calcium tungstate slowed the transport of tungsten particles from the alveolus to the lymph nodes (Grande et al., 1990).

In dogs and rats orally administered a solution of sodium tungstate (25 or 50 mg/kg [0.085 or 0.17 mmol/kg]), absorption of tungsten occurred between one and two hours. In beagle dogs, uptake of tungsten was from 57 to 74% (Le Lamer et al., 2000). As in dogs, absorption in rats was 40 to 92% when tungsten was administered as tungstate and only 1% when administered as tungstic acid (Ballou, 1960; Fleshman et al., 1966; Kaye, 1968; Le Lamer et al., 2000).

Distribution and Retention: *In vivo* experiments using various species, routes of administrations, and compounds showed that a majority of the administered tungsten is rapidly removed from blood (Lagarde and Leroy, 2002). Injection, inhalation, or ingestion of tungsten generally produced higher tungsten levels in the liver compared to other soft tissues, which may be explained by the ability of tungsten to replace molybdenum in certain liver enzymes (e.g., see Aamodt, 1975; Ekman et al., 1977; Ando et al., 1989). The other soft tissues, which accumulate a significant amount of deposited tungsten immediately after entering the blood, eliminate it within a few hours (Lagarde and Leroy, 2002).

When male and pregnant female mice were injected with ^{185}W -tungstate, an increase in tungsten levels was found in the skeleton, kidneys, liver, and spleen; tungsten was then rapidly excreted in urine and feces. High concentrations were also detected in the thyroid, adrenal medulla, pituitary, and seminal vesicles of males and in the follicles of ovaries in females. Transfer of tungsten from mother to fetus, particularly in late gestation, was observed. Significant retention of the compound was found in the maternal skeleton, kidneys, and spleen and in the visceral yolk sac epithelium and skeleton of the fetus (Wide et al., 1986).

In guinea pigs orally or subcutaneously (s.c.) given sodium tungstate (500 mg [1.70 mmol]), tungsten was detected in the blood and urine, as well as the liver, kidneys, lungs, stomach, and intestines. The lungs and kidneys had maximal radioactivity, whereas other tissues contained only about 10% of the administered dose. Total body burdens of radioactivity were 37% in the

skeleton, 31% in lungs, 15% in kidneys, 9.7% in liver, and 5.7% in skeletal muscle (Karantassis, 1924a).

Elimination: Injection or oral administration of tungstate is rapidly eliminated via urine or feces; the former appears to be the major excretion pathway (Lagarde and Leroy, 2002). In rats and dogs, 80-95% is excreted within 24 hours after administration (Aamodt, 1973, 1975; Ando et al., 1989; Kaye, 1968; Durbin, 1960).

9.1.3 Acute Exposure

Acute toxicity values for tungsten and its compounds are presented in the table below.

Table 1. Acute Toxicity Values for Tungsten and Its Compounds

Route	Species*	LD ₅₀ (unless otherwise specified)	Reference(s)
<i>Tungsten metal powder</i>			
i.p.	rat	5 g/kg (0.03 mol/kg)	Budavari (1996); RTECS (2002b)
<i>Sodium tungstate</i>			
oral	mouse	240 mg/kg (0.817 mmol/kg)	Nadeenko (1966; cited by NIOSH, 1977); RTECS (2002d)
		1904.1 mg/kg (6.4805 mmol/kg)	Fernandez-Alvarez et al. (2000a; cited by Domingo, 2002)
	rat	1190 mg/kg (4.050 mmol/kg)	Nadeenko (1966; cited by NIOSH, 1977); RTECS (2002d)
		1928.4 mg/kg (6.5632 mmol/kg)	Fernandez-Alvarez et al. (2000a; cited by Domingo, 2002)
	guinea pig	550 mg/kg (1.87 mmol/kg)	Karantassis (1924b; cited by Lagarde and Leroy, 2002)
		1152 mg/kg (3.921 mmol/kg)	Lewis (1996; cited by HSDB, 2002a); RTECS (2002d)
rabbit	875 mg/kg (2.98 mmol/kg)	Lewis (1996; cited by HSDB, 2002a); RTECS (2002d)	
i.m.	rabbit	105 mg/kg (0.357 mmol/kg)	ACGIH (1991; cited by HSDB, 2002a); RTECS (2002d)
i.p.	mouse	80 mg W/kg (0.44 mmol/kg)	Caujolle et al. (1959; cited by Lagarde and Leroy, 2002)
	rat	112 mg W/kg (0.609 mmol/kg)	
i.v.	mouse	107.1 mg/kg (0.3645 mmol/kg)	Fernandez-Alvarez et al. (2000a; cited by Domingo, 2002)
	rat	61.0 mg/kg (0.208 mmol/kg)	
		154 mg W/kg (0.838 mmol/kg)	Pham-Huu and Som (1968; cited by Lagarde and Leroy, 2002)
	rabbit	59 mg W/kg (0.32 mmol/kg)	

Table 1. Acute Toxicity Values for Tungsten and Its Compounds (Continued)

Route	Species*	LD ₅₀ (unless otherwise specified)	Reference(s)
<i>Sodium tungstate (continued)</i>			
s.c.	rat	140-160 mg W/kg bw (0.761-0.870 mmol/kg bw)	ACGIH (1991; cited by HSDB, 2002a)
		240 mg/kg (0.817 mmol/kg)	Lewis (1996; cited by HSDB, 2002a); RTECS (2002d)
	guinea pig	450 mg/kg (1.53 mmol/kg)	Karantassis (1924b; cited by Lagarde and Leroy, 2002)
		LD _{Lo} = 810 mg/kg (2.76 mmol/kg)	RTECS (2002d)
	rabbit	71 mg W/kg (0.39 mmol/kg)	Lusky et al. (1949; cited by Lagarde and Leroy, 2002)
		LD _{Lo} = 78 mg/kg (0.27 mmol/kg)	RTECS (2002d)
<i>Tungsten trioxide</i>			
oral	rat	1059 mg/kg (4.568 mmol/kg)	RTECS (2002c)

*Sex and strain were not provided.

