3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of tungsten. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal), since this factor influences the body's response to some substances, and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is

considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Pulmonary fibrosis, memory and sensory deficits, and increased mortality due to lung cancer have been attributed to occupational exposure to dusts generated during the manufacture or use of high tensile strength tungsten (hard metal) (see Bech 1974; Bech et al. 1962; Coates and Watson 1971; Jordan et al. 1990; Kaplun and Mezentseva 1959; Lasfargues et al. 1994; Mezentseva 1967; Miller et al. 1953; Moulin et al. 1998; Vengerskaya and Salikhodzhaev 1962; Wild et al. 2000). Hard metal is produced by sintering a mixture of powders (typically tungsten carbide and cobalt) to form a tungsten alloy. Variations can include the replacement of tungsten carbide with tungsten, the addition of other metals (yttrium, thorium, copper, nickel, iron, or molybdenum) to achieve specific metallurgical properties, and the omission of cobalt. The term “hard-metal disease” has been coined to describe pulmonary effects resulting from inhaled hard metal dust. It is generally believed that the health effects observed in hard metal workers are the result of exposure to cobalt (see Davison et al. 1983; Harding 1950) or other metals (e.g., nickel), not tungsten. Refer to the ATSDR Toxicological Profile for Cobalt (Agency for Toxic Substances and Disease Registry 2004) and the ATSDR Toxicological Profile for Nickel (Agency for Toxic Substances and Disease Registry 2005) for health effects information on cobalt and nickel, respectively. It has been suggested that tungsten carbide could increase the solubility of cobalt, effectively increasing cobalt-induced toxicity (Lasfargues et al. 1995; Lison et al. 1995, 1996), although such a mechanism has not been experimentally demonstrated.

3.2.1.1 Death

No reports were located in which death in humans could be specifically associated with exposure to airborne tungsten or tungsten compounds. Increased mortality has been attributed to occupational exposure to dusts containing tungsten carbide and cobalt among hard metal workers. It is generally believed that the health effects observed in hard metal workers are the result of exposure to cobalt (see Davison et al. 1983; Harding 1950) or other metals (e.g., nickel), not tungsten. Refer to the ATSDR Toxicological Profile for Cobalt (Agency for Toxic Substances and Disease Registry 2004) and the ATSDR Toxicological Profile for Nickel (Agency for Toxic Substances and Disease Registry 2005) for health effects information on cobalt and nickel, respectively.

Information in animals is restricted to reports of no deaths during 14 days following single 4-hour exposure of rats to atmospheres of sodium tungstate dihydrate powder at a concentration of 5.01 mg/L (Huntingdon Life Sciences Ltd 1999a) or tungsten metal powder at a concentration of 5.4 mg/L (Huntingdon Life Sciences Ltd 1999b). However, the particulate concentrations available for inhalation were likely much lower than those reported, due to rapid settling of the particles. Lasfargues et al. (1992) found intratracheally-instilled hard metal (tungsten carbide and cobalt alloy) to be more acutely lethal to rats than either tungsten carbide or cobalt alone. It has been suggested that tungsten carbide could increase the solubility of cobalt, effectively increasing cobalt-induced toxicity (Lasfargues et al. 1995; Lison et al. 1995, 1996), although such a mechanism has not been experimentally demonstrated.

3.2.1.2 Systemic Effects

Available information in humans is limited to occupational exposure to dusts containing tungsten and other substances such as cobalt in the hard metal industry, and reported systemic effects have been associated with cobalt rather than tungsten. Therefore, human data are not included in Table 3-1 and Figure 3-1. Reliable LOAELs for respiratory and ocular effects in animals exposed to selected tungsten compounds are recorded in Table 3-1 and plotted in Figure 3-1.

No reports were located in which cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or dermal effects were associated with inhalation exposure of humans or animals to tungsten or tungsten compounds.

Table 3-1 Levels of Significant Exposure to Tungsten - Inhalation

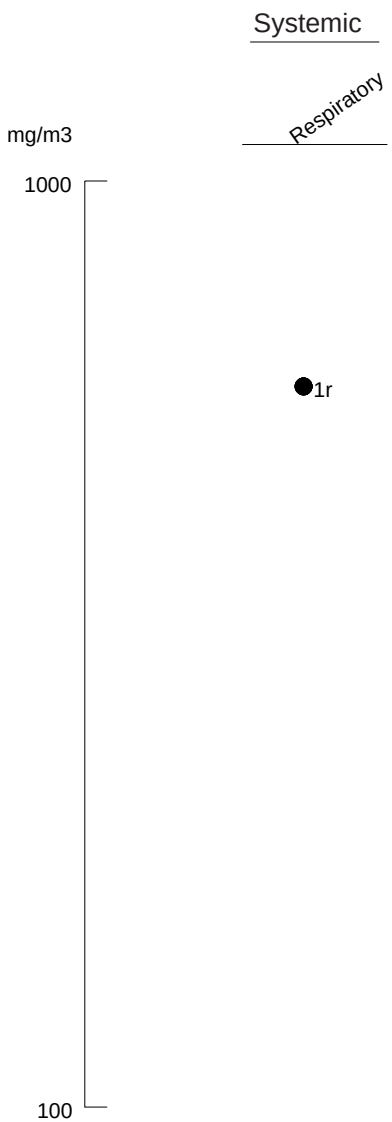
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Systemic							
1	Rat (NS)	5 mo 1hr/d	Resp			600 (pulmonary fibrosis)	Mezentseva 1967 tungsten carbide

a The number corresponds to entries in Figure 3-1

LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 3-1 Levels of Significant Exposure to Tungsten - Inhalation

Intermediate (15-364 days)



c-Cat	-Humans	f-Ferret	n-Mink
d-Dog	k-Monkey	j-Pigeon	o-Other
r-Rat	m-Mouse	e-Gerbil	
p-Pig	h-Rabbit	s-Hamster	
q-Cow	a-Sheep	g-Guinea Pig	

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Respiratory Effects. Respiratory effects were reported in workers who were occupationally exposed to airborne dusts containing tungsten trioxide, tungsten dioxide, metallic tungsten, and tungsten carbide in areas where high tensile strength tungsten was prepared (Mezentseva 1967). Of 54 workers examined, 5 exhibited early radiographic signs of pulmonary fibrosis after having been employed for 2–3 years (3 workers) or 19 or 24 years. The study of Mezentseva (1967) lacks critical information regarding smoking, medical, and work histories of the examined workers. Furthermore, other potentially hazardous substances may have also been present in the workplace air. It is generally believed that the health effects observed in hard metal workers are the result of exposure to cobalt (see Davison et al. 1983; Harding 1950) or other metals (e.g., nickel), not tungsten. Refer to the ATSDR Toxicological Profile for Cobalt (Agency for Toxic Substances and Disease Registry 2004) and the ATSDR Toxicological Profile for Nickel (Agency for Toxic Substances and Disease Registry 2005) for health effects information on cobalt and nickel, respectively. See Kerley et al. (1996) and NIOSH (1977) for discussions of respiratory effects associated with the hard metal industry.

Few reports were located regarding respiratory effects in animals. Signs of mild pulmonary fibrosis were noted in rats exposed to atmospheres containing tungsten carbide at a concentration of 600 mg/m^3, 1 hour/day for 5 months (Mezentseva 1967). Other rats exhibited similar signs of pulmonary fibrosis following intratracheal instillation of metallic tungsten, tungsten trioxide, or tungsten carbide and subsequent observations for up to 8 months postinstillation (Mezentseva 1967). Guinea pigs that received 3 weekly doses of tungsten metal dust or tungsten carbide and carbon dust via intratracheal instillation were examined for up to 12 months post treatment (Delahant 1955; Schepers 1955a, 1955b). Gross histological examinations of the lungs revealed pigmented lung lesions that did not appear to involve lymphoid tissue; the results were not suggestive of pulmonary fibrosis. The lungs of mice exhibited no signs of a fibrotic response following intratracheal instillation of tungsten carbide (Lardot et al. 1998).

Lasfargues et al. (1992) reported severe acute pulmonary edema in rats that had received hard metal (tungsten carbide and cobalt alloy) via intratracheal instillation, but not in rats similarly exposed to tungsten carbide or cobalt alone. In a subsequent study of repeated intratracheal instillation (Lasfargues et al. 1995), it was demonstrated that intratracheally-instilled tungsten carbide and cobalt in combination, but not alone, induced interstitial pulmonary fibrosis.

Ocular Effects. Signs of slight conjunctival irritation were noted in rabbits following single ocular instillation of 100 mg of sodium tungstate dihydrate powder or tungsten metal powder (Huntingdon Life Sciences Ltd 1999c, 2000).

3.2.1.3 Immunological and Lymphoreticular Effects

No reports were located regarding immunological or lymphoreticular effects in humans or animals following inhalation exposure to tungsten or tungsten compounds.

Intratracheal instillation of 250 µg of water-insoluble calcium tungstate crystals (in saline) in mice resulted in a marked inflammatory response characterized by infiltration of leukocytes with cellular peaks at days 1 and 14 postinstillation (Peão et al. 1993). The inflammatory response was likely the result of local irritation rather than an adverse immunological effect.

3.2.1.4 Neurological Effects

Signs of memory and sensory deficits have been reported among workers in the hard metal industry who were exposed to atmospheres of hard metal dusts (Jordan et al. 1990; Kaplun and Mezentseva 1959; Vengerskaya and Salikhodzhaev 1962). Cobalt was the likely causative agent, not tungsten. Potential contributions of dust from other metals that may have been present in the workplace air were not assessed. It is generally believed that the health effects observed in hard metal workers are the result of exposure to cobalt (see Davison et al. 1983; Harding 1950) or other metals (e.g., nickel), not tungsten. Refer to the ATSDR Toxicological Profile for Cobalt (Agency for Toxic Substances and Disease Registry 2004) and the ATSDR Toxicological Profile for Nickel (Agency for Toxic Substances and Disease Registry 2005) for health effects information on cobalt and nickel, respectively.

Information in animals is limited to a single report of a series of inhalation exposures to airborne sodium tungstate powder (Idiyatullina 1981). Muzzle scratching and increased activity (interpreted by the author as anxiety manifestations) were noted in male rats continuously exposed to atmospheres containing sodium tungstate powder at concentrations of 100 and 600 mg/m^3 for up to 30 days. Statistically significantly depressed blood cholinesterase activity (magnitude not specified in the available account of the original study) was noted following 18 hours of exposure at a concentration of 600 mg/m^3 and following 720 hours of exposure to a concentration of 10 mg/m^3. In rats exposed to concentrations of

0.5 and 1.0 mg/m^3 for 4 months, blood cholinesterase levels were depressed by 22 and 25%, respectively, relative to controls, and diffuse sclerosis was noted in brain tissue. These effects were not seen at a lower concentration (0.1 mg/m^3). The low magnitude blood cholinesterase depression renders the results of questionable toxicological significance.

3.2.1.5 Reproductive Effects

No reports were located regarding reproductive effects in humans following inhalation exposure to tungsten or tungsten compounds.

Decreased sperm motility (10–12% lower than controls) was reported in male rats continuously exposed to atmospheres containing sodium tungstate powder for 17 weeks at concentrations of 1.0 and 0.5 mg/m^3, but not at 0.1 mg/m^3 (Idiyatullina 1981).

3.2.1.6 Developmental Effects

No reports were located regarding developmental effects in humans or animals following inhalation exposure to tungsten or tungsten compounds.

3.2.1.7 Cancer

No reports were located in which cancer in humans or animals could be associated with inhalation exposure to tungsten or tungsten compounds.

3.2.2 Oral Exposure

The toxicity of ingested tungsten in humans is not known. In an early report, Kruger (1912) reported no adverse effects on patients administered 25–80 g of tungsten powder as a substitute for barium in radiological exams. Nausea, followed by seizure, 24-hour coma, temporary renal failure, and subsequent tubular necrosis and anuria were reported in a male subject who had accidentally consumed metallic tungsten in a mixture of beer and wine (Marquet et al. 1997). However, these effects could not be attributed to the consumption of tungsten per se. The toxicity of orally-administered tungsten has not

been widely studied in animals. Available reports implicate reproductive, developmental, and neurological effects as end points of concern following oral exposure to tungsten (Karantassis 1924; Nadeenko 1966; Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, these reports are lacking in some study details, thus limiting their value for purposes of quantitative risk assessment.

3.2.2.1 Death

No reports were located in which death in humans was associated with oral exposure to tungsten or tungsten compounds.

