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 vanadium. 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.

Elemental vanadium does not occur in nature; however, vanadium compounds exist in 65 different mineral ores and in association with fossil fuels. It has six oxidation states (2-, 1-, 0, 2+, 3+, 4+, and 5+) of which 3+, 4+, and 5+ are the most common (Crans et al. 1998). The toxicologically significant compounds are vanadium pentoxide (V_2O_5), sodium metavanadate ($NaVO_3$), sodium orthovanadate (Na_3VO_4), vanadyl sulfate ($VOSO_4$), and ammonium vanadate (NH_4VO_3). Vanadium pentoxide dust is usually encountered in occupational settings, and humans would be exposed via the inhalation route. Organic vanadium compounds, such as bis(maltolato)oxyvanadium (IV), bis(ethylmaltolato)oxyvanadium (IV), and vanadyl acetyl acetonate, have been synthesized for use in the treatment of diabetes and cancer. Because these compounds likely have different toxicokinetic properties from inorganic vanadium compounds, they are not included in this toxicological profile.

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) 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 the general population 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

3.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to vanadium.

Increases in mortality have been observed in several studies of laboratory animals exposed to vanadium pentoxide. Deaths occurred in rabbits exposed to 114 mg vanadium/m^3 for 1 hour, but not in rabbits exposed to 43 mg vanadium/m^3 (Sjöberg 1950). Exposure to 18 mg vanadium/m^3 as vanadium pentoxide resulted in death in three of five rats exposed for 6 days (NTP 2002). Intermediate-duration exposure resulted in deaths in rats exposed to 9 mg vanadium/m^3 and mice exposed to 18 mg vanadium/m^3 (NTP

2002). A decrease in survival was observed in mice chronically exposed to 2.2 mg vanadium/m^3 (NTP 2002). The LOAEL values are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Although a number of studies have reported respiratory effects in humans exposed to vanadium, in particular vanadium pentoxide, very few provide reliable quantitative exposure data. In an experimental study, persistent coughing lasting 8 days after exposure termination was observed in two subjects exposed to 0.6 mg vanadium/m^3 for 8 hours; no alterations in lung function (lung function parameters assessed: forced vital capacity, 0.5 and 1 second forced expiratory volume, maximal expiratory flow, 200–1,200 cc flow rate, maximal midexpiratory time, and forced inspiratory vital capacity) were observed (Zenz and Berg 1967). At 0.1 mg vanadium/m^3, five subjects reported productive coughing without other subjective complaints, alterations in lung function, or changes in daily activities; this concentration level was considered a NOAEL. Workers exposed to a range of vanadium pentoxide dust levels for as little as 1 day (Levy et al. 1984; Musk and Tees 1982; Thomas and Stiebris 1956; Zenz et al. 1962) or as long as ≥6 years (Irsigler et al. 1999; Lewis 1959; NIOSH 1983; Sjöberg 1956; Vintinner et al. 1955; Wyers 1946), show mild respiratory distress, such as cough, wheezing, chest pain, runny nose, or sore throat. One study of chronically-exposed workers showed increased neutrophils in the nasal mucosa (Kiviluoto 1980; Kiviluoto et al. 1979b, 1981a). More severe pathology has not been reported. Symptoms are reversible within days or weeks after exposure ceases. Data were not located to assess the relationship of exposure level or duration to severity of response. Chest x-rays and pulmonary function tests were normal in most cases. Chronic effects were infrequently reported. In a study of 40 vanadium pentoxide workers with persistent respiratory symptoms (Irsigler et al. 1999), 12 were found to have bronchial hyperresponsiveness to inhaled histamine or exercise challenge. No significant alterations in baseline lung function were found. The mean urine vanadium level (assessed via spot urine samples) in the hyperresponsive group was 52.7 µg/g creatinine compared to 30.7 µg/g creatinine in 12 matched subjects with persistent respiratory symptoms and without bronchial hyperreactivity; statistical comparisons of the two groups were not made. Five to 23 months after removal from exposure, bronchial hyperreactivity was still present in nine of the subjects, although the response was less severe in five of them and more severe in one subject.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rabbit	1 d 7 hr/d (NS)				114 (2/4 died)	Sjoberg 1950 VANADIUM PENTOXIDE	
Systemic								
2	Monkey (Cynomolgus)	6 hr (NS)	Resp	0.34 M	2.5 M (impaired lung function)		Knecht et al. 1985 VANADIUM PENTOXIDE	
3	Monkey (Cynomolgus)	6 hr	Resp	0.28 M	1.7 M (impaired lung function)		Knecht et al. 1992 VANADIUM PENTOXIDE	
4	Rat (Fischer- 344)	6 hr/d 5 d/wk 6 or 13 d	Resp		0.56 F[b] (histiocytic infiltrate and inflammation in lungs)		NTP 2002 VANADIUM PENTOXIDE	
5	Mouse (B6C3F1)	6 hr/d 5 d/wk 6 or 13 d	Resp		1.1 F (hyperplasia of alveolar and bronchiole epithelium and inflammation in lungs)		NTP 2002 VANADIUM PENTOXIDE	
INTERMEDIATE EXPOSURE								
Death								
6	Rat (Fischer- 344)	6 hr/d 5 d/wk 16 d				18 M (3/5 males died)	NTP 2002 VANADIUM PENTOXIDE	
7	Rat (Fischer- 344)	6 hr/d 5 d/wk 3 mo				9 (7/10 males and 3/10 females died)	NTP 2002 VANADIUM PENTOXIDE	