Abbreviations: bw = body weight; i.m. = intramuscular(ly); i.p. = intraperitoneal(ly); i.v. = intravenous(ly); LD₅₀ = lethal dose for 50% of test animals; LD_{Lo} = lethal dose, low; s.c. = subcutaneous(ly); W = tungsten

Tungsten

In rats, an intraperitoneal (i.p.) injection of tungsten (5 g/kg [0.03 mol/kg]) caused regional or general vascular dilation, liver damage (not otherwise specified [n.o.s.]), and blood changes (n.o.s.) (RTECS, 2002b). White rats given a single intratracheal (i.t.) dose of metallic tungsten (50 mg [0.27 mmol]) and sacrificed four, six, or eight months later exhibited a proliferative reaction of the lymphoid and mild fibrosis (Friberg et al., 1979; cited by HSDB, 2002b). Dust-chamber exposures of animals to tungsten produced minor changes (ACGIH, 1991; cited by HSDB, 2002b).

In guinea pigs receiving an i.t. suspension of tungsten metal dust (150 mg [0.816 mmol]) as three equal doses and observed for up to one year, focal interstitial pneumonitis and bronchiolitis, focal interstitial infiltration, atrophic emphysema, peribronchial and periarterial fibrocellular reaction, and endarteritis obliteration were observed (Friberg et al., 1979; cited by HSDB, 2002b).

When applied to the skin and eyes of rabbits for 24 hours, tungsten (500 mg [2.72 mmol]) was a mild irritant (RTECS, 2002b). A particle of tungsten (<1 mm diameter) inserted into the midvitreal region of the eyes of rabbits showed no effects at a final pathological examination at the end of one year; tungsten was classified as "completely inert" (Lauring and Wergeland, 1970; cited by Langård, 2001). Tungstic acid and soluble tungstates were also found not to be hazardous to the eyes (Bech, 1974; cited by Langård, 2001).

Sodium Tungstate

When administered orally or intravenously (i.v.), mice and rats exhibited decreased motor activity and muscle tone, ataxia, palpebral ptosis, hunched back, pallor, prostration, and dyspnea (Fernandez-Alvarez et al., 2000a; cited by Domingo, 2002). In both species, i.p. injection of sodium tungstate produced asthenia, adynamia, prostration, coma, and ultimately death (Caujolle et al., 1959; Pham-Huu and Som, 1968; both cited by Lagarde and Leroy, 2002). When given s.c. to rats, a severe drop in rectal temperature occurred. When given parenterally, sodium tungstate caused enlargement of the kidneys and adrenals (Gosselin et al., 1976; cited by HSDB, 2002a). [Doses were not provided for the studies.]

In guinea pigs, oral administration or injection produced anorexia, colic, confusion, tremors, and dyspnea (Karantassis, 1924b; cited by Lagarde and Leroy, 2002). When sodium tungstate (dose[s] not provided) was applied directly to the corneal stroma of rabbits, it produced toxic effects in the pH range of 7 to 9 (Fredenwald et al., 1946; cited by Langård, 2001). Administered intramuscularly (i.m.), the compound (105 mg/kg [0.357 mmol/kg]) affected food intake and caused convulsions, hypermotility, and diarrhea in the animals (RTECS, 2002d).

Tungsten Trioxide

Oral administration of the LD₅₀ value for tungsten trioxide (1059 mg/kg [4.568 mmol/kg]) affected the behavior of rats; they exhibited somnolence, excitement, and muscle weakness (RTECS, 2002c). A single i.t. injection of tungsten trioxide (50 mg [0.22 mmol]) in white rats produced histological changes in the lung, consisting of proliferative reaction of the lymphoid and histiocytic element and eventually mild fibrosis. The walls of small vessels became thick, while their endothelium became swollen (Friberg et al., 1979; cited by HSDB, 2002d).

9.1.4 Short-term and Subchronic Exposure

Tungsten

In weanling rats fed tungsten metal powder at concentrations of 2, 5, and 10% of the diet for 70 days, no effect on the growth rate was observed in male rats. In females, however, a 15% reduction in weight gain was reported (Patty, 1963; cited by HSDB, 2002b).

Sodium Tungstate

Sodium tungstate (equivalent to 2% tungsten) orally administered to young rats caused the deaths of all animals within ten days. When diets were reduced to contain an equivalent of 0.5% tungsten, death occurred in 75% of rats by the end of the 70-day exposure period (Friberg et al., 1979; cited by HSDB, 2002a).

When given by gavage or in drinking water to young rats, sodium tungstate (15-1000 mg/kg [0.051-3.403 mmol/kg] per day) for four or 13 weeks produced emesis, anorexia, cachexia, pallor, and dyspnea. At the high dose, levels of urea, creatinine, and total cholesterol were increased, while erythrocyte count and glucose, AST/ALT, protein, hematocrit, and hemoglobin levels were decreased; all parameters returned to normal after a recovery period of six weeks (Fernandez-Alvarez et al., 2000b; cited by Domingo, 2002).

Tungsten Trioxide

Inhalation of tungsten trioxide ($490 \mu\text{g}/\text{m}^3$ [51.7 ppb]) for 24 hours a day for 15 continuous weeks produced impairment in liver function tests, changes in true cholinesterase, and changes in leukocyte count (RTECS, 2002c).

Oral administration of tungsten trioxide (equivalent to 3.96% tungsten) was significantly toxic, causing initial weight loss and then death in all animals within ten days. In diets having an equivalency of 0.5% tungsten, the compound caused deaths in 75% of rats by the end of the 70-day exposure period. A decrease in growth rate was also observed (Friberg et al., 1979; cited by HSDB, 2002d).

9.1.5 Chronic Exposure

Tungsten

In rat and guinea pigs, tungsten metal was "not very toxic" (Delahant, 1955; Harding, 1950; Kaplun and Mezencewa, 1960; Schepers, 1955; all cited by Lagarde and Leroy, 2002). [No other details were provided in the review.]

Sodium Tungstate

In Long Evans rats, sodium tungstate (5 ppm [0.02 mmol/kg]) in the drinking water for a lifetime significantly reduced longevity in males (Schroeder and Mitchener, 1975). In male Wistar rats, daily oral administration of the compound ($<150 \text{ mg}/\text{kg}$ [0.511 mmol/kg] body weight [bw]) for up to 300 days produced no significant effects on body and organ weights, nor on survival (Sato et al., 1999). When administered orally for 30 weeks intermittently, sodium tungstate (106 mg/kg [0.361 mmol/kg]) caused alterations of classical conditioning in the animals. Inhalation of the compound ($504 \mu\text{g}/\text{m}^3$ [41.9 ppb]) for 24 hours per day for 17 continuous weeks resulted in changes in blood (n.o.s.), true cholinesterase, and other protein levels (RTECS, 2002d).