Acute oral exposure to tungsten does not appear to be a particular toxicity concern, based on acute oral LD_{50} values ranging from 240 to 11,300 mg/kg/day for several soluble tungsten compounds (Table 3-2). Death was reported in guinea pigs following single oral (gavage) administration of sodium tungstate at doses ≥780 mg/kg (Karantassis 1924). Concentrations of 2.0% tungsten (as sodium tungstate), 4% tungsten (as tungstic oxide), or 5.0% tungsten (as ammonium paratungstate), in the daily diet of rats resulted in 100% mortality within 10 days following the initiation of test diet (Kinard and Van de Erve 1941). Diets containing the equivalent of 0.5% tungsten (as sodium tungstate, tungstic oxide, or ammonium paratungstate) resulted in mortality of 3/6 males and 4/6 females, 4/5 males and 5/5 females, and 0/5 males and 0/5 females, respectively. No deaths occurred in rats receiving 0.1% tungsten (as sodium tungstate or tungstic oxide) in the diet for 70 days. In another study, no deaths were reported in rats administered diets containing as much as 10% tungsten metal powder for 70 days (Kinard and Van de Erve 1943). Approximately 15% decreases in longevity were observed in male, but not female, rats administered tungsten (as sodium tungstate) in the drinking water at a concentration of 5 mg/L for life (up to 3 years) (Schroeder and Mitchener 1975a, 1975b).

Available information regarding mortality and LD_{50} values in animals orally exposed to selected tungsten compounds is recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No human data were located in which systemic toxicity could be associated with oral exposure to tungsten or tungsten compounds. Reliable NOAELs and LOAELs for body weight changes in animals orally exposed to tungsten or tungsten compounds are recorded in Table 3-3 and plotted in Figure 3-2.

Table 3-2. Oral LD_{50} (mg/kg) Values for Selected Tungsten Compounds

Species	Tungstic trioxide	Sodium tungstate	Ammonium-p-tungstate	Sodium phosphotungsten
Mouse	NA	240±13.5[a]	NA	700±79[a]
Rat	840[a]	1,190±129.5[a]	11,300[b]	1,600±201[a]
Rabbit	NA	875[a]	NA	NA
Guinea pig	NA	1,152[a]	NA	NA

[a]Nadeenko 1966
[b]Smyth et al. 1969

LD_{50} = dose of substance causing death in 50% of population; NA = not available

Table 3-3 Levels of Significant Exposure to Tungsten - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (NS)	Once (NS)				1190 (LD50)	Nadeenko 1966 sodium tungstate
2	Rat	Once				1600 (LD50)	Nadeenko 1966 sodium phosphotungstate
3	Rat (NS)	Once (NS)				840 (LD50)	Nadeenko 1966 tungstic trioxide
4	Rat (Wistar)	Once (G)				11300 M (LD50)	Smyth et al. 1969 ammonium paratungstate
5	Mouse	Once				240 (LD50)	Nadeenko 1966 sodium tungstate
6	Mouse	Once				700 (LD50)	Nadeenko 1966 sodium phosphotungstate
7	Gn Pig	Once				1152 (LD50)	Nadeenko 1966 sodium tungstate
8	Rabbit	Once				875 (LD50)	Nadeenko 1966 sodium tungstate
INTERMEDIATE EXPOSURE							
Death							
9	Rat (NS)	70 d (F)				2000 (80% mortality)	Kinard and Van de Erve 1941 ammonium paratungstate
10	Rat (NS)	70 d (F)				500 (80% mortality)	Kinard and Van de Erve 1941 tungstic oxide

Table 3-3 Levels of Significant Exposure to Tungsten - Oral (continued)

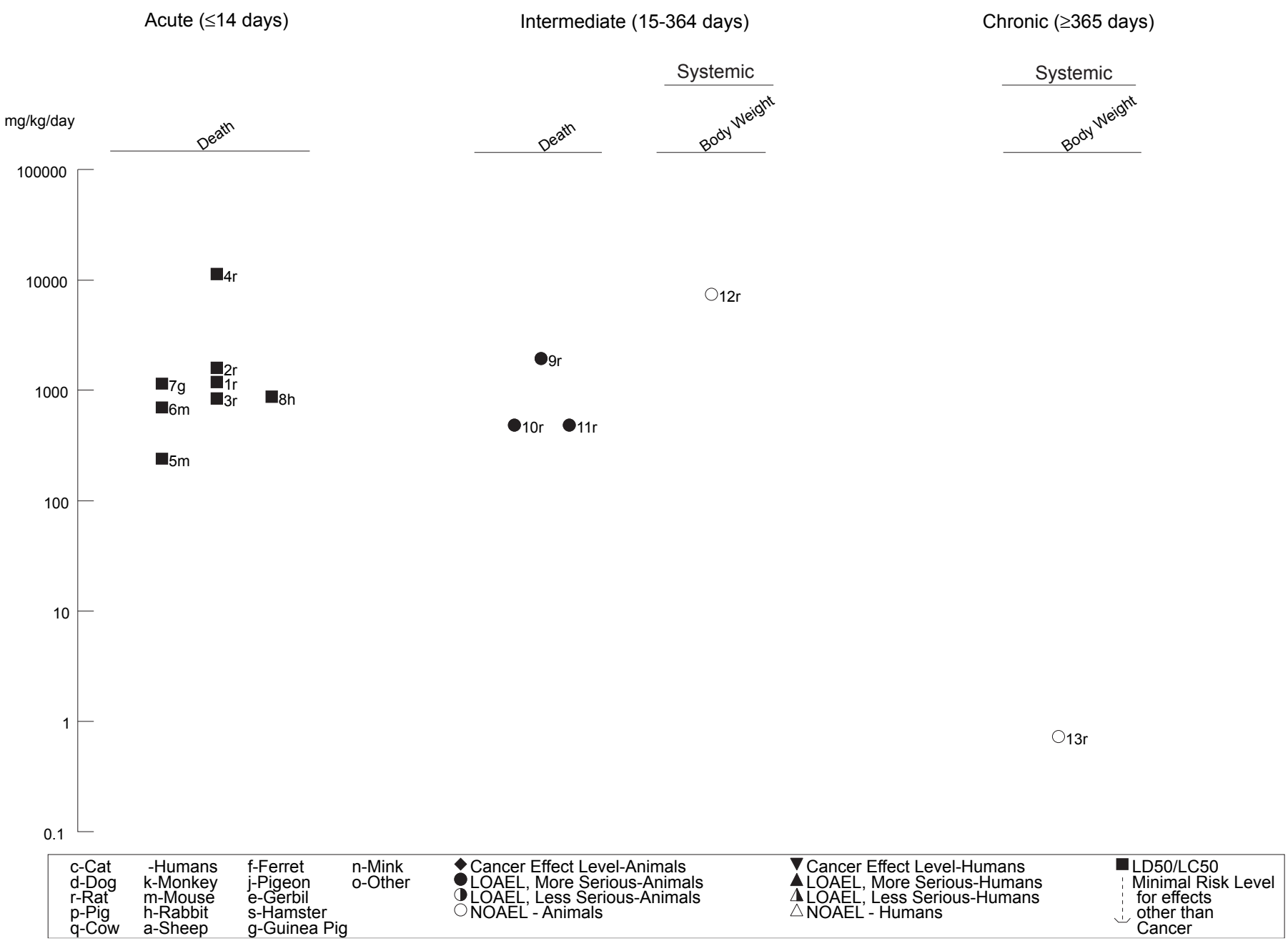
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
11	Rat (NS)	70 d (F)				500	(mortality of 3/6 males and 4/6 females)	Kinard and Van de Erve 1941 sodium tungstate
Systemic								
12	Rat	70 d (F)	Bd Wt	8256 M 7650[b] F				Kinard and Van de Erve 1943 metallic tungsten
CHRONIC EXPOSURE								
Systemic								
13	Rat (Long- Evans)	Lifetime (W)	Bd Wt	0.75[b] M 1 F				Schroeder and Mitchener 1975a sodium tungstate

a The number corresponds to entries in Figure 3-2

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd Wt = body weight; F = female; (F) = feed; LD50 = dose producing 50% death; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; (NS) = not specified; (W) = drinking water

Figure 3-2. Levels of Significant Exposure to Tungsten - Oral



No reports were located in which respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, endocrine, dermal, or ocular effects were associated with oral exposure of humans or animals to tungsten or tungsten compounds.

Renal Effects. Available information in humans is restricted to an account of temporary renal failure and subsequent tubular necrosis and anuria in a male subject 1 day following the accidental consumption of metallic tungsten in a mixture of beer and wine that had been poured into the hot barrel of a 155-mm gun (Marquet et al. 1997). The author estimated the absorbed dose of tungsten to be in the range of 5–12 mg/kg. The subject fully recovered. The renal effects could not be attributed to tungsten *per se*, and Lison et al. (1997) suggested that nitroaromatics used as propellants for large caliber ammunition may have contributed to the renal toxicity.

No information was located regarding renal effects in animals following oral exposure to tungsten or tungsten compounds.

Body Weight Effects. No information was located regarding body weight effects in humans following oral exposure to tungsten or tungsten compounds.

Available information regarding tungsten-induced body weight effects in animals is limited to reports by a single group of investigators (Kinard and Van de Erve 1941, 1943). Reduced body weight gains were noted in rats exposed to sublethal concentrations of tungsten (0.5%, as ammonium paratungstate; 0.1%, as sodium tungstate or tungstic oxide) in the diet for 70 days (Kinard and Van de Erve 1941). Body weight gain in these treated groups ranged from 3.9 to 10.6% lower than respective controls. Weight gain in female rats, administered a diet that included 10% tungsten (as insoluble tungsten metal) for 70 days, was approximately 15.5% less than that of controls; weight gain in similarly dosed male rats was described as “normal” (Kinard and Van de Erve 1941). The authors stated that diets containing 2 or 5% tungsten (as tungsten metal) were “without marked effect” on growth. Statistically significantly increased body weights were noted at some time points in male and female rats administered tungsten (as sodium tungstate) in the drinking water at a concentration of 5 mg/L for a lifetime (Schroeder and Mitchener 1975a). Since the body weights were less than 10% higher than controls and were only seen in males at 180–540 days of treatment and in females at the 360-day examination period, the increased body weight is not considered to be biologically significant.

3.2.2.3 Immunological and Lymphoreticular Effects

No reports were located regarding immunological or lymphoreticular effects in humans or animals following oral exposure to tungsten or tungsten compounds.

3.2.2.4 Neurological Effects

Information in humans is restricted to a single account of nausea, followed by seizure and 24-hour coma in a male subject who had accidentally consumed metallic tungsten in a mixture of beer and wine that had been poured into the hot barrel of a 155-mm gun (Marquet et al. 1997). The author estimated the absorbed dose of tungsten to be in the range of 5–12 mg/kg. The subject fully recovered.

Available early animal data indicate that orally administered tungsten may induce neurological effects. Guinea pigs exhibited clinical signs that included trembling and abnormal locomotor behavior following single oral (gavage) administration of sodium tungstate at ultimately lethal doses (≥780 mg/kg) (Karantassis 1924). Decreased blood cholinesterase activity and impaired conditioned reflexes were reported in rats orally exposed to sodium tungstate at doses in the range of 0.05–5.0 mg/kg/day for 7 months (Nadeenko 1966). Deficiencies in study details render the results of this Russian study of limited value for purposes of quantitative risk assessment.

3.2.2.5 Reproductive Effects

No information was located regarding reproductive effects in humans following oral exposure to tungsten or tungsten compounds.

Information in animals is limited to reports of embryotoxicity in rats following oral administration of an unspecified tungsten compound at dose levels as low as 0.005 mg/kg for up to 8 months before and during pregnancy (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, these reports are lacking in some study details, thus limiting their value for purposes of quantitative risk assessment.

3.2.2.6 Developmental Effects

No information was located regarding developmental effects in humans following oral exposure to tungsten or tungsten compounds.

Information in animals is limited to reports of delayed fetal skeletal ossification following oral exposure to tungsten at reported dose levels as low as 0.005 mg/kg to pregnant rat dams (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, these reports are lacking in some study details, thus limiting their value for purposes of quantitative risk assessment.

3.2.2.7 Cancer

Information regarding the carcinogenicity of ingested tungsten in humans is restricted to a single report of the Center for Disease Control (CDC 2003b) in which no statistically significant association (odds ratio 0.78, p-value 0.57) was found between exposure to tungsten in the drinking water and leukemia observed in a population of Churchill County, Nevada.

Gross tumor incidences in rats administered tungsten (as sodium tungstate) in the drinking water at a concentration of 5 mg/L for life were similar to those of controls (Schroeder and Mitchener 1975a). Male rats administered sodium tungstate (100 ppm) in the drinking water for 19 or 30 weeks did not exhibit treatment-related evidence of carcinoma in the esophagus or forestomach; nor did sodium tungstate treatment enhance the carcinogenic effect of *N*-nitrososarcosine ethyl ester, a chemical known to induce esophageal cancer in rats (Luo et al. 1983). In a study designed to assess the effect of systemic sulfite on benzo[*a*]pyrene-induced lung carcinoma in rats, Gunnison et al. (1988) administered sodium tungstate to induce sulfite oxidase deficiency, thus increasing systemic sulfite. In this study, sodium tungstate did not statistically significantly affect the initiation of squamous cell carcinoma of the respiratory tract of benzo[*a*]pyrene-treated rats or incidences of mammary gland tumors. Results of Wei et al. (1987) indicated that tungsten may act as a tumor promoter in rats administered 150 ppm of tungsten in the drinking water followed by intravenous injection of the known carcinogen, N-nitroso-N-methylurea.

3.2.3 Dermal Exposure

3.2.3.1 Death

No reports were located in which death in humans was associated with dermal exposure to tungsten or tungsten compounds.

Available information in animals was limited to a single report of death in 0/2, 2/2, and 2/2 rabbits following dermal application of a 5% tungsten chloride solution in single doses of 100, 200, and 1,000 mg/kg, respectively (Dow Chemical Company 1982). The results of this study are recorded in Table 3-4.

3.2.3.2 Systemic Effects

No reports were located in which respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects were associated with dermal exposure of humans or animals to tungsten or tungsten compounds.

Dermal Effects. No reports were located in which dermal exposure to tungsten compounds in humans could be associated with dermal effects. Although dermatitis has been reported among employees of the hard metal industry, results of patch testing implicated cobalt, not tungsten (Schwartz et al. 1945; Skog 1963).

In the only available report of dermal effects in animals following dermal exposure to tungsten, single or repeated dermal application of a 5% tungsten chloride solution in rabbits resulted in contact dermatitis (Dow Chemical Company 1982). The results of this study are recorded in Table 3-4.

Ocular Effects. No reports were located in which dermal exposure to tungsten compounds in humans could be associated with ocular effects.

Instillation of a 5% tungsten chloride solution into the rabbit eye resulted in conjunctivitis, iritis, and corneal haziness that resolved within 14 days postinstillation (Dow Chemical 1982). The results of this study are recorded in Table 3-4.

Table 3-4 Levels of Significant Exposure to Tungsten - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
ACUTE EXPOSURE								
Other								
Rabbit (NS)				5 Percent (%)	(temporary ocular irritation)			Dow Chemical Company 1982 tungsten chloride
Rabbit (NS)	NS			5 Percent (%)	(contact dermatitis)			Dow Chemical Company 1982 tungsten chloride
Rabbit (NS)	Once					200 mg/kg	(mortality in 2/2 rabbits)	Dow Chemical Company 1982 tungsten chloride

LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; (NS) = not specified

No reports were located regarding the following health effects in humans or animals following dermal exposure to tungsten or tungsten compounds:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

No reports were located in which systemic (other than possible hematological effects), neurological, or reproductive effects were associated with exposure of humans or animals to tungsten or tungsten compounds by routes other than inhalation, oral, or dermal exposure.

Death. Parenteral injection studies that have been performed using laboratory animals were designed to establish lethal doses of tungsten compounds and to assess the efficacy of methods to reduce toxicity (see also Section 3.11). An LD_{50} value of 500 mg/kg was reported for intraperitoneally injected tungsten metal in rats; tungsten carbide was considered to be essentially inert, although dose levels were not included in the report (Fredrick and Bradley 1946). An LD_{50} was between 140 and 160 mg/kg for tungsten (as sodium tungstate) subcutaneously injected into 66-day-old rats; younger rats appeared to be less sensitive (Kinard and Van de Erve 1940). Intramuscular injection of a 10% aqueous solution of sodium tungstate in rats (Sivjakov and Braun 1959) and rabbits (Lusky et al. 1949) resulted in LD_{50} values of 220.6 and 105 mg/kg, respectively.

Hematological Effects. The results of Kalinich et al. (2005) indicate the potential for tungsten alloy-induced hematotoxicity (expressed by increases in leukocyte and erythrocyte counts, hemoglobin, and hematocrit). However, since the tungsten alloy pellets consisted of nickel and cobalt in addition to tungsten, the role of tungsten in the observed effects is not known. Results of *in vitro* testing by one group of investigators (Miller et al. 2001, 2002) indicate the potential for synergistic effects following exposure to tungsten alloys such as tungsten-cobalt-nickel and tungsten-nickel-iron.

Immunological and Lymphoreticular Effects. The results of Kalinich et al. (2005) indicate the potential for tungsten alloy-induced immunotoxicity (expressed by increased spleen weight and decreased thymus weight). However, since the tungsten alloy pellets consisted of nickel and cobalt in addition to tungsten, the role of tungsten in the observed effects is not known. Results of *in vitro* testing by one group of investigators (Miller et al. 2001, 2002) indicate the potential for synergistic effects following exposure to tungsten alloys such as tungsten-cobalt-nickel and tungsten-nickel-iron.

Developmental Effects. Wide (1984) assessed the potential for tungsten to induce developmental toxicity in mice. Pregnant dams were administered a single intravenous injection (0.1 mL) of a 25 mM sodium tungstate solution on gestation day 8. Although there was no indication of tungsten-induced fetal malformations at examination on gestation day 17, a significantly increased incidence of resorptions was noted.

Cancer. Kalinich et al. (2005) recently assessed the potential health consequences of intramuscularly implanted weapons-grade tungsten alloy pellets in male F344 rats. Within 4–5 months, all of the tungsten alloy-implanted (n=92) rats developed extremely aggressive localized tumors (high-grade pleomorphic rhabdomyosarcomas) that rapidly metastasized to the lungs, necessitating euthanasia. No tumors were found in a group of 46 rats implanted with an inert control metal (tantalum), even up to 12 months postimplantation. The tungsten alloy pellets consisted of 91.1% tungsten, 6% nickel, and 2.9% cobalt. Kalinich et al. (2005) also embedded 36 rats with nickel pellets to serve as positive controls for the tungsten-alloy embedded rats since intramuscularly-injected nickel has previously been demonstrated to cause injection-site tumors (Heath and Daniel 1964). All of the nickel-embedded rats developed tumors similar to those observed in the tungsten alloy-embedded rats (Kalinich et al. 2005). Previous experiments with intramuscularly-injected cobalt have also demonstrated a carcinogenic effect (Heath 1954, 1956). Since both nickel and cobalt, components of the tungsten-alloy pellets used by Kalinich et al. (2005), are known to be carcinogenic when injected intramuscularly, the potential role of tungsten in the carcinogenic effect of the tungsten alloy pellets used by Kalinich et al. (2005) could not be determined.

3.3 GENOTOXICITY

The genotoxic potential of tungsten and tungsten compounds has not been extensively assessed. Sodium tungstate demonstrated mutagenic activity in a bacterial bioluminescence test in *Photobacterium fischeri*

(Pf-13) (Ulitzur and Barak 1988). Sodium tungstate induced lambda prophage in *Escherichia coli* WP2s (λ) (Rossman et al. 1984, 1991) and gene conversion at *trp* 5 and reverse mutation at *ilv* 1 in *Saccharomyces cerevisiae* strain D7 (Singh 1983), and increased recombinant frequency in strain DIS13 (Sora et al. 1986). Positive results were obtained for tungstate anion in Chinese hamster lung V79 cells using the HGPRT forward mutation assay (Zelikoff et al. 1986). Tungsten (form not specified) enhanced mutagenic activity in *Salmonella typhimurium* strain TA98 and Ames mixed strains (TA7001-7006) (Miller and Page 1999).

Sodium tungstate did not increase sister chromatid exchanges in human whole blood cultures or cause chromosome aberrations in human lymphocytes or Syrian hamster embryo cells (Larramendy et al. 1981). The chemical did not induce morphological transformation in Syrian hamster cells (DiPaolo and Casto 1979).

Dose- and time-dependent increases in DNA single strand breaks (comet and alkaline elution tests) and micronucleus induction were observed in human peripheral lymphocytes incubated in either tungsten carbide cobalt alloy or cobalt alone, but not in tungsten carbide alone (Anard et al. 1997; Van Goethem 1997). In each of these tests, the genotoxic effect of the tungsten carbide cobalt alloy was greater than that of cobalt alone, which is consistent with a suggestion that physicochemical properties of the alloy may result in increased production of hydroxyl radicals (see also Section 3.5.2). Using human osteoblast cells, Miller et al. (2001) found that heavy metal-tungsten alloys composed of tungsten (92%), nickel (5%), and either cobalt (3%) or iron (3%) are capable of inducing neoplastic transformation (characterized by anchorage-dependent growth, tumor formation in nude mice, and expression of high levels of the K-*ras* oncogene), as well as increased DNA strand breakage and micronuclei at rates exceeding that of nickel sulfide (a well-known transforming agent and carcinogen). More recently, Miller et al. (2004) demonstrated that pure tungsten is capable of inducing a similar effect, but at a significantly reduced magnitude relative to the heavy metal-tungsten alloys.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No quantitative data were located concerning absorption of tungsten in humans following inhalation exposure to tungsten or tungsten compounds. However, absorption of airborne tungsten was indicated by

a report that tungsten levels in urine, toenails, and hair of workers occupationally exposed to airborne tungsten were higher than those of controls without known inhalation exposure (Nicolaou et al. 1987).

Available animal data, derived primarily from studies that employed radioactive tungsten isotopes that are identical to their respective nonradioactive isotopes with respect to toxicokinetics, demonstrate absorption following exposure to airborne tungsten. Beagle dogs were exposed (nose only) once (duration unspecified) to particulate aerosols of tungstic oxide ($^{181}WO_3$) (Aamodt 1975). Inhaled radioactivity was determined to range from 1.9 to 8 µCi and the inhaled radioactivity exhibited an activity median aerodynamic diameter (AMAD) of 0.7 µm and a geometric standard deviation of 1.5 µm. An estimated 60% of the inhaled radioactivity was deposited in the respiratory tract, approximately half of which was contained in the tracheobronchial and pulmonary regions. These estimates were based on periodic measurements of radioactivity in inspired versus expired air, in the lung region versus the lower body, and in the urine and feces. An estimated 33% of the radioactivity deposited in the lung was absorbed directly into the blood, most of which had entered the blood within the first 10 days following exposure. Based on measurements of radioactivity in the urine and feces, an estimated 66% of the initial lung burden was cleared to the gastrointestinal tract via the ciliary escalator system. Comparison with results of the investigator's ingestion experiment using a single beagle dog indicated that one-fourth of the radioactivity entering the gastrointestinal tract may have been absorbed to the blood. Therefore, about half of the amount that was initially deposited in the lungs, corresponding to about one-third of the inhaled amount, may have eventually been absorbed to blood.

3.4.1.2 Oral Exposure

No quantitative data were located concerning absorption of tungsten in humans following oral exposure to tungsten or tungsten compounds. However, total intake and urinary and fecal excretion of tungsten and other nonessential elements were recorded for four healthy human volunteers given controlled diets for 5 days (Wester 1974). Assuming that the subjects were in tungsten balance, that the intake was primarily via the diet, and that daily urinary excretion of tungsten (approximately 6 µg/day) was proportional to the daily intake (approximately 10 µg/day), approximately 60% of the ingested tungsten appeared to have been absorbed from the gastrointestinal tract. Additional indication of the absorption of ingested tungsten derives from the findings of high concentrations of tungsten in blood, urine, hair, and nail samples of a 19-year-old male who had consumed a mixture of beer and wine that contained a high concentration of metallic tungsten (Marquet et al. 1997). The tungsten concentrations were measured by inductively

coupled plasma (ICP) emission-spectrometry, a procedure that did not detect tungsten in samples taken from individuals without known exposure to tungsten at levels above normal background.

Results of animal studies suggest that tungsten is readily absorbed following oral administration of soluble tungsten compounds. In rats, approximately 40% of an orally administered dose of ^{185}W sodium tungstate (Na_2WO_4) was collected in the 24-hour urine (Ballou 1960; Kaye 1968). Approximately 25% of the activity in a single gavage dose of tungstic oxide was excreted in the urine of a single dog (Aamodt 1975), which indicates that tungsten is readily absorbed from the gastrointestinal tract of the dog as well. Poucheret et al. (2000) and LeLamer et al. (2000) assessed the absorption of tungsten (as sodium tungstate) following single oral administration in rats (36 mg sodium tungstate/kg) and dogs (25 mg sodium tungstate/kg) by plotting plasma tungsten concentrations at a number of time points (up to 24 hours) postadministration and comparing the area under the curve (AUC) in each plot to that obtained from species-specific animals that had received single intravenously-administered doses of 8.97 mg sodium tungstate/kg. Using this approach, absorption of tungsten was calculated to approximate 92% in the rat and 65% in the dog. Absorption of tungsten was calculated to approximate 55% during repeated oral dosing of dogs at 5–20 mg sodium tungstate/kg, 3 times/day for 13 weeks (LeLamer et al. 2001).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption of tungsten in humans or animals following dermal exposure to tungsten or tungsten compounds. However, the report of death in rabbits following dermal application of a 5% tungsten chloride solution in single doses of 100–1,000 mg/kg (Dow Chemical Company 1982) indicates that dermal absorption of tungsten occurs to some extent.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No reports were located regarding quantifiable distribution of tungsten in humans following inhalation exposure to tungsten or tungsten compounds. However, when compared to controls without known occupational exposure to tungsten, higher levels of tungsten in hair and nails of workers occupationally exposed to airborne tungsten serves as indication that inhaled tungsten may be distributed to these sites (Nicolaou et al. 1987).