In rabbits, oral administration of sodium tungstate (1214 mg/kg [4.132 mmol/kg]) for 35 weeks intermittently caused biochemical changes in true cholinesterase and phosphatases (RTECS, 2002d).

9.1.6 Synergistic/Antagonistic Effects

In mammals, tungsten has been found capable of serving as a substitute for molybdenum in enzymes (U.S. EPA, 2002a). In studies with rats, chickens, goats, and cows, tungsten was an antagonist toward molybdenum; it decreased sulfite and xanthine oxidase activities and hepatic molybdenum levels (Higgins et al., 1956; Johnson and Rajagopalan, 1974; Hart et al., 1967; all cited by Lagarde and Leroy, 2002). Sodium tungstate antagonizes molybdate's role as a metal carrier for xanthine oxidase. When rats maintained on a low molybdenum diet were given tungstate, a loss of xanthine oxidase and sulfite oxidase activities occurred, and the animals were more susceptible to bisulfite toxicity (Cohen et al., 1973; cited by Kazantzis, 1977). In addition, the compound inhibited the intestinal deposition of xanthine oxidase in the rat (Higgins et al., 1956; cited by Kazantzis, 1977). Furthermore, its ability to activate brain glutaminase and inactivate liver glutaminase shows that it can act at more than one enzyme site (Langård, 2001).

Tungstate, like molybdate, can also replace phosphate in bone (Fleshman et al., 1966; cited by Lagarde and Leroy, 2002). At 5 ppm (0.02 mmol/kg), it can reduce the toxic effects of selenium (Venugopal and Luckey, 1978; cited by HSDB, 2002a).

Small doses of the metals tungsten, molybdenum, nickel, lead, and copper in drinking water can cause nonspecific changes in metabolic processes. When rats were given tungsten in drinking water at an effective dose (ED) for six months, molybdenum and copper decreased in bone tissue and kidneys; at a threshold dose (TD), both elements increased in bone tissue. With molybdenum at an ED, tungsten decreased in the liver, kidneys, and blood. When tungsten, molybdenum, and copper were simultaneously ingested, accumulation of each element in individual organs was similar to those (i.e., same ratio) in controls (Nadeenko et al., 1990).

9.1.7 Cytotoxicity

In *in vitro* assays using murine embryonic cells, tungstate inhibited cartilage production in limb bud mesenchymal cultures at concentrations similar to those found *in vivo* (Wide et al., 1986; cited by Domingo, 2002).

9.2 Reproductive and Teratological Effects

Tungsten

In female rats, oral administration of tungsten (1210 µg/kg [6.581 µmol/kg; TL_{L0}]) for 35 weeks before pregnancy resulted in post-implantation mortality (e.g., dead and/or resorbed implants per total number of implants) and developmental abnormalities in the musculoskeletal system. When tungsten (1150 µg/kg kg [6.255 µmol/kg; TL_{L0}]) was administered 30 weeks before pregnancy and on days 1 through 20 of pregnancy, only the latter effects were seen (RTECS, 2002b).

Sodium Tungstate

In mice, a single dose of sodium tungstate (concentration not specified) given at early organogenesis produced a high frequency of resorptions but did not induce any fetal malformations (Wide, 1984; cited by Domingo, 2000 and Lagarde and Leroy, 2002).

In male rats, inhalation of sodium tungstate (504 µg/m³ [41.9 ppb]) for 24 hours a day for 17 weeks affected spermatogenesis, including genetic material, sperm morphology, motility, and count (RTECS, 2002d). In pregnant rats, tungstate inhibited the production of xanthine oxidase, and high doses (not specified) caused death in fetuses (Cohen et al., 1974; cited by Lagarde and Leroy, 2002). When administered to pregnant rats at doses that did not produce maternal toxicity (not specified), sodium tungstate increased embryonal lethality and inhibited bone ossification in fetuses (Nadeenko et al., 1978; cited by Domingo, 2002).

In embryonic rat calvaria, sodium tungstate (0.1 mM [29 µg/mL]) had no affect on collagen synthesis (Srivastava et al., 1976).

9.3 Carcinogenicity

When administered in the drinking water for a lifetime, sodium tungstate (5 ppm [0.02 mmol/kg]) produced tumors in four of 25 (16%) male rats and in 13 of 20 (65%) female rats.

The numbers of malignant tumors were two and five, respectively (Schroeder and Mitchener, 1975).

9.4 Initiation/Promotion Studies

Tungsten

When male Sprague-Dawley rats were administered benzo[*a*]pyrene (BaP) simultaneously with systemic sulfite (drinking solution containing tungsten [0, 100, or 400 ppm; 0, 0.544, or 2.18 mmol/kg] plus sodium molybdate), deaths from pulmonary squamous cell carcinoma was not significantly different from controls. A slight nonsignificant increase in mammary tumors occurred in rats treated with tungsten; however, the data did not support a cocarcinogenic role for sulfite with BaP-induced cancer (Gunnison et al., 1988).

In another study, rats given tungsten (200 ppm [1.99 mmol/kg]) in the drinking water for 19 weeks with *N*-nitrososarcosine ethyl ester (NSEE) had more hyperplastic and precancerous lesions than animals not receiving tungsten (Luo et al., 1982).

Sodium Tungstate

In Sprague-Dawley female rats administered *N*-methyl-*N*-nitrosourea (MNU), oral pretreatment with sodium tungstate [13472-45-2] (150 ppm [0.511 mmol/kg] in drinking water daily for 140 or 213 days beginning 15 days before carcinogen treatment) did not cause significant multiplicity in papillary carcinomas in mammary glands. At 140 days, a significant incidence of carcinomas was observed. The high incidence of carcinomas in the control group suggested that the dose of MNU may have been too high (5 mg/100 g bw) and therefore prevented tungsten from showing a countering effect on molybdenum. At 213 days, the incidence of tumors was not significant. In a similar study, sodium tungstate [11120-01-7] (150 ppm [0.511 mmol/kg] in drinking water daily for 198 days beginning at 35-days-old) produced a significant incidence of MNU-induced mammary carcinomas at 125 days (Wei et al., 1985; cited by CCRIS, 1994b).