Beagle dogs were exposed (nose only) once (duration unspecified) to particulate aerosols of tungstic oxide ($^{181}WO_3$) (Aamodt 1975). Inhaled radioactivity was determined to range from 1.9 to 8 µCi, and the inhaled radioactivity exhibited a mean aerodynamic diameter (AMAD) of 0.7 µm and a geometric standard deviation of 1.5 µm. Approximately 70% of the initial tungsten lung burden, which was estimated to have been approximately 60% of the inhaled radioactivity, was removed with a half-time of 4 hours. Another 20–25% was removed with a half-time of 20 hours, and approximately 5% with a half-time of 6.3 days. A small amount of tungsten may have been retained by the lung for months. Approximately 33% of the tungsten that was removed from the lung entered the blood directly. An estimated 66% was transported upwards via mucociliary action and swallowed, most of which was subsequently excreted in the feces. At sacrifice (approximately 165 days postexposure), the average body burden calculated from organ and tissue samples was 0.017 (1.7%) of the inhaled activity. The highest concentrations were in the lungs and kidneys. Radioactivity measured in bone, gall bladder, liver, and spleen was approximately 10-fold lower than that of lungs and kidneys. Measurable activity was also found in decreasing concentration in testes, pancreas, large intestine, small intestine, diaphragm, stomach, heart, and skeletal muscle, respectively. In terms of total activity in individual organs and tissues, activity was highest in bone (37% of the body burden at sacrifice), followed by lung (31%), kidneys (15%), liver (9.7%), and skeletal muscle (5.7%).

3.4.2.2 Oral Exposure

No reports were located regarding quantifiable distribution of tungsten in humans following oral exposure to tungsten or tungsten compounds. However, findings of measurable levels of tungsten in blood, urine, hair, and nail samples, taken from a 19-year-old male who had consumed a mixture of beer and wine that contained a high concentration of metallic tungsten (Marquet et al. 1997), indicated that ingested tungsten is absorbed by the blood and distributed systemically. The presence of tungsten in the urine of subjects who voluntarily consumed diets that were supplemented with tungsten is further indication that ingested tungsten is distributed systemically (Wester 1974).

Results of animal studies indicate that orally administered tungsten (in soluble form) rapidly enters the blood and is distributed via systemic circulation. In rats, most of the radioactivity in an initial oral (gavage) dose of sodium tungstate (activity of 34.3 µCi) had been eliminated in the first 24 hours postadministration (Ballou 1960). However, approximately 2% of the initial radioactivity was retained. On day 1 postadministration, the highest concentrations of radioactivity were measured in the gastrointestinal tract, followed by spleen, kidneys, pelt, and skeleton. Measurable concentrations were

also noted in liver > ovaries > pancreas > lung > heart > blood > fat > muscle. At 102 days postadministration, the highest concentrations of retained radioactivity were in the spleen and skeleton. Total skeletal deposition was about 0.4% of the administered dose.

Similar results were reported by Kaye (1968). Rats were administered single gavage doses of solutions containing radiotungsten (^{187}W or ^{185}W) as tungstate. Distribution and elimination of radioactivity was examined for 72 hours (^{187}W) or 254 days (^{185}W) postadministration. During the first 24 hours following dosing, virtually all of the radioactivity measured in the blood was associated with the plasma portion. During the next 2 days of measurements, radioactivity appeared in the cellular portion and accounted for approximately two-thirds of the radioactivity in the blood 72 hours following dosing, at which time, approximately 97% of the initially administered dose of radiotungsten had been eliminated from the body. During the first week after dosing, highest concentrations of radiotungsten in soft tissues were observed in spleen, hair, kidney, uterus, liver, prostate, and ovary. After 100 days, >99% of the remaining total body burden (approximately 0.4% of the administered dose) was retained in bone.

Results of an earlier rat study (Kinard and Aull 1945) also indicated that bone and spleen retained the highest concentrations of tungsten following dietary administration of tungsten (as tungstic oxide, sodium tungstate, ammonium paratungstate, or tungsten metal) for 100 days.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of tungsten in humans or animals following dermal exposure to tungsten or tungsten compounds. However, a report of death in rabbits following a single dermal application of a 5% tungsten chloride solution (Dow Chemical Company 1982) is evidence of systemic distribution of dermally-applied tungsten.

3.4.2.4 Other Routes of Exposure

Intravenous injection studies of radiotungsten ($Na_2{}^{181}WO_4$) support the results of inhalation and oral studies (Ando et al. 1989; Wase 1955; Wide et al. 1986). Three hours postadministration, levels of radiotungsten in rats were as follows: kidney > bone > liver >lung > adrenal > spleen > pancreas > blood > thymus > cardiac muscle > skeletal muscle > brain (Ando et al. 1989). At 48 hours postadministration, the highest levels of radiotungsten were found in bone > kidney > lung and liver > spleen. Lesser

amounts were noted in the other examined tissues and organs. Eight hours following intraperitoneal injection of ^{185}W (as $K_2{}^{185}WO_4$) in mice, relative concentrations of radioactivity were: bone > gastrointestinal tract > spleen > kidney > red blood cells > heart > lung > liver > plasma > brain (Wase 1955). After 48 hours postadministration, nearly all of the measurable radioactivity was in the bone.

Wide et al. (1986) demonstrated that intravenously injected tungstate (^{185}W) readily crossed the placenta of pregnant rats and was distributed to the fetus. Embryonic uptake was greater in dams injected at later stages of gestation (day 17) as opposed to earlier stages (day 8 or 12). Radiotungsten accumulated in yolk sac epithelium at all examined gestational stages. The highest level of fetal retention was noted in the skeleton.

3.4.3 Metabolism

Tungsten ion in the body is not known to be metabolized. It has been postulated that tungsten may preferentially occupy enzyme sites normally reserved for the essential element, molybdenum, because sodium tungstate has been shown to antagonize the normal metabolic action of molybdate in its role as cofactor for the enzymes xanthanine dehydrogenase (Higgins et al. 1956a, 1956b), sulfite oxidase, and aldehyde oxidase (Johnson and Rajagopalan 1974), and xanthine oxidase secretion to milk (Owen and Proudfoot 1968) in animal systems. See Section 3.5.2 for detailed information regarding mechanisms of tungsten-induced toxicity.

3.4.4 Elimination and Excretion

Elimination and excretion of tungsten is discussed without subdividing data according to route of exposure. Once tungsten has been systemically distributed following inhalation, oral, or dermal exposure or parenteral injection, the pattern of elimination is similar across exposure routes.

Information concerning elimination and excretion of tungsten in humans is limited to findings of measurable amounts of tungsten in urine of individuals exposed to tungsten either in the workplace air (see Barborik 1972; Nicolaou et al. 1987) or by controlled (Wester 1974) or accidental (Marquet et al. 1997) ingestion of tungsten.

Inhalation, oral, and parenteral injection studies in laboratory animals all indicate that absorbed tungsten is rapidly eliminated from the blood and quickly excreted in large quantities in the urine. Combined urinary and fecal excretion of radiotungsten from dogs following inhalation exposure to particulate aerosols of $^{181}WO_3$ was described by three exponential components (Aamodt 1975). Approximately 90% of the inhaled radioactivity was removed with a biological half-time of about 14 hours; 6% with a half-time of 5.8 days, and 4% with a half-time of 63 days. The average urine to fecal ratio was 1.14 for the 100 days of postexposure measurements, including the portion of tungsten that entered the blood directly from the lungs (approximately 33% of the deposited dose) as well as that which was deposited in the gastrointestinal tract via mucociliary clearance (approximately 66% of the initial lung burden).

Radiotungsten was rapidly excreted from rats following oral dosing (Kaye 1968). In a study of rats administered single gavage doses of ^{185}W and followed for 72 hours, approximately 40% of the administered dose of radiotungsten had been eliminated in the urine in the first 12 hours postadministration; an additional 3% was eliminated during the subsequent 60 hours. The initial rate of fecal excretion was lower than that of urinary excretion; however, by 72 hours, fecal excretion had accounted for approximately 53% of the administered dose. Thus, 72-hour urinary and fecal excretion accounted for 97% of the administered dose. Other rats were similarly administered ^{185}W and followed for up to 254 days. During the first 3 days following dosing, approximately 36 and 39% of the administered dose had been recovered in the urine and feces, respectively. By day 33 postadministration, radiotungsten could no longer be detected in the feces. Trace amounts of radiotungsten were still detected in urine analyses conducted until day 191 and correlated with slow elimination of ^{185}W from bone. In dairy cows that were orally administered radiotungsten, approximately 0.4% of the administered dose was recovered in the milk during the first 84 hours postadministration (Mullen et al. 1976).

Following intravenous injection of dogs with ^{181}W (as sodium tungstate), elimination from the blood was rapid (Aamodt 1973). By 24 hours, 91% of the injected radioactivity had been excreted in the urine. An initial urinary to fecal ratio of 49 on day 1 was reduced to a constant value of 38 by day 7.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of

potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994).

PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for tungsten exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

International Commission for Radiological Protection (ICRP 1981) Biokinetic Model for Tungsten

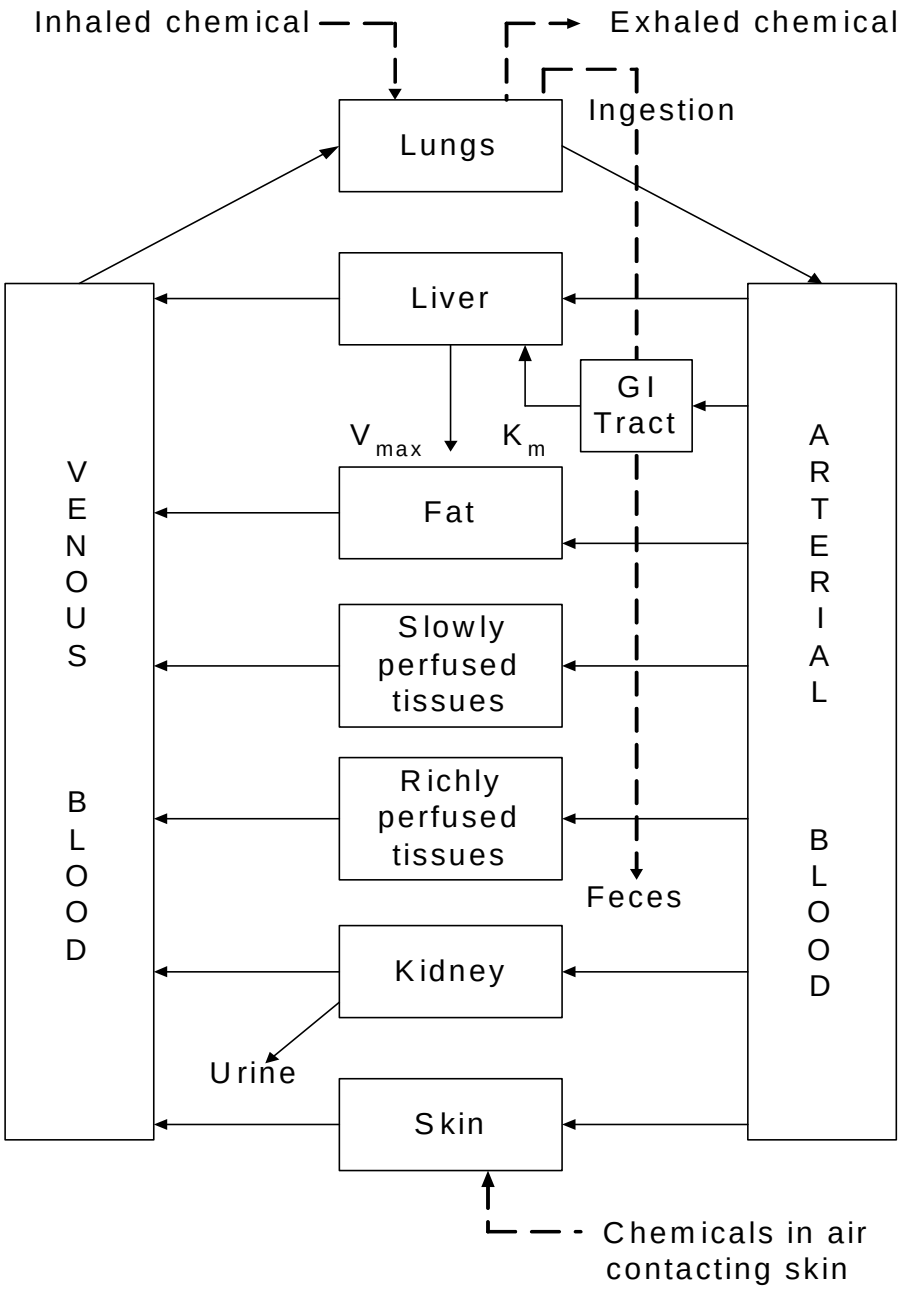
The ICRP's modular approach to biokinetic modeling.

In ICRP documents addressing occupational or environmental exposures to radionuclides, the biokinetic model for an element consists of three submodels: a respiratory tract model, a gastrointestinal tract model, and an element-specific systemic biokinetic model. For a given element, the generic respiratory tract model is used to describe the deposition and retention of inhaled material in the respiratory tract and subsequent clearance to blood or the gastrointestinal tract via mucociliary transport and swallowing. The generic gastrointestinal tract model is used to describe the movement of swallowed or endogenously secreted material through the stomach and intestines, and, together with an element-specific gastrointestinal absorption fraction (f_1 value), to describe the rate and extent of absorption of the element to blood. An element-specific systemic biokinetic model is used to describe the time-dependent distribution and excretion of the element after its absorption into blood.

The ICRP's gastrointestinal model (ICRP 1979) as applied to tungsten (ICRP 1981).

The ICRP's generic gastrointestinal tract model divides the gastrointestinal contents into stomach (S), small intestine (SI), upper large intestine (ULI), and lower large intestine (LLI). Material moves from S to SI at the rate of 24 day^{-1}, from SI to ULI at 6 day^{-1}, from ULI to LLI at 1.8 day^{-1}, and from LLI to feces at 1 day^{-1}. Absorption to blood is represented as transfer from SI to blood. In the absence of radioactive decay, the fraction f_1 of the ingested element moves from SI to blood and the fraction $1-f_1$ moves from SI to ULI. The transfer coefficient from SI to blood is $6f_1/(1-f_1)$ day^{-1}. An absorption fraction f_1 of 0.3 is applied to compounds of tungsten other than tungstic acid, for which an absorption fraction of 0.1 is used.

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Differences in the values for f_1 reflect measured differences in fractional absorption of various tungsten compounds in rats (Ballou 1960; Kaye 1968).

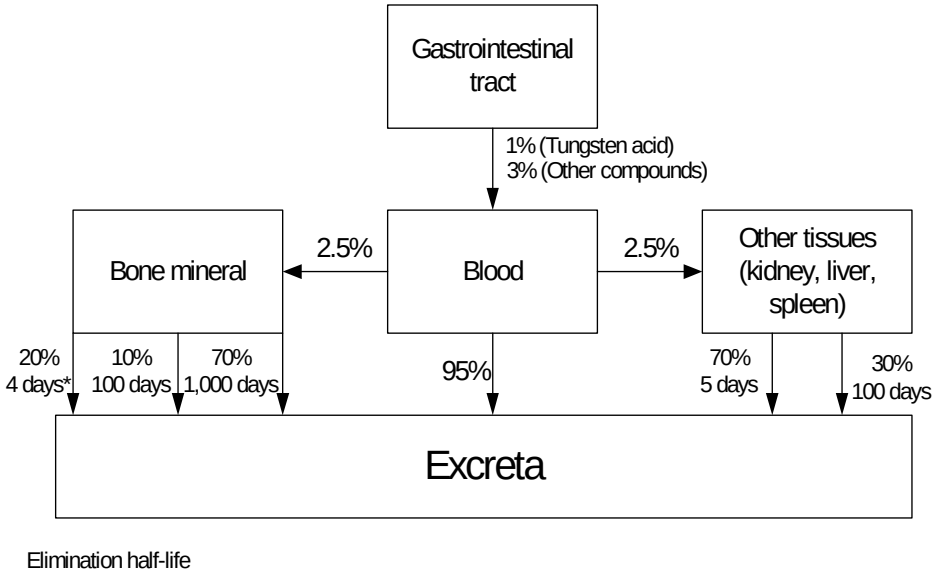
The ICRP's respiratory model (ICRP 1994a) as applied to tungsten (ICRP 1995).

The ICRP uses a generic respiratory model (ICRP 1994a) to describe deposition and retention of inhaled elements in the respiratory tract, absorption to blood, and transfer to the stomach via movement up the tracheobronchial tree in mucus and subsequent swallowing. The kinetics of swallowed activity is described by the gastrointestinal tract model summarized above. Elements or specific compounds of elements inhaled in particulate form are assigned to one of three "absorption types" representing the rate of transfer of material from the lungs to blood, which in turn is related to the rate of dissolution of the material in the respiratory tract. The three absorption types are Type F, representing fast absorption; Type M, representing moderately slow absorption; and Type S, representing slow absorption. There are numerous parameter values associated with each absorption type; these will not be listed here. Compounds of tungsten are assumed to be dissolved fairly rapidly in the respiratory tract and, thus, are assigned to Type F (ICRP 1994b).

The ICRP's systemic biokinetic model for tungsten (ICRP 1981).

The ICRP uses an element-specific systemic biokinetic model to describe the kinetics of the element after its absorption to blood from the respiratory tract or gastrointestinal tract, or entry from wounds or direct injection into blood. The ICRP's current systemic biokinetic model for tungsten (ICRP 1981) was developed in the 1970s. The model (Figure 3-4) consists of exponential curve fits to selected data on the relatively short-term behavior of tungsten in dogs, goats, and rats. In the development of the model, no attempt was made to reflect the physiological processes that control the biokinetics of tungsten or to depict actual paths of movement of this element in the body. Absorbed tungsten is assumed to enter the blood, from which 95% immediately transfers to excreta by unspecified routes, 2.5% transfers to bone mineral, 1% transfers to kidney, 1% transfers to liver, and 0.5% transfers to spleen. Tungsten in bone is removed in excretion with half-times of 4 days (20%), 100 days (10%), and 1,000 days (70%). Tungsten in any other tissue is removed to excretion with half-times of 5 days (70%) and 100 days (30%).

Figure 3-4. ICRP (1981, 2001) Biokinetics Model for Tungsten



Validation of the model.

The extent to which the ICRP model has been validated is not described in ICRP (1981).

Risk assessment.

The model has been used to establish radiation dose equivalents (Sv/Bq) of ingested and inhaled radioactive tungsten isotopes for ages 1 day to 50 years (ICRP 2001).

Target tissues.

The model is designed to calculate intake limits for radioactive tungsten, based on radiation dose to all major organs, including the bone surfaces, bone marrow, and soft tissues.

Species extrapolation.

The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation.

The ICRP's systemic biokinetic model for tungsten can be applied to any route of exposure (e.g., from the respiratory or GI tract, wounds, through the skin, or via intravenous injection), provided information is available on the time-course of entry of tungsten into blood.

Leggett (1997) Model of the Biokinetics of Absorbed Tungsten

Description of the model.

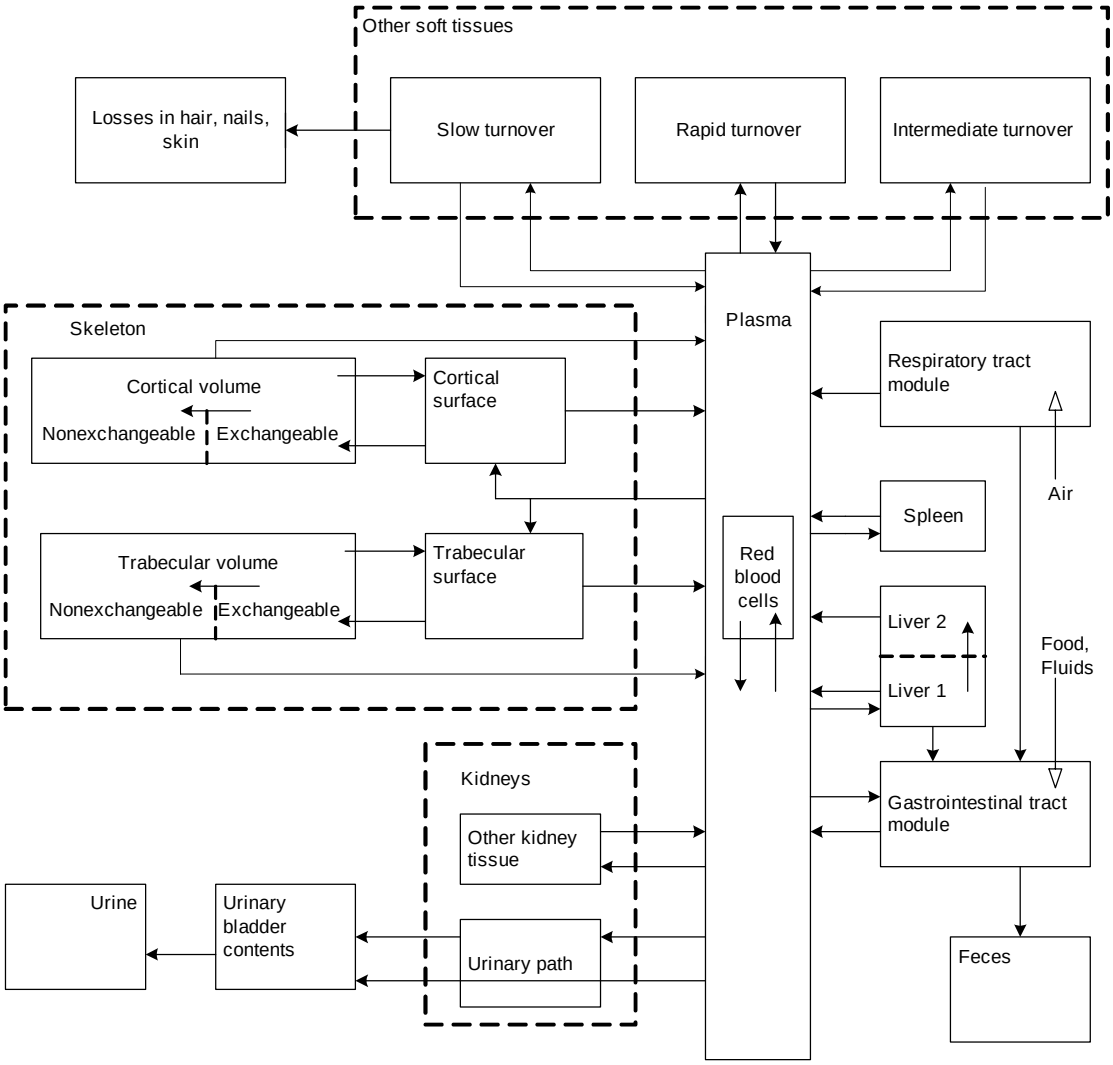
Leggett (1997) developed a compartmental model of the biokinetics of absorbed tungsten in adult humans that can be linked to the ICRP's gastrointestinal tract model (ICRP 1979, 1981) or respiratory model

(ICRP 1994). The model differs considerably from the ICRP's systemic biokinetic model for tungsten with regard to structure, basis for parameter values, and predicted retention of tungsten in tissues. The model structure (Figure 3-5) is intended to depict physiologically realistic directions of movement of tungsten in the human body, including the systemic redistribution of tungsten that enters blood after removal from tissues. Model parameters are based on results of biokinetic studies of tungsten in dogs, swine, sheep, goats, cows, and rodents. Although tungsten biokinetics has been studied more frequently in rats than other species, data for rats were given low weight in selection of most parameter values because of known qualitative differences between rats and humans in the handling of molybdenum, a chemical and physiological analogue of tungsten. It is suspected that membrane transport may not distinguish between analogous compounds of tungsten and molybdenum, although biokinetic differences between tungsten and molybdenum arise, probably because molybdenum compounds are more easily reduced in biological systems (Callis and Wentworth 1977). The species differences recognized for molybdenum may apply to tungsten as well, as suggested by the much faster excretion of tungsten by rats than other studied species and apparent differences in the distribution of retained tungsten. On the other hand, some aspects of the biokinetics of tungsten or molybdenum, including long-term skeletal retention due to substitution of tungstate or molybdate for phosphate in bone, are expected to be independent of species.

The structure of the model for tungsten (Figure 3-5) is essentially the same as that applied in ICRP Publication 69 (1995) to a set of "bone-volume-seeking" elements, including calcium, strontium, barium, radium, lead, and uranium. It is assumed that the kinetics of tungsten that deposits in bone can be related to the kinetics of the major components of bone mineral, calcium, and phosphorus.

Transport of tungsten between compartments is assumed to follow first-order kinetics. Three compartments are used to describe the kinetics of circulating tungsten: (1) blood plasma, (2) red blood cells, and (3) a rapid-turnover soft-tissue compartment representing extracellular fluids. The rapid-turnover soft-tissue compartment is used to depict an early build-up of tungsten in extravascular spaces followed by relatively rapid feedback to blood. The total transfer rate from plasma to all destinations is set at 16.64 day^{-1}, corresponding to a removal half-time of 1 hour. The rapid-turnover soft-tissue compartment receives 30% of tungsten leaving plasma and returns tungsten to plasma with a half-time of 2 hours. The division of tungsten leaving the circulation, defined as atoms moving from plasma to compartments other than rapid-turnover soft-tissues, is as follows: 75% to the urinary bladder contents; 5% to kidney tissue; 5% to the contents of the upper large intestine (representing all secretions into the gastrointestinal tract); 4% to liver; 8% to bone surfaces; 2.5% to other soft tissues; and 0.5% to

Figure 3-5. Leggett (1997) Biokinetics Model for Tungsten



Adapted from Leggett 1997

red blood cells. The assigned removal half-times from the various compartments within these tissues vary from 1 day (from bone surfaces) to about 23 years (from cortical bone volume). Tungsten removed from the skeleton, certain kidney tissue, liver tissue, remaining soft tissues, and red blood cells is assigned to plasma and redistributed to excretion pathways and tissues in the same ratio as the initial input into plasma. Most of the tungsten removed from kidney tissue is assigned to the urinary bladder contents.