In Sprague-Dawley male rats administered NSEE, oral pretreatment with sodium tungstate (100 ppm [0.340 mmol/kg] in drinking water daily for 19 or 30 weeks beginning 21 days before carcinogen treatment) did not induce a significant incidence of carcinoma in the esophagus or the forestomach (Luo et al., 1983; cited by CCRIS, 1994b).

9.5 Anticarcinogenicity

No data were available.

9.6 Genotoxicity

Sodium Tungstate

In *Saccharomyces cerevisiae*, sodium tungstate (100 mmol/L [29.4 mg/mL]) produced gene conversion, mitotic recombination, and sex chromosome loss and nondisjunction. In *Escherichia coli*, the compound (5 mmol/L [1 mg/mL]) caused phage inhibition capacity (RTECS, 2002d). In Syrian hamster embryo cells, sodium tungstate did not induce morphological transformation, sister chromatid exchange (SCE), or chromosome aberration (CA); the latter two were also not seen in human lymphocytes (Dipaolo and Casto, 1979; Larramendy et al., 1981).

In *S. cerevisiae*, sodium tungstate dihydrate [10213-10-2] (dose[s] not provided) induced disomic and diploid meiotic products (Sora et al., 1986). In a test for SCE in human lymphocytes, no conclusion could be made regarding its mutagenicity (GENETOX, 1995).

Tungsten Alloys

Tungsten alloys used in military projectiles were genotoxic in SCE, micronuclei, and alkaline filter elution assays. Like DU compounds, they were neoplastic transforming agents but at a lower frequency, suggesting a possible relationship between long-term exposure and the development of neoplastic disease (Miller et al., 2002).

9.7 Cogenotoxicity

No data were available.

9.8 Antigenotoxicity

No data were available.

9.9 Immunotoxicity

No data were available.

9.10 Other Data

When orally administered to streptozotocin (STZ)-induced diabetic rats, sodium tungstate (0.7 mg/mL [2 mM] for the first three weeks and then 2 mg/mL [7 mM] for the remainder of the eight-month treatment period) in the drinking water decreased serum glucose levels, restored pyruvate kinase activity and fructose 2,6-bisphosphate concentrations, prevented diabetes-induced morphological changes in the kidney and ocular lens, and reduced mortality.

Additionally, because no hypoglycemic episodes or undesirable side effects were noted in both the treated diabetic or healthy rats, the results support the possible use of tungstate as a long-term treatment of diabetes mellitus (Barberà et al., 2001). When administered to Zucker diabetic fatty (ZDF) rats with moderate hyperglycemia, sodium tungstate (dose[s] not provided) caused the animals to become normoglycemic for about ten days before glycemia began to rise again, stabilizing at ~200 mg/dL (Muñoz et al., 2001; cited by Domingo, 2002).

Additionally, sodium tungstate may be useful in the treatment of diet-induced obesity. When diet-induced obese Wistar rats were given sodium tungstate (2 g/L [7 mM]) in the drinking water for 32 days, body weight gain was significantly decreased, as was triglyceride, free fatty acid, and insulin plasma levels. No toxic effects were observed. The animals quickly gained body weight during a recovery period of 35 days (Claret et al., Undated).

In male Wistar rats, sodium tungstate exerted radioprotective effects on hematopoietic injury caused by exposure to ⁶⁰cobalt γ -rays (Sato et al., 1999).

When rats were exposed to tungsten trioxide (0.25 mg/m³ [0.026 ppm] [5 km from nonferrous-metal works] or 0.46 mg/m³ [0.049 ppm] [500 m from the works]) for 135 days, the number of reticulocytes was increased, blood histamine was decreased, fluctuations in the urinary elimination of hippuric acid were seen, and porphyrin metabolism was disturbed in a dose-dependent manner. At 500 m from the works, the numbers of leukocytes and segmented-nucleus

neutrophils were increased, while the numbers of lymphocytes and thrombocytes were decreased. Additionally, the relative weights of the kidneys and spleen were decreased, blood cholinesterase was inhibited, and coproporphyrin elimination was lowered (Voronož, 1983).

10.0 Structure-Activity Relationships

Numerous tungsten compounds exist. A summary of the literature available for selected tungsten compounds is included in Appendix B.

Tungsten Hexachloride [13283-01-7]

In Syrian hamster embryo (SA7/SHE) cells, tungsten hexachloride was negative for mutagenicity (GENETOX, 1992a).

Tungstoantimonic acid, ammonium salt [59372-48-4]

In Syrian hamster embryo (SA7/SHE) cells, tungstoantimonic acid, ammonium salt induced cell transformation and viral enhancement (GENETOX, 1992b).

Ammonium 21-tungsto-9-antimonate (Antimoniotungstate; HPA-23) [89899-81-0]

The antiviral activity of HPA-23 has been demonstrated in mice; administered via the i.p. route, the LD₅₀ value is 750 mg/kg. It has also exhibited *in vitro* inhibition of the rabies virus (Budavari, 1996; RTECS, 2002a). The drug has been proposed for use as an AIDS vaccine. After i.v. injection of various doses of the drug in the rat, high amounts were found in the lysosomes and localized in the macrophages of different tissues—thymus, spleen, and bone marrow. The tungsten to antimony ratio was identical in each macrophage (Berry and Galle, 1990).

11.0 Online Databases and Secondary References

11.1 Online Databases

Chemical Information System Files

TSCATS (Toxic Substances Control Act Test Submissions)

STN International Files

AGRICOLA	HSDB
BIOSIS	IPA
BIOTECHNO	LIFESCI
CA	MEDLINE
CABA	NIOSHITICS
CANCERLIT	NTIS
CAPLUS	Registry
EMBASE	RTECS
ESBIOBASE	TOXCENTER

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSH [®]	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

Databases Available on the Internet

Code of Federal Regulations (CFR), National Archives and Records Administration

In-House Databases

Current Contents on Diskette[®]

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Appendix A: Units and Abbreviations