Bone is divided into cortical and trabecular portions and each of these is further divided into a bone surface compartment and exchangeable and nonexchangeable bone volume compartments. Approximately 55% of tungsten entering the skeleton is assigned to trabecular surfaces and 45% to cortical surfaces. Tungsten is removed from bone surface with a half-time of 1 day, with 5/6 returning to plasma and 1/6 entering the corresponding exchangeable bone volume compartment. It is removed from exchangeable bone volume with a half-time of 100 days, with 60% assigned to the corresponding nonexchangeable bone volume compartment and 40% to the corresponding bone surface compartment. Removal from nonexchangeable bone to plasma occurs at the rate of bone turnover, estimated as 0.03 $year^{-1}$ for cortical bone (half-time of ~23 years) and 0.18 $years^{-1}$ for trabecular bone (half-time approximately 4 year).

The model predicts a rapid decline in body burden of tungsten after cessation of exposure; approximately 15% of the burden remains after 1 day, 5% after 1 week, 3% after 1 month, 1.6% after 1 year, and 0.4% after 10 years. The slowest component of the decline represents stores in bone volume; therefore, over time, the fraction of the body burden associated with bone increases to 60% after 1 year and 90% after 4 years. Steady state in soft tissue is predicted after approximately 300–500 days of continuous exposure, whereas, bone continues to accumulate tungsten with chronic exposure.

Validation of the model.

An evaluation of the extent to which the model has been validated was not located. Predictions from the model were compared to those from the ICRP (1981) model (Leggett 1997). Over the first few years after intake, the two models yield reasonably consistent predictions of total-body retention, but noticeably different predictions of retention in specific tissues. For example, the ratio of predicted retention values, ICRP model:Leggett model, at 1 day after acute uptake of tungsten to blood is 0.75 for the total body, but 0.44 for bone or kidney, 0.28 for liver, and 8.5 for spleen. For times greater than a few years after intake, the ICRP model predicts considerably faster decline of activity in all tissues, with the ratio ICRP model:Leggett model at 10,000 days after acute intake being <0.01 for total body or bone retention and

<0.001 for retention in all other tissues. Differences in predictions of the two models result in part from differences in the databases considered, in that the ICRP restricted attention to specific data sets and relied heavily on data for rats, which were generally given low weight in the model of Leggett. Predictive differences also arise from differences in the method of extrapolation to times beyond the periods of observation of tungsten retention in laboratory animals. For example, in the ICRP model, a removal half-time from bone of 1,000 days is arbitrarily applied to represent "a very long-term component of retention in the skeleton" (ICRP 1981). In the Leggett model, long-term removal of tungsten from bone is assumed to occur at the rate at which human bone is remodeled.

Risk assessment.

The extent to which the model has been applied to risk assessment is not described in Leggett (1997). The model is configured to be applicable for estimation of time-integrated target tissue doses, blood tungsten levels, and tungsten excretion.

Target tissues.

The model output includes tungsten levels in bone, blood, kidney, liver, other soft tissues, and plasma.

Species extrapolation.

Parameter values of the model were derived for adult humans. The model structure is applicable to other mammalian species, but application to other species would require the derivation of appropriate parameter values based on species-specific information.

Interroute extrapolation.

The Leggett systemic biokinetic model for tungsten can be applied to any route of exposure (e.g., from the respiratory or gastrointestinal tract, wounds, through the skin, or via intravenous injection), provided information is available on the time-course of entry of tungsten into blood.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Absorption of inhaled tungsten has been demonstrated in dogs (Aamodt 1975). Approximately one-third of a dose of radiotungsten ($^{181}WO_3$) that was deposited in the respiratory tract was transferred to the blood. Based on relatively rapid clearance of a portion of the deposited activity from the lungs (70% was cleared with a half-time of 4 hours), diffusion may account for at least a portion of the dose entering the blood. Experimental data also indicate that tungsten particles may be dissolved within alveolar macrophages (De Sousa Pereira et al. 1992; Grande et al. 1990; Peão et al. 1993) and transported to the lymphatic system (Águas et al. 1991; Grande et al. 1990). The relative solubility of a given tungsten compound also likely dictates the degree and rate of absorption. At least a portion of tungsten inhaled as hard metal dust may be retained in lung tissue for an extended period (Cugell et al. 1990; Edel et al. 1990).

Ingested tungsten appears to be largely absorbed from the lower ileum, based on results of an *in vitro* study using the rat small intestine (Cardin and Mason 1976). Results of both *in vitro* and *in vivo* studies in rats indicate that gastrointestinal absorption and transport of tungsten probably occurs via the same pathways employed by the essential element molybdenum (Cardin and Mason 1976; Johnson and Rajagopalan 1974; Johnson et al. 1974). The results further indicate that a transport system common to molybdenum and tungsten is subject to competitive inhibition.

No information was located regarding mechanisms involved in absorption of tungsten through the skin. However, a report of death in rabbits following a single dermal application of a 5% tungsten chloride solution (Dow Chemical Company 1982) is evidence of absorption and systemic distribution of dermally-applied tungsten.

Distribution. Absorbed tungsten is rapidly distributed throughout the body and quickly eliminated predominantly via the urine. Mechanisms involved in the distribution of absorbed tungsten are not currently understood. However, rapid distribution via the blood and elimination via the kidney serve as indication that distribution does not likely include major binding to cellular components or proteins in blood. Retention of tungstate by the liver may be related to the findings that tungsten inhibits the binding of the essential element molybdenum to selected liver proteins (Johnson and Rajagopalan 1974). Retention of tungsten in bone has led to the suggestion that tungstate anions interact with calcium, thereby forming the relatively insoluble calcium tungstate (Wase 1955). In physiological systems such as

cells and blood, molecules binding anionic forms of tungsten might release these anions to water in exchange for dissolved phosphate ion, for which they may have greater affinity, as suggested by Wide et al. (1986).

Excretion. Inhalation, oral, and parenteral injection studies in laboratory animals all indicate that absorbed tungsten is rapidly eliminated from the blood and quickly excreted in large quantities in the urine (Aamodt 1973, 1975; Kaye 1968). Specific mechanisms involved in the excretion of tungsten were not identified in available reports.

3.5.2 Mechanisms of Toxicity

Specific mechanisms of tungsten-induced toxicity have not been elucidated. Pulmonary fibrosis in hard metal workers exposed to dusts containing tungsten carbide and cobalt has been historically attributed to the presence of cobalt, not tungsten (see Davison et al. 1983; Harding 1950). Based on results of studies in which pulmonary fibrosis was induced in rats following intratracheal instillation of tungsten carbide and cobalt in combination, but not in rats exposed to tungsten carbide or cobalt alone (Lasfargues et al. 1995), it has been proposed that tungsten carbide, a relatively good conductor of electrons, may facilitate the oxidation of cobalt metal to ionic cobalt, which could increase both the solubility of cobalt and the generation of active oxygen species (Lasfargues et al. 1995; Lison et al. 1995). *In vitro* evidence for this mechanism includes the ability of hard metal particles, but neither cobalt nor tungsten carbide alone, to generate oxidant species and cause lipid peroxidation (Lison et al. 1995; Zanetti and Fubini 1997). Hard metal particles have also been shown to increase the levels of inducible nitric oxide synthase (iNOS); the gene for iNOS is responsive to oxidant stress (Rengasamy et al. 1999).

Leanderson and Sahle (1995) demonstrated that respirable tungsten oxide fibers, which were measured in the air of hard metal industries (80% of the fibers were $\leq$0.3 μm in diameter) (Sahle 1992; Sahle et al. 1994), are capable of generating hydroxyl radicals in human lung cells *in vitro*, and that these fibers were more cytotoxic than crocidolite asbestos. It could be argued that generation of hydroxyl radicals might contribute toward the development of pulmonary fibrosis in individuals occupationally exposed to fibrous tungsten oxide in the hard metal industry. However, any attempt to link tungsten with the development of pulmonary fibrosis via a mechanism that includes the generation of hydroxyl radicals is speculative because such a mechanism has not been demonstrated *in vivo*.

In animals administered high levels of tungsten in combination with low dietary levels of molybdenum, the competitive agonistic properties of the two metals can be manifested by reduced levels of molybdenum and decreased activity of enzymes such as xanthine oxidase, sulfite oxidase and aldehyde oxidase, which normally incorporate molybdenum as a metal carrier (De Renzo 1954; Higgins et al. 1956a, 1956b; Johnson and Rajagopalan 1974; Johnson et al. 1974). Although these effects can be observed following exposure to elevated levels of tungsten, only very small amounts of supplemental molybdenum are required to reverse these tungsten-induced effects. The competitive agonistic properties of tungsten and molybdenum have not been associated with any observable signs of toxicity.

3.5.3 Animal-to-Human Extrapolations

No data were located concerning major interspecies differences in pharmacokinetics or health effects associated with exposure to tungsten or tungsten compounds. However, the rat exhibits a remarkably low requirement for molybdenum, relative to other animal species (Higgins et al. 1956b). The apparently low dietary requirement of molybdenum in the rat, as well as the competitive agonistic properties of molybdenum and tungsten and their chemical similarities, is suggestive evidence of species-specific differences in the biokinetics of tungsten.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors,* initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to

the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997c). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No information was located regarding the potential of tungsten or tungsten compounds to disrupt endocrine function.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a

particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No information was located regarding age-related differences in pharmacokinetics or toxicity of tungsten or tungsten compounds in humans. In one animal study, increased embryonic uptake of tungsten was observed via rat dams administered tungstate (^{185}W) intravenously during late gestation (day 17) compared to earlier treatment (gestation days 8 or 12) (Wide et al. 1986). Both pre- and post-implantation losses and delayed fetal skeletal ossification were reported in rats following oral administration of tungsten before and during pregnancy (Nadeenko and Lenchenko 1977; Nadeenko et al.

1977, 1978). However, deficiencies in study details render the reports of limited value for purposes of quantitative health risk assessment. Particular sensitivity to tungsten during fetal development and postnatal periods of nursing may be of concern since absorption of tungsten in pregnant animals can result in the accumulation of tungsten in fetal tissues (Wide et al. 1986), and tungsten can enter the milk of tungsten-exposed animals (Mullen et al. 1976). However, no information was located regarding the ability of tungsten to cross the placenta or enter the breast milk of humans.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to tungsten and tungsten compounds are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung

capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by tungsten and tungsten compounds are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations that are Unusually Susceptible.”

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Tungsten and Tungsten Compounds

The presence of tungsten in the blood, urine, or feces serves as a biomarker of exposure to tungsten or tungsten compounds. Levels in these media may be used in conjunction with biokinetic models to estimate previous exposure levels.

3.8.2 Biomarkers Used to Characterize Effects Caused by Tungsten and Tungsten Compounds

Biomarkers of effect for tungsten or tungsten compounds were not identified in available literature.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Hard metal, consisting of tungsten carbide and cobalt, has been shown to present a more significant health concern than either tungsten carbide or cobalt alone (Lasfargues et al. 1995). Potential mechanisms for this phenomenon are discussed in Section 3.5.2.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to tungsten and tungsten compounds than will most persons exposed to the same level of tungsten and tungsten compounds in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to

other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of tungsten or tungsten compounds, or compromised function of organs affected by tungsten or tungsten compounds. Populations who are at greater risk due to their unusually high exposure to tungsten and tungsten compounds are discussed in Section 6.7, Populations with Potentially High Exposures.

Individuals with compromised respiratory function may exhibit increased sensitivity to airborne tungsten due to irritant properties of tungsten particles that may be deposited in the lungs. Individuals with compromised renal function may also experience particular sensitivity to tungsten since decreased urinary excretion could result in increased tungsten retention. Russian studies (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978) indicate that developing fetuses may be particularly sensitive to tungsten. However, these studies are limited in reporting of study details, which renders them of limited value for purposes of risk assessment.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to tungsten or tungsten compounds. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to tungsten or tungsten compounds. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

No texts were located regarding treatment following exposures to tungsten or tungsten compounds.

3.11.1 Reducing Peak Absorption Following Exposure

No data were located regarding reduction of peak absorption of tungsten following exposure. Cathartics such as magnesium sulfate, as well as gastric lavage, might shorten the transit time of ingested tungsten in the gastrointestinal tract. Oral administration of activated charcoal shortly following oral exposure to tungsten might be effective in reducing peak absorption.

3.11.2 Reducing Body Burden

No data were located regarding reducing the body burden of tungsten.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No data were located regarding reduction of the toxic effects of tungsten through interfering with mechanisms of action.

3.12 ADEQUACY OF THE DATABASE

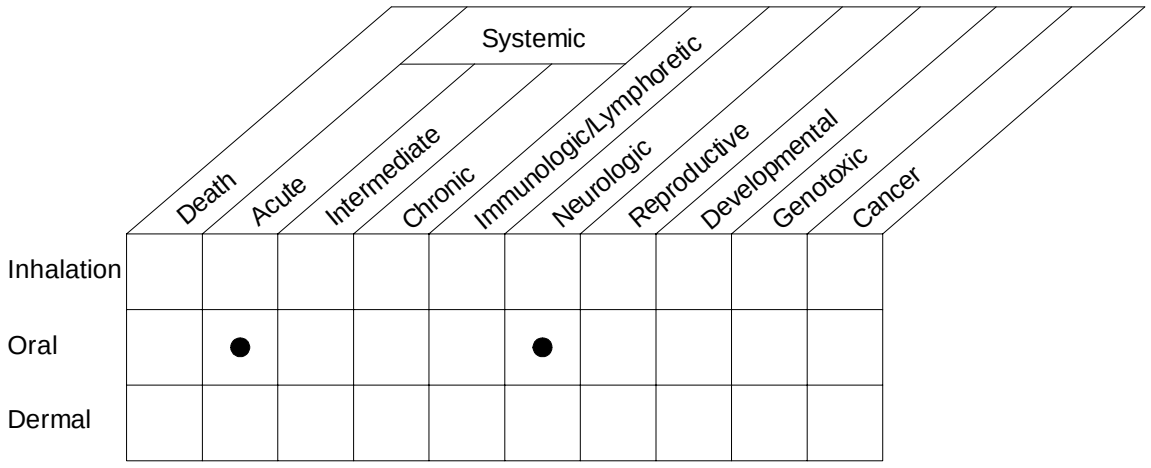
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of tungsten and tungsten compounds is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of tungsten and tungsten compounds.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

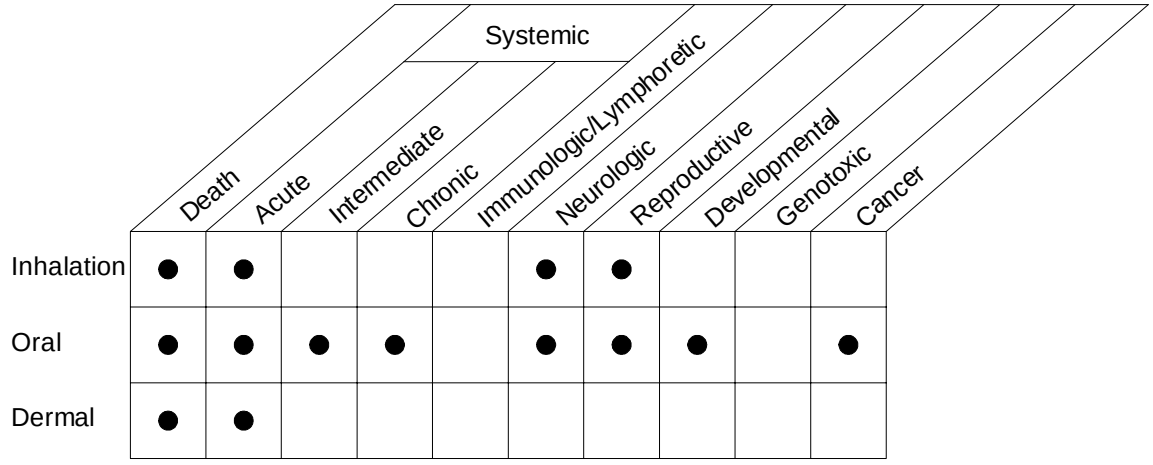
3.12.1 Existing Information on Health Effects of Tungsten and Tungsten Compounds

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to tungsten and tungsten compounds are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of tungsten and tungsten compounds. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct

Figure 3-6. Existing Information on Health Effects of Tungsten and Tungsten Compounds



Human



Animal

● Existing Studies

comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Available data regarding health effects in humans exposed to tungsten predominantly involves occupational exposure to dusts that include particles of tungsten and other metals (particularly cobalt) at facilities in which hard metal is produced. It is generally considered that cobalt is the source of adverse health effects such as pulmonary fibrosis and dermatitis in hard metal workers, not tungsten. A single case report was located concerning acute oral exposure to tungsten in a male subject. However, reported symptoms could not be specifically attributed to tungsten.

Relatively few reports were located regarding health effects in animals following acute-, intermediate-, or chronic-duration exposure to tungsten or tungsten compounds. Several early Russian reports were located, mainly originating from a single group of investigators. The reports predominantly assessed acute lethality or reproductive or developmental effects following oral exposure to soluble tungsten compounds. The carcinogenicity and genotoxicity of tungsten and tungsten compounds has not been adequately assessed in humans or animals. However, tungsten has been recently nominated by the National Center for Environmental Health for toxicological characterization including carcinogenicity (NTP 2003).

3.12.2 Identification of Data Needs

Acute-Duration Exposure. No human studies were located regarding health effects associated with acute-duration inhalation exposure to tungsten. Information in animals is restricted to exposure via intratracheal instillation of tungsten compounds. Intratracheal instillation of water-insoluble calcium tungstate crystals resulted in an inflammatory response in mice (Peão et al. 1993). Acute pulmonary edema was reported in rats that had received hard metal (tungsten carbide and cobalt alloy) via intratracheal instillation, but not in rats exposed to tungsten carbide or cobalt alone (Lasfargues et al. (1992). Due to the lack of information concerning adverse effects and targets of toxicity following acute-duration inhalation exposure to tungsten or tungsten compounds, no acute-duration inhalation MRLs were derived. Results of acute-duration inhalation toxicity studies that adequately characterize dose-response characteristics and target organs could serve as a basis to derive acute-duration inhalation MRLs for tungsten and tungsten compounds.

Information regarding health effects in humans following acute-duration oral exposure to tungsten is restricted to a single case report in which a male subject experienced neurological (nausea, seizure, and 24-hour coma) and renal (temporary renal failure, tubular necrosis, and anuria) effects following the accidental consumption of metallic tungsten in a mixture of beer and wine (Marquet et al. 1997). However, the observed effects could not be specifically attributed to tungsten. Reports of tungsten-induced adverse health effects in animals following acute-duration oral exposure to tungsten consist primarily of reports in which lethality was assessed (Karantassis 1924; Kinard and Van de Erve 1941; Nadeenko 1966; Smyth et al. 1969). Guinea pigs exhibited clinical signs that included trembling and abnormal locomotor behavior following single oral administration of sodium tungstate at ultimately lethal doses (≥780 mg/kg) (Karantassis 1924). Due to the lack of information concerning adverse effects and targets of toxicity following acute-duration oral exposure to tungsten or tungsten compounds, no acute-duration inhalation MRLs were derived. Results of acute-duration oral toxicity studies that adequately characterize dose-response characteristics and target organs could serve as a basis to derive acute-duration oral MRLs for tungsten and tungsten compounds.

Information concerning dermal effects in humans exposed to tungsten is restricted to a report of dermatitis in employees of the hard metal industry, but results of patch testing implicated cobalt, not tungsten, as the causative agent (Schwartz et al. 1945; Skog 1963). Relatively little information is available concerning adverse effects in animals following acute-duration dermal exposure to tungsten. Contact dermatitis was reported in rabbits following dermal application of a 5% tungsten chloride solution in single doses ≥100 mg/kg; doses ≥200 mg/kg also resulted in death (Dow Chemical Company 1982). Instillation of a 5% tungsten chloride solution into the rabbit eye resulted in initial ocular irritation that resolved within 14 days postinstillation (Dow Chemical Company 1982). Additional animal studies could be designed to assess the sublethal systemic toxicity of tungsten and selected tungsten compounds following acute-duration dermal exposure.

Intermediate-Duration Exposure. No human studies were located regarding health effects associated with intermediate-duration inhalation exposure to tungsten. Rats that were repeatedly exposed to atmospheres containing tungsten carbide at a concentration of 600 mg/m^3 exhibited signs of pulmonary fibrosis and clinical signs that were interpreted as anxiety manifestations (Mezentseva 1967). Decreased sperm motility was noted in rats continuously repeatedly exposed to atmospheres containing sodium tungstate at concentrations ≥0.5 mg/m^3 (Idiyatullina 1981). Mixed results were reported in laboratory animals following intratracheal instillation of selected tungsten compounds and examinations that spanned intermediate-duration post instillation periods. Signs of pulmonary fibrosis were reported in rats

observed for up to 8 months following intratracheal instillation of metallic tungsten, tungsten trioxide, or tungsten carbide (Mezentseva 1967). Lung lesions in the absence of apparent pulmonary fibrosis were reported in guinea pigs that had received 3 weekly doses of intratracheally-instilled metallic tungsten or tungsten carbide and carbon dust, followed by up to 12 months of posttreatment examination (Delahant 1955; Schepers 1955a, 1955b). No signs of a fibrotic response were seen in the lungs of mice that had received tungsten carbide via intratracheal instillation (Lardot et al. 1998). Due to the lack of information concerning adverse effects and targets of toxicity following intermediate-duration inhalation exposure to tungsten or tungsten compounds, no intermediate-duration inhalation MRLs were derived. Results of intermediate-duration inhalation toxicity studies that adequately characterize dose-response characteristics and target organs could serve as a basis to derive intermediate-duration inhalation MRLs for tungsten and tungsten compounds.

No human studies were located regarding health effects associated with intermediate-duration oral exposure to tungsten. In rats, early reports have associated repeated oral exposure to tungsten with neurological (Karantassis 1924), reproductive (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978), and developmental (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978) effects. Body weight changes, in the absence of other signs of toxicity, were reported in rats following repeated oral exposure to various tungsten compounds (Kinard and Van de Erve 1941, 1943). However, the available animal studies did not include critical dose-response information and other details (including methods used in statistical analysis of data), which precludes their usefulness for the purpose of MRL derivation. Therefore, no intermediate-duration oral MRLs were derived for tungsten. Results of intermediate-duration oral toxicity studies that adequately characterize dose-response characteristics could serve as a basis to derive intermediate-duration inhalation and oral MRLs for tungsten and tungsten compounds.

No human or animal data were located regarding noncancer or cancer end points associated with intermediate-duration dermal exposure to tungsten or tungsten compounds. Intramuscularly-implanted tungsten alloy (91.1% tungsten, 6.0% nickel, and 2.9% cobalt) was recently shown to rapidly cause aggressive tumors in rats (Kalinich et al. 2005). However, since both nickel and cobalt are known to cause tumors following intramuscular injection in rats (Heath 1954, 1956; Heath and Daniel 1964), the carcinogenic role of tungsten itself was not determined.

Chronic-Duration Exposure and Cancer. Information regarding chronic exposure of humans to tungsten primarily involves respiratory effects such as pulmonary fibrosis, memory and sensory deficits, and increased mortality due to lung cancer in hard metal workers exposed to dusts that include particles of

tungsten and other metals (particularly cobalt) (see Bech 1974; Bech et al. 1962; Coates and Watson 1971a, 1971b; Jordan et al. 1990; Kaplun and Mezentseva 1959; Lasfargues et al. 1994; Mezentseva 1967; Miller et al. 1953; Moulin et al. 1998; Vengerskaya and Salikhodzhaev 1962; Wild et al. 2000). It is generally considered that cobalt is the source of major toxicity concern, not tungsten (see Davison et al. 1983; Harding 1950). However, it has been suggested that tungsten oxide fibers may contribute to the development of pulmonary fibrosis in hard metal workers (Sahle 1992). No studies were located regarding chronic-duration inhalation exposure of laboratory animals to tungsten or tungsten compounds. Based on the lack of human and animal data, no chronic-duration inhalation MRLs were derived for tungsten or tungsten compounds. Results of well-designed chronic-duration inhalation studies in animals could serve as a basis to derive chronic-duration inhalation MRLs for tungsten and tungsten compounds.

No human studies were located regarding noncancer or cancer end points associated with chronic-duration oral exposure to tungsten. Information concerning health effects in animals following chronic-duration oral exposure to tungsten or tungsten compounds is restricted to reports by Schroeder and Mitchener (1975a, 1975b) in which tungsten-treated (5 ppm of tungsten as sodium tungstate in the drinking water for a lifetime) and control rats and mice exhibited similar growth patterns and incidences of gross tumors. However, these studies were limited to assessment of growth, gross tumor incidence, and longevity. Limited study design, including lack of both dose-response data and comprehensive histopathologic examinations preclude their usefulness for MRL derivation. Results of well-designed chronic-duration oral studies in animals could serve as a basis to derive chronic-duration oral MRLs for tungsten and tungsten compounds.

Recent findings of elevated tungsten body burdens in residents of Churchill County (City of Fallon), Nevada (CDC 2003b), and the discovery that a relatively limited amount of information is available concerning the potential for long-term adverse health effects following exposure to tungsten, have resulted in the nomination of tungsten by the National Center for Environmental Health (NCEH) for toxicological characterization, which includes carcinogenicity (NTP 2003).

No human or animal data were located regarding noncancer or cancer end points associated with chronic-duration dermal exposure to tungsten or tungsten compounds. Intramuscularly-implanted tungsten alloy (91.1% tungsten, 6.0% nickel, and 2.9% cobalt) was recently shown to rapidly cause aggressive tumors in rats (Kalinich et al. 2005). However, since both nickel and cobalt are known to cause tumors following intramuscular injection in rats (Heath 1954, 1956; Heath and Daniel 1964), the carcinogenic role of tungsten itself was not determined.