°C = degrees Celsius
µg/L = microgram(s) per liter
µg/m³ = microgram(s) per cubic meter
µg/mL = microgram(s) per milliliter
µM = micromolar
ACGIH = American Conference of Governmental Industrial Hygienists
BHL = biological half-life
bw = body weight
DU = depleted-uranium
EPA = Environmental Protection Agency
g = gram(s)
g/mL = gram(s) per milliliter
HSDB = Hazardous Substances Data Bank
i.m. = intramuscular(ly)
i.p. = intraperitoneal(ly)
i.t. = intratracheal(ly)
i.v. = intravenous(ly)
kg = kilogram(s)
L = liter(s)
LD₅₀ = lethal dose for 50% of test animals
LD_{Lo} = lethal dose, low
mg/kg = milligram(s) per kilogram
mg/m³ = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimole(s) per kilogram
mo = month(s)
mol = mole(s)
mol. wt. = molecular weight
NIEHS = National Institute of Environmental Health Sciences
NIOSH = National Institute for Occupational Safety and Health
n.o.s. = not otherwise specified
ppb = parts per billion
ppm = parts per million
ppt = parts per trillion
s.c. = subcutaneous(ly)
SCE = sister chromatid exchange
STEL = short-term exposure limit
TSCA = Toxic Substances Control Act
TWA = time-weighted average

Appendix B: Literature Search Availability for Selected Tungsten Compounds

Name	CAS RN	CA/ CAOLD (9/18, 10/01, 10/04/02)	Biomedical Databases (x is ≥3)	RTECS/ HSDB	TSCA Inventory TS = Test Submission
Aluminum tungstate	15123-82-7	120/1	TOXCENTER	0/0	x
Ammonium antimony sodium tungsten oxide; HPA 23 [(NH ₄) ₁₇ Sb ₉ Na ₂ W ₂₁ O ₈₆]	89899-81-0	49/0	x	1/0	no
Ammonium antimony tungsten oxide; Ammonium tungstoantimonate (NH ₄ OSbW)	59372-48-4	12/0	x	1/0	no
Ammonium metatungstate; Ammonium tungstate(VI) [(NH ₄) ₆ H ₂ W ₁₂ O ₄₀]	12028-48-7	257/3	NIOSHTIC, TOXCENTER	0/0	x
Ammonium paratungstate; Ammonium tungstate; Decaammonium tungstate [(NH ₄) ₁₀ (OH) ₂ W ₁₂ O ₄₀]	11120-25-5	191/4	x	0/0	x
Ammonium paratungstate [(NH ₄) ₆ W ₇ O ₂₄]	12028-06-7	213/8	BIOSIS, TOXCENTER	0/0	no
Ammonium paratungstate hexahydrate [(NH ₄) ₆ W ₇ O ₂₄ ·6H ₂ O]; Hexammonium tungstate (W ₇ O ₂₄ ⁶⁻) hexahydrate	12208-54-7	3/0	NIOSHTIC, TOXCENTER	1/0	no
Ammonium phosphotungstate [NH ₄ (OH)O ₄ POW]	12704-02-8	64/0	x	0/0	no
Ammonium phosphotungstate trihydrate [(NH ₄) ₃ W ₁₂ PO ₄₀ ·3H ₂ O]	1311-90-6	2/1	MRCK	0/0	no
Ammonium tetrathiotungstate; Ammonium tungsten sulfide [(NH ₄) ₂ WS ₄]	13862-78-7	239/11	MEDLINE, TOXCENTER	0/0	no
Ammonium tungstate; Diammonium tungstate [(NH ₄) ₂ WO ₄]	15855-70-6	180/14	TOXCENTER	0/0	no
Ammonium tungstate (H ₄ NOW)	11140-77-5	225/0	TOXCENTER	0/0	no
Barium tungstate (BaWO ₄)	7787-42-0	383/20	TOXCENTER	0/0	x
Cadmium tungstate (CdWO ₄)	7790-85-4	359/17	MEDLINE, MRCK	0/0	x
Calcium tungstate (CaWO ₄)	7790-75-2	1587/23	x	0/0	x
Cobalt tungstate (CoWO ₄)	10101-58-3	165/22	TOXCENTER	0/0	x
Copper tungstate (CuWO ₄)	13587-35-4	117/20	x	0/0	x
Copper tungstate dihydrate (CuWO ₄ ·2H ₂ O)	10031-46-6	0/0	0	0/0	no
HPA 23 (see Ammonium antimony sodium tungsten oxide)					
Lead tungstate [indefinite composition]	12737-98-3	91/0	TOXCENTER	0/0	no
Lead tungstate (PbWO ₄)	7759-01-5	598/25	TOXCENTER	0/1	x
Lithium tungstate	13568-45-1	259/20	TOXCENTER	0/0	x
Magnesium tungstate	13573-11-0	230/24	TOXCENTER	0/0	x
Phosphotungstic acid (unspecified formula)	12067-99-1	791/42	x	1/0	x
Phosphotungstic acid (H ₃ PW ₁₂ O ₄₀) hydrate	12501-23-4	77/0	TOXCENTER	0/0	no
Potassium tungstate (K ₂ WO ₄)	7790-60-5	406/35	x	0/0	x
Potassium tungstate(VI) (K ₂ W ₄ O ₁₃)	12311-19-2	14/7	0	0/0	no
Silicotungstic acid; Tungstosilicic acid (H ₄ SiW ₁₂ O ₄₀)	12027-38-2 DR 12520-88-6 (one of many DRs)	959/46 7/0	x	0/0	x
Silicotungstic acid hydrate; Tungsten hydroxide oxide silicate [W ₁₂ (OH) ₄ O ₃₂ (SiO ₄)] hydrate	12027-43-9	51/1	NIOSHTIC, TOXCENTER	0/0	no
Sodium metatungstate; Hexasodium tungstate; Sodium tungstate(VI) (Na ₆ H ₂ W ₁₂ O ₄₀)	12141-67-2	39/3	TOXCENTER	0/0	TS Bayer Corp. 28-day, gavage, rats
Sodium metatungstate hydrate; Sodium polyoxotungstate (Na ₆ H ₂ W ₁₂ O ₄₀ ·H ₂ O)	12333-13-0	3/0	0	0/0	no
Sodium phosphotungstate; Sodium tungstophosphate (HONaO ₄ POW)	51312-42-6	92/0	x	1/1	x
Sodium tungstate (Na ₂ WO ₄); Disodium tetraoxotungstate(2-); Sodium tungsten oxide; Sodium wolframate	13472-45-2	2367/4	x	1/1	x
Sodium tungstate; Sodium tungsten oxide (9CI) [no specified formula]; Tungstic acid, sodium salt; Tungstic acid, sodium salt, dihydrate	11120-01-7 DR 11140-64-0 DR 53125-86-3	595/0	x	0/0	no
Sodium tungstate dihydrate (Na ₂ WO ₄ ·2H ₂ O)	10213-10-2	108/0	x	1/1	no
Tungsten; Tungsten element; Wolfram	7440-33-7	66,712/0	x	1/1	x
Tungsten boride (WB)	12007-09-9	286/29	TOXCENTER	0/0	x
Tungsten(IV) bromide; Tungsten tetrabromide	14055-81-3	15/4	0	0/0	no
Tungsten carbide (WC)	12070-12-1	7914/1	x	1/1	x
Tungsten carbonyl; Tungsten hexacarbonyl [W(CO) ₆]	14040-11-0	2620/49	x	0/0	TS Cincinnati Milacron Chem. Inc. & PPG Indus. eye, rbt
Tungsten(IV) chloride; Tungsten tetrachloride	13470-13-8	152/12	TOXCENTER	0/0	no

Name	CAS RN	CA/ CAOLD (9/18, 10/01, 10/04/02)	Biomedical Databases (x is ≥3)	RTECS/ HSDB	TSCA Inventory TS = Test Submission
Tungsten(VI) chloride; Tungsten hexachloride	13283-01-7	2201/45	x	1/0	TS Dow Chem. Co., acute oral, skn, eye
Tungsten dioxide; Tungsten(IV) oxide	12036-22-5	720/52	TOXCENTER	0/0	x
Tungsten disulfide; Tungsten(IV) sulfide (WS ₂)	12138-09-9	1368/0	TOXCENTER	0/0	x
Tungsten(VI) fluoride; Tungsten hexafluoride	7783-82-6	1864/31	x	1/0	x
Tungsten hexacarbonyl [See Tungsten carbonyl.]					
Tungsten(VI) oxide; Tungsten oxide; Tungsten trioxide; Tungstic anhydride; Tungsten Blue (WO ₃ , W ₂ O ₆ , W ₃ O ₉ , W ₄ O ₁₂)	1314-35-8	13,349/5	x	1/1	x
Tungsten oxychloride (WOCl ₃); Tungsten chloride oxide (WCl ₄ O); Tungsten(VI) oxochloride	13520-78-0	426/23	TOXCENTER	0/0	no
Tungsten oxychloride (WO ₂ Cl ₂); Tungsten chloride oxide (WCl ₂ O ₂)	13520-76-8	139/25	TOXCENTER	0/0	no
Tungsten pentabromide	13470-11-6	49/11	0	0/0	no
Tungsten pentachloride	13470-14-9	150/19	TOXCENTER	0/0	no
Tungsten silicide (WSi ₂)	12039-88-2	1847/38	x	0/0	x
Tungsten trisulfide (WS ₃)	12125-19-8	60/12	TOXCENTER	0/0	no
Tungstic acid; Tungstic(VI) acid (H ₂ WO ₄)	7783-03-1	529/13	x	0/0	x
Tungstic acid; Tungstic oxide hydrate (WO ₃ .nH ₂ O)	11105-11-6	375/0	x	1/0	no
Tungstic acid hydrate; Tungsten trioxide dihydrate (WO ₃ .2H ₂ O)	23321-70-2 DR 10101-79-8	52/0 3/1	TOXCENTER	0/0	no

DR denotes a discontinued CAS RN.

Note that multiple compounds with approximately the same name but different molecular formulas exist for tungsten. Examples are given below for sodium tungstate and ammonium paratungstate. These lists are from the complete name (CN) index of the STN International Registry file.