Genotoxicity. No information was located regarding tungsten-induced genotoxicity following inhalation, oral, or dermal exposure to tungsten or tungsten compounds in humans or laboratory animals. Sodium tungstate was found to induce mutagenic activity in a bacterial bioluminescence test (Ulitzur and Barak 1988), lambda prophage in *E. coli* (Rossman et al. 1984, 1991), and gene conversion and reverse mutation in *Saccharomyces cerevisiae* (Singh 1983). An unspecified form of tungsten enhanced mutagenic activity in *Salmonella typhimurium* (Miller and Page 1999). Tungstate anion induced forward mutation in Chinese hamster lung V79 cells *in vitro* (Zelikoff et al. 1986). Sodium tungstate did not increase sister chromatid exchanges in human whole blood cultures or cause chromosome aberrations in human lymphocytes or Syrian hamster embryo cells (Larramendy et al. 1981). Nor did sodium tungstate induce morphological transformation in Syrian hamster cells (DiPaolo and Casto 1979). Heavy metal-tungsten alloys are capable of inducing neoplastic transformation of human osteoblast cells (Miller et al. 2001). Pure tungsten is capable of inducing a similar effect (Miller et al. 2004), but at a significantly reduced magnitude relative to the heavy metal-tungsten alloys. Additional studies could be designed to further assess the potential for tungsten and tungsten compounds to induce genotoxicity.

Reproductive Toxicity. No information was located regarding reproductive toxicity in humans following inhalation exposure to tungsten or tungsten compounds. Information in animals is restricted to a single account of decreased sperm motility (10–12% lower than controls) in male rats continuously exposed to atmospheres containing sodium tungstate powder for 17 weeks at concentrations of 1.0 and 0.5 mg/m^3, but not at 0.1 mg/m^3 (Idiyatullina 1981).

No information was located regarding reproductive toxicity in humans following oral exposure to tungsten or tungsten compounds. Information in animals is restricted to reported embryotoxicity (expressed as increased percentages of pre- and post-implantation losses, relative to controls) following oral administration of an unspecified tungsten compound to adult female rats at a single dose level of 0.005 mg/kg for up to 8 months before and during pregnancy (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, deficiencies in study details regarding exposure and quantitative results render the results of these Russian studies of limited value for purposes of quantitative risk assessment. Additional well-designed animal studies would be useful to adequately assess the reproductive toxicity of orally-administered tungsten and tungsten compounds. Such studies could include standard reproductive toxicity studies as well as conventional intermediate-duration oral toxicity studies that would include an assessment of reproductive organ pathology.

No information was located regarding reproductive toxicity in humans or animals following dermal exposure to tungsten or tungsten compounds. However, inhalation is the most likely significant route of exposure to tungsten or tungsten in workers employed in industries that produce or use tungsten-containing products. Elevated levels of tungsten in groundwater, such as was detected in well water in Churchill County (City of Fallon), Nevada (CDC 2003b), indicate the potential for significant oral exposure to tungsten and tungsten compounds as well. It does not appear that additional studies of health effects associated with dermal exposure to tungsten or tungsten compounds are necessary at this time.

Developmental Toxicity. No information was located regarding developmental toxicity in humans or animals following inhalation exposure to tungsten or tungsten compounds. Animal studies could be performed to assess the potential for tungsten-induced developmental effects via the inhalation exposure route.

No information was located regarding developmental toxicity in humans following oral exposure to tungsten or tungsten compounds. Information in animals is restricted to reported delayed fetal skeletal ossification following oral administration of an identified tungsten compound to adult female rats at a single dose level of 0.005 mg/kg for up to 8 months before and during pregnancy (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, deficiencies in study details regarding exposure and quantitative results render the results of these Russian studies of limited value for purposes of quantitative risk assessment. Additional well-designed animal studies should be performed to adequately assess both pre- and post-natal potential for tungsten-induced developmental effects via the oral exposure route.

No information was located regarding developmental toxicity in humans or animals following dermal exposure to tungsten or tungsten compounds. However, inhalation is the most likely significant route of exposure to tungsten in workers employed in industries that produce or use tungsten-containing products. Elevated levels of tungsten in groundwater, such as was detected in well water in Churchill County (City of Fallon), Nevada (CDC 2003b), indicate the potential for significant oral exposure to tungsten and tungsten compounds as well. It does not appear that additional studies of health effects associated with dermal exposure to tungsten or tungsten compounds are necessary at this time.

Immunotoxicity. No information was located concerning tungsten-induced immunotoxicity in humans or animals following inhalation, oral, or dermal exposure to tungsten or tungsten compounds. A

single report was located in which a marked inflammatory response characterized by infiltration of leukocytes in the lungs of mice following intracheal instillation of water-insoluble calcium tungstate powder (Peão et al. 1993). The inflammatory response was likely the result of local irritation rather than an adverse immunological effect. Repeated exposure animal studies by the inhalation exposure route could be designed to assess the immunotoxicity potential of tungsten.

Neurotoxicity. No human data were located in which neurological signs could be associated with inhalation, oral, or dermal exposure to tungsten. Signs of memory and sensory deficits have been reported among workers in the hard metal industry who were exposed to atmospheres of hard metal dusts (Jordan et al. 1990; Kaplun and Mezentseva 1959; Vengerskaya and Salikhodzhaev 1962); however, these effects likely reflect exposure to cobalt, not tungsten. No studies were located regarding neurological effects in animals following inhalation exposure to tungsten or tungsten compounds. Results of available animal studies indicated clinical signs of neurotoxicity following acute oral dosing at levels resulting in death (Karantassis 1924) and learning deficits and brain lesions following repeated oral dosing (Nadeenko 1966) at sublethal doses. However, clinical signs at lethal doses are not a reliable indicator of primary neurotoxicity and the report of Nadeenko (1966) was not designed to adequately assess neurotoxicity end points. Additional well-designed neurotoxicity studies in animals exposed to tungsten or tungsten compounds via inhalation or oral exposure routes might serve to adequately assess the potential for tungsten to induce neurotoxicity.

Epidemiological and Human Dosimetry Studies. Pulmonary fibrosis, memory and sensory deficits, and increased mortality due to lung cancer have been associated with occupational exposure to dusts generated in the hard metal industry (Bech 1974; Bech et al. 1962; Coates and Watson 1971a, 1971b; Jordan et al. 1990; Kaplun and Mezentseva 1959; Lasfargues et al. 1994; Mezentseva 1967; Miller et al. 1953; Moulin et al. 1998; Vengerskaya and Salikhodzhaev 1962). Hard metal is an alloy or encapsulated mixture that is composed of tungsten or tungsten carbide and cobalt (primarily, although the alloys may also contain yttrium, thorium, copper, nickel, iron, or molybdenum). Historically, the respiratory and neurological effects observed in hard metal workers have been attributed to cobalt, not tungsten (see Davison et al. 1983; Harding 1950). However, based on the presence of tungsten oxide fibers in air samples taken at some hard metal facilities (Sahle 1992; Sahle et al. 1994) and demonstrations that tungsten oxide fibers are capable of generating hydroxyl radicals in human lung cells *in vitro* (Leanderson and Sahle 1995), it has been suggested that tungsten oxide fibers may contribute to the development of pulmonary fibrosis in hard metal workers.

The most likely identifiable subpopulations exposed to tungsten are workers in the hard metal industry. Available human and animal data do not appear to clearly identify targets of toxicity for tungsten. Additional epidemiological studies of tungsten should attempt to identify exposure scenarios that may not be confounded by other known toxicants. Such exposure scenarios might provide valuable information regarding potential tungsten-induced toxicity. Studies of dosimetry would be useful in future epidemiological studies.

Biomarkers of Exposure and Effect.

Exposure. Tungsten can be detected in blood (Bowen 1966; Hartung 1991), urine (Paschal et al. 1998), feces , and tissue samples (Bowen 1966; Iyengar et al. 1978). Since a large percentage of absorbed tungsten is rapidly eliminated from the body, detection would be most effective within a few days following short-term exposure or termination of longer-term exposure. Additional information regarding relationships between tungsten body burden and exposure levels could improve the ability to monitor workers' exposure to tungsten.

Effect. Biomarkers of effect for tungsten and tungsten compounds have not been definitively identified. Additional animal studies designed to assess health effects associated with tungsten should elucidate biomarkers of effect.

Absorption, Distribution, Metabolism, and Excretion. Human reports demonstrate that inhaled and ingested tungsten may be absorbed, distributed systemically, and eliminated to a large extent in the urine (Marquet et al. 1997; Nicolaou et al. 1987; Wester 1974). Animal studies support the human data and further demonstrate that distribution is rapid and widespread and that urinary excretion is also rapid (Aamodt 1975; Ballou 1960; Kaye 1968). Tungsten that is deposited in bone (Kaye 1968; Kinard and Aull 1945) may be slowly released to the blood and also eliminated mainly in the urine (Kaye 1968). Insoluble forms of orally-administered tungsten are chiefly eliminated in the feces. Tungsten has been detected in hair and nail samples of hard metal workers (Nicolaou et al. 1987). Tungsten ion in the body is not known to be metabolized as such. Additional quantitative information regarding absorption and distribution of inhaled or ingested tungsten and tungsten compounds could be used to improve existing PBPK models of the biokinetics of tungsten (ICRP 1981, 2001; Leggett 1997). Although the dermal exposure route does not appear to be a major human exposure route for tungsten, animal studies could be designed to quantify the toxicokinetics of tungsten following dermal exposure.

Comparative Toxicokinetics. Relatively little information is available regarding comparative toxicokinetics for tungsten and tungsten compounds. Available information concerning absorption, distribution, and elimination of tungsten in rats and dogs (Aamodt 1975; Ballou 1960; Kaye 1968) do not indicate major species-specific differences in biokinetics, Available toxicokinetic data in humans (Marquet et al. 1997; Nicolaou et al. 1987; Wester 1974), which have qualitatively demonstrated that airborne and ingested tungsten is absorbed and eliminated, do not indicate that the biokinetics of tungsten may differ greatly between humans and laboratory animals. Apparent species-specific differences in the dietary requirement for molybdenum (Higgins et al. 1956b), coupled with similarities in the biokinetics of molybdenum and tungsten, suggest that significant species-specific differences in the biokinetics of tungsten may exist. Additional animal toxicokinetic studies could be designed to identify species-specific differences that could serve to improve existing biokinetic models and elucidate specific mechanisms of action for tungsten.

Methods for Reducing Toxic Effects. Mechanisms concerning absorption, distribution, and toxic action of tungsten have not been studied to date; studies should be designed to identify such mechanisms. No established methods or treatments for reducing the body burden of tungsten were identified in literature searches. No information was located regarding treatments to repair damage or improve compromised function resulting from exposure to tungsten. Well-designed mechanistic studies might provide valuable information that could aid in elucidating treatments to reduce tungsten body burden or repair tungsten-induced damage.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Results of studies published in Russian journals suggest that developing fetuses may be particularly sensitive to tungsten (Nadeenko and Lenchenko 1977; Nadeenko et al. 1977, 1978). However, deficiencies in study details regarding exposure and quantitative results render the results of these Russian studies of limited value for purposes of quantitative risk assessment. Tungsten has been observed to cross the placenta of pregnant rats and to be distributed to the fetus (Wide et al. 1986). Measurable amounts of tungsten have been observed in the milk of lactating cows (Mullen et al. 1976). However, no information was located regarding potentially significant age-related differences in the biokinetics of tungsten. No information was located regarding the potential for tungsten to interact with other chemicals in such a way to produce age-related differences in resulting toxicity. Based on the lack of information regarding

the toxic effects of tungsten and potential for age-related differences in susceptibility, animal studies should be designed to further assess health effects that may be related to tungsten. Some of these studies could be designed to test for potential age-related differences in susceptibility and biokinetics as well.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing research has been identified in the Federal Research in Progress database (FEDRIP 2004). However, tungsten has been nominated by the National Center for Environmental Health for toxicological characterization including carcinogenicity (NTP 2003). Rationale for the nomination includes the use of tungsten in industrial materials and insufficient available data to assess human health implications of elevated urinary tungsten levels. The NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) has recommended that toxicological studies should focus on a representative soluble tungsten compound.

The Armed Forces Radiological Research Institute (AFRRI) is currently receiving funding from the United States Army Medical Research and Material Command (USAMRMC) to assess the potential for embedded uranium and the heavy-metal tungsten alloy (tungsten/nickel/cobalt) to induce carcinogenicity and immunotoxicity in rats (principal investigator: Dr. J.F. Kalinich) and genetic damage in male mice and their offspring (principal investigator: Dr. A.C. Miller).

The following three AFFRI proposals have been submitted to the USAMRMC for review:

- Carcinogenicity of embedded tungsten alloy in mice (principal investigator: Dr. D.E. McClain). This project aims to support the findings of the earlier study in rats (Kalinich et al. 2005).
- Carcinogenicity and immunotoxicity assessment of tungsten alloy components in the rat (principal investigator: Dr. J.F. Kalinich). This project will assess the carcinogenic and immunotoxic potential of the heavy-metal tungsten alloy (tungsten/nickel/iron), as well as the individual metals of the alloy.
- Preconceptional paternal exposure to embedded tungsten alloy fragments: Lifespan study of offspring carcinogenesis (principal investigator: Dr. A.C. Miller). The objective of this study is

to investigate whether paternal preconceptional exposure to embedded tungsten alloy causes neoplasia in unexposed offspring.