=> EXPAND SODIUM TUNGSTATE/CN

```

...
E3      2 --> SODIUM TUNGSTATE/CN
E4      1 SODIUM TUNGSTATE (NA0.02WO3)/CN
E5      1 SODIUM TUNGSTATE (NA0.1WO3)/CN
E6      1 SODIUM TUNGSTATE (NA0.25WO3)/CN
E7      1 SODIUM TUNGSTATE (NA0.2WO3)/CN
E8      1 SODIUM TUNGSTATE (NA0.33WO3)/CN
E9      1 SODIUM TUNGSTATE (NA0.3WO3)/CN
E10     1 SODIUM TUNGSTATE (NA0.45WO3)/CN
E11     1 SODIUM TUNGSTATE (NA0.4WO3)/CN
E12     1 SODIUM TUNGSTATE (NA0.53WO3)/CN
E13     1 SODIUM TUNGSTATE (NA0.54WO3)/CN
E14     1 SODIUM TUNGSTATE (NA0.58WO3)/CN
E15     1 SODIUM TUNGSTATE (NA0.5WO3)/CN
E16     1 SODIUM TUNGSTATE (NA0.62WO3)/CN
E17     1 SODIUM TUNGSTATE (NA0.6WO3)/CN
E18     1 SODIUM TUNGSTATE (NA0.7WO3)/CN
E19     1 SODIUM TUNGSTATE (NA0.8WO3)/CN
E20     1 SODIUM TUNGSTATE (NA0.9WO3)/CN
E21     1 SODIUM TUNGSTATE (NA10H2W12O42)
          HEXACOSAHYDRATE/CN
E22     1 SODIUM TUNGSTATE (NA10W12O41)/CN
E23     1 SODIUM TUNGSTATE (NA2(WO4))/CN
E24     1 SODIUM TUNGSTATE (NA2(WO4)),
          DIHYDRATE/CN
E25     1 SODIUM TUNGSTATE (NA2181WO4)/CN
E26     1 SODIUM TUNGSTATE (NA2W2O7)/CN
E27     1 SODIUM TUNGSTATE (NA2W3O10)/CN
E28     1 SODIUM TUNGSTATE (NA2W4O13)/CN
E29     1 SODIUM TUNGSTATE (NA2W6O19)/CN
E30     1 SODIUM TUNGSTATE (NA2WO3)/CN
E31     1 SODIUM TUNGSTATE (NA2WO4.2H2O)/CN
E32     1 SODIUM TUNGSTATE (NA3WO4)/CN
E33     1 SODIUM TUNGSTATE (NA4W7O23)/CN
E34     1 SODIUM TUNGSTATE (NA6H2W12O40)/CN
E35     1 SODIUM TUNGSTATE (NAWO3)/CN
E36     1 SODIUM TUNGSTATE (VI) (H3NA5O22W6)/CN
E37     1 SODIUM TUNGSTATE (VI) (NA10W12O42)/CN
E38     1 SODIUM TUNGSTATE (VI) (NA2W2O7)/CN
E39     1 SODIUM TUNGSTATE (VI) (NA2W3O10)/CN
E40     1 SODIUM TUNGSTATE (VI) (NA2W4O13)/CN
E41     1 SODIUM TUNGSTATE (VI) (NA2WO4)/CN
E42     1 SODIUM TUNGSTATE (VI) (NA3H3W6O21)/CN
E43     1 SODIUM TUNGSTATE (VI) (NA6H2W12O40)/CN
E44     1 SODIUM TUNGSTATE (VI)
          (NA6H4W12(OH)2O40)/CN
E45     1 SODIUM TUNGSTATE (VI)
          (NA6W7O24)/CN
E46     1 SODIUM TUNGSTATE (VI)
          (NA8H6WO10)/CN
E47     1 SODIUM TUNGSTATE-181W/CN
...
=> EXPAND AMMONIUM PARATUNGSTATE/CN
...
E3      2 --> AMMONIUM PARATUNGSTATE/CN
E4      1 AMMONIUM PARATUNGSTATE
          ((NH4)10W12O41.5H2O)/CN
E5      1 AMMONIUM PARATUNGSTATE
          (5(NH4)2O.12WO3.5H2O)/CN

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Appendix C: Search Description for Tungsten and Tungsten Compounds

Results from a limited search in TOXLINE (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE>) on 10 September 2002 were examined to prepare a list of keywords that might be excluded from future searches (? is a truncation symbol on STN International). Other keywords were used during the simultaneous biomedical databases search on STN International after examining samples of search results in the KWIC format (keyword in context):

anode?	filament*	irradiated	radiation	target*
atomizer*	foil*	Kjeldahl	shield*	TIG*
bulb	furnace*	lamp?*	silica	uric
carbide?*	GTAW*	needle?	silicosis	weld?*
coil?*	hard metal*	plant	stain?	wire*
electrode?*	illuminat?	precipitat?*	Ta 178	x ray?

A simultaneous search was done on 19 September 2002 in the databases MEDLINE, CANCERLIT, AGRICOLA, NIOSHTIC, CABA, BIOTECHNO, EMBASE, ESBIODBASE, IPA, BIOSIS, TOXCENTER, and LIFESCI on STN International. Preliminary answer sets before duplicate removal had the following number of records:

tungsten NOT [the terms above followed by asterisks]	10,375
paratungst?	96
phosphotungst? OR tungstophosph?	5,335
silicotungst? OR tungstosilic?	417
tungstate	3,277

Combination of these sets gave 18,932 records before duplicate removal. Several reviews of interest were identified that had been published in 1997-2002. To reduce the set of 18,932 records (L16), the set was combined with several desirable terms as follows:

L16 AND (toxic? OR genotoxic? OR neurotoxic?)	1,502 (L24)
L16 AND (leukem? OR leukaem?)	108 (L25)
L16 AND (chromosom? OR chromatid? OR SCE OR micronucle? OR muta?)	802 (L26)
L16 AND (rats OR mice OR cats OR dogs OR sheep OR swine OR pigs OR rabbits OR gerbils OR voles)	2,638 (L27)
(L16 AND (cancer? OR carcino? OR tumor? OR tumour? OR neoplas?)) NOT (HPA 23 OR cancer(4A)(treat? OR therap? OR antineoplastic OR needle? OR stain? OR x ray? OR radiation)	451 (L35)

The resulting sets were combined:

L24 OR L25 OR L26 OR L27 OR L35 4,635 (L36)

and then further reduced:

L36 NOT (needle? OR stain? OR x ray? OR radiation) 3,451 (L37)

L37 NOT (Ta 178 OR tantalum 178 OR plant OR Kjeldahl) 3,337 (L38)

Duplicate removal for L38 gave 1,747 records. Additional terms were excluded from this set (L39):

L39 NOT (illuminat? OR uric OR irradiat? OR bulb OR anode? OR synthe? OR acriflavine)
1,583 (L40)

The 1,583 records of set L40 were distributed among the databases as follows:

MEDLINE	647	EMBASE	154
CANCERLIT	10	ESBIOBASE	13
AGRICOLA	23	IPA	2
NIOSH TIC	118	BIOSIS	178
CABA	53	TOXCENTER	370
BIOTECHNO	18	LIFESCI	17

Because toxicology reviews published in 2001 and 2002 cited limited numbers of recent references, the answer set was limited to publications from 1990 to 2002. The resulting 694 records were sorted alphabetically by title. The printed titles were examined for further duplicate removal and compared with 616 TOXLINE titles online that had also been sorted alphabetically. The 616 TOXLINE titles resulted from the following search statement:

(tungsten OR tungstate) NOT (carbide OR "hard metal" OR WC)

Sixty-three new TOXLINE records of interest that had not been retrieved in the 10 September search (about 290 records) were printed in full at this time. Unique records in the STN International biomedical databases (159) were marked and later printed in full format.

Registry records were retrieved on 18 September for several tungsten compounds listed in the initial Toxic Substances Control Act (TSCA) "Candidate List of Chemical Substances" (April 1977), a 1998-1999 Aldrich catalog *Inorganics and Organometallics*, and the CD of *The Merck Index*, 1996 edition. These were supplemented on 1 October and 4 October with records for metatungstates, tetrathiotungstates, and selected other compounds that appeared in the database records examined. Some anhydrous compounds were sought when only hydrates were listed. In addition, clarification was sought when synonyms common to more than one compound were found. For several compounds, up to 10 of the most recent records in Chemical Abstracts (CA) were printed along with the Registry record.

RTECS and HSDB records were retrieved when their existence was indicated on the Registry records. TSCA test submissions were identified by a search of the TSCATS database on the Chemical Information System.

The table in Appendix B displays the literature availability for tungsten and 55 tungsten compounds. No attempt was made to tally TOXLINE results for specific compounds.

Since tungsten is known to perturb the activity of molybdenum-based enzymes such as sulfite oxidase, brief, informal PubMed and TOXLINE searches sought any records linking molybdenum or the molybdenum-based enzymes to induction of cancer, especially leukemia. While feeding rats tungstate and a molybdenum-deficient diet will deplete sulfite oxidase activity and increase susceptibility to sulfur dioxide poisoning, no increases in tumors were noted in the database records. [Sulfite process pulp mills have been associated with excess human cancers, including leukemia, in epidemiological studies of pulp and paper workers (for example, Rix et al. 1997. *Scandinavian Journal of Work, Environment and Health*, 23(6):458-461).]

The searcher sorted the TOXLINE and fee-based database records alphabetically by surname of the first author and assigned subject codes and later assigned report-value codes after all of the records had been scanned. The records were then organized by subject codes and turned over to the technical writer.

Internet searches primarily used the Google and Scirus search engines. Searches retrieved tungsten, tungsten oxide, and ammonium paratungstate import and U.S. consumption information from the U.S. Geological Survey (USGS) web site plus information from the web sites of the U.S. Environmental Protection Agency (U.S. EPA), the Centers for Disease Control (CDC), the National Institute for Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR), and tungsten trade associations.

The tungsten assignment was prompted by the recent news stories on the occurrence of leukemia clusters in children residing in Fallon, Nevada, and Sierra Vista, Arizona, where unusually high tungsten concentrations were found in human urine and in tree rings from the past 20 years. Possible environmental sources were investigated by Internet searches. The searches found that Nevada has geothermal springs associated with high tungsten levels. In addition, Fallon, Nevada, has six Superfund sites including one associated with a tungsten carbide manufacturer. (Cobalt concentrations were also elevated in urine of Fallon residents.) Both Fallon and Sierra Vista are near military bases. Recently developed tungsten alloys used in munitions might be contaminating firing ranges, and information was collected on these topics. Old tungsten mines are found in the vicinity of Sierra Vista at higher elevations.

In-house literature searches included chemical catalogs, *Chemyclopedia 2002*, *The Merck Index* CD-ROM, Current Contents on Diskette® and on CD-ROM, and metals publications in the searcher's personal library.

Appendix D: Tungsten Trade Data (2001)

Information retrieved January 21, 2003 from U.S. Trade Quick-Reference Tables, Office of Trade and Economic Analysis (OTEA), International Trade Administration, U.S. Department of Commerce. Available at: <http://www.ita.doc.gov/td/industry/otea/trade-detail/>

Chapter 28: INORGANIC CHEMICALS; ORGANIC OR INORGANIC COMPOUNDS OF PRECIOUS METALS, OF RARE-EARTH METALS, OF RADIOACTIVE ELEMENTS OR OF ISOTOPES: December 2001 Imports/Exports
<http://www.ita.doc.gov/td/industry/otea/Trade-Detail/Latest-December/Imports/28/index.html>

Chapter 81: BASE METALS NESOI; CERMETS; ARTICLES THEREOF: December 2001 Imports/Exports
<http://www.ita.doc.gov/td/industry/otea/Trade-Detail/Latest-December/Imports/81/index.html>

Chapter 26: ORES, SLAG AND ASH: December 2001 Imports/Exports
<http://www.ita.doc.gov/td/industry/otea/Trade-Detail/Latest-December/Exports/26/index.html>

Chapter 72: IRON AND STEEL: December 2001 Imports/Exports
<http://www.ita.doc.gov/td/industry/otea/Trade-Detail/Latest-December/Imports/72/index.html>

HTS 6-Digit Subheading or 10-Digit Code	Description	U.S. Domestic Exports, 2001, World Total (Kg)	U.S. Imports For Consumption, 2001, World Total (Kg)
<i>Tungsten Compounds</i>			
282590	Inorganic Bases; Other Metal Oxides, Hydroxides And Peroxides, NESOI	NA	NR
2825.90.3000 282739	Tungsten Oxides	NR	1,993,193
2827.39.4000 284180	Chlorides, NESOI	NR	NR
2827.39.4000 284180	Tungsten Chloride	NR	980
2841.80.0010 2841.80.0020	Tungstates (Wolframates)	NR	NR
2841.80.0010 2841.80.0020	Tungstates (Wolframates) Of Ammonium (Tungsten Content)	257,337	3,361,778
2841.80.0020 2841.80.0040	Tungstates (Wolframates) Of Calcium (Tungsten Cnt)	NR	159,249
2841.80.0040 2841.80.0050	Tungstates (Wolframates), Exc Of Ammonium, NESOI I	594,255	NR
2841.80.0050 284990	Tungstates (Wolframates), Except Of Ammonium And Calcium (Tungsten Content), NESOI	NR	19,665
284990	Carbides, NESOI, Whether Or Not Chemically Defined	NR	NR
2849.90.3000	Carbides, Whether Or Not Chemically Defined, Of Tungsten	1,945,748	1,001,883
285000	Hydrides, Nitrides, Azides, Silicides & Borides, Whether Or Not Chemically Defined, Other Than Compounds Which Are Also Carbides Of Heading 2849	NA	NR
2850.00.1000	Hydrides, Nitrides, Azides, Silicides And Borides, Whether Or Not Chemically Defined, Of Tungsten	NR	25,882

Toxicological Summary for Tungsten and Selected Tungsten Compounds

Jan/03

HTS 6-Digit Subheading or 10-Digit Code	Description	U.S. Domestic Exports, 2001, World Total (Kg)	U.S. Imports For Consumption, 2001, World Total (Kg)
<i>Tungsten Metal Products</i>			
8101.10.0000	Tungsten (Wolfram) Powders	711,722	994,895
8101.91.0000	Tungsten, Unwrought, Including Bars And Rods Obtained Simply By Sintering; Tungsten Waste And Scrap	1,388,845	NR
8101.91.1000	Tungsten Waste And Scrap	NR	1,145,517
8101.91.5000	Tungsten, Unwrought	NR	12,910
8101.92.0000	Tungsten (Wolfram) Bars And Rods, Other Than Those Obtained Simply By Sintering; Tungsten Profiles, Plates, Sheets, Strip And Foil	248,555	118,162
8101.93.000	Tungsten Wire	224,810	37,644
8101.99.0000	Tungsten, Wrought, NESOI	89,664	128,458
<i>Tungsten (other)</i>			
2611.00.0000	Tungsten Ores and Concentrates	425,619	NR
2611.00.3000	Tungsten Ores	NR	1,103,459
2611.00.6000	Tungsten Concentrates	NR	3,212,038
7202.80.0000	Ferrotungsten and Ferrosilicon Tungsten	1,500	450,584

NR: No imports or exports reported for this subheading/code

NA: Aggregated data reported at subheading level only; not meaningful