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
8	Mouse (B6C3F1)	6 hr/d 5 d/wk 16 d				18 M (5/5 males died)	NTP 2002 VANADIUM PENTOXIDE	
Systemic								
9	Monkey (Cynomolgus)	6 hr/d 5 d/wk 26 wk	Resp		0.62 M (audible wheezing and coughing in 3/8 monkeys)		Knecht et al. 1992 VANADIUM PENTOXIDE	
10	Rat (Fischer- 344)	6 hr/d 5 d/wk 16 d	Resp	1.1	2.2 (localized inflammatory response)		NTP 2002 VANADIUM PENTOXIDE	
			Bd Wt	4.5	9 (12-13% decreased body weight gain)	9 (25-40% decreased body weight gain)		
11	Rat (Fischer- 344)	6 hr/d 5 d/wk 3 mo	Resp	0.56	1.1 (epithelial hyperplasia and inflammation in lungs)		NTP 2002 VANADIUM PENTOXIDE	
			Cardio	4.5				
			Gastro	4.5				
			Musc/skel	4.5				
			Hepatic	4.5				
			Renal	4.5				
			Dermal	4.5				
			Bd Wt	4.5		9 (30-60% decreased body weight gain)		

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
12	Mouse (B6C3F1)	6 hr/d 5 d/wk 16 d	Resp	1.1	2.2 (lung inflammation)		NTP 2002 VANADIUM PENTOXIDE	
			Bd Wt	9		18 (28% decreased body weight gain)		
13	Mouse (B6C3F1)	6 hr/d 5 d/wk 3 mo	Resp	0.56	1.1 (lung inflammation and epithelial hyperplasia)		NTP 2002 VANADIUM PENTOXIDE	
			Cardio	9				
			Gastro	9				
			Hepatic	9				
			Renal	9				
			Bd Wt	4.5 F	9 F (12% decreased body weight gain)			
Immuno/ Lymphoret								
14	Rat (Fischer- 344)	6 hr/d 5 d/wk 16 d			2.2 (decr phagocytosis and incr bactericidal activity)		NTP 2002 VANADIUM PENTOXIDE	
15	Mouse (B6C3F1)	6 hr/d 5 d/wk 16 d		18			NTP 2002 VANADIUM PENTOXIDE	
Reproductive								
16	Rat (Fischer- 344)	6 hr/d 5 d/wk 3 mo		9 M 2.2 F	4.5 F (increased estrous cycle length)		NTP 2002 VANADIUM PENTOXIDE	

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
17	Mouse (B6C3F1)	6 hr/d 5 d/wk 3 mo		2.2 M 9 F	4.5 M (decreased epididymal spermatozoa motility)		NTP 2002 VANADIUM PENTOXIDE	
CHRONIC EXPOSURE								
Death								
18	Mouse (B6C3F1)	6 hr/d 5 d/wk 2 yr				2.2 M (decreased survival in males)	NTP 2002 VANADIUM PENTOXIDE	
Systemic								
19	Rat (Fischer- 344)	6 hr/d 5 d/wk 2 yr	Resp		0.28[c] (hyperplasia of alveolar and bronchiolar epithelium, degeneration and hyperplasia of epiglottis epithelium, and goblet cell hyperplasia in nasal respiratory epithelium)		NTP 2002 VANADIUM PENTOXIDE	
			Cardio	1.1				
			Gastro	1.1				
			Musc/skel	1.1				
			Hepatic	1.1				
			Renal	1.1				
			Bd Wt	1.1				

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)		LOAEL Serious (mg V/m³)		Reference Chemical Form	Comments
20	Mouse (B6C3F1)	6 hr/d 5 d/wk 2 yr	Resp		0.56	(hyperplasia and chronic inflammation in lungs; squamous metaplasia of epiglottis epithelium and nasal respiratory epithelium; atrophy and degeneration of nasal olfactory epithelium)			NTP 2002 VANADIUM PENTOXIDE	
			Cardio	2.2						
			Gastro	2.2						
			Hepatic	2.2						
			Renal	2.2						
			Dermal	2.2						
			Bd Wt	0.56	1.1	(15-20% decreased body weight gain)	2.2	(20-29% decreased body weight gain)		
Cancer										
21	Rat (Fischer- 344)	6 hr/d 5 d/wk 2 yr					0.28 M	(lung tumor incidence higher than historical controls)	NTP 2002 VANADIUM PENTOXIDE	

Table 3-1 Levels of Significant Exposure to Vanadium - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)		Reference Chemical Form	Comments
22	Mouse (B6C3F1)	6 hr/d 5 d/wk 2 yr				0.56	(alveolar/bronchiolar carcinoma)	NTP 2002 VANADIUM PENTOXIDE	

a The number corresponds to entries in Figure 3-1

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.0008 mg vanadium/m3; concentration adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the Regional Deposited Dose Ratio (RDDR) of 0.732 for the thoracic region, and divided by an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to human with dosimetric adjustment, and 10 for human variability).

c Used to derive a chronic-duration inhalation MRL of 0.0001 mg vanadium/m3 calculated using benchmark dose analysis. The BMCL10 of 0.04 mg vanadium/m3 was adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the RDDR of 0.423 for the extrathoracic region, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = Female; Gastro = gastrointestinal hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); yr = year(s)

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

Acute (≤14 days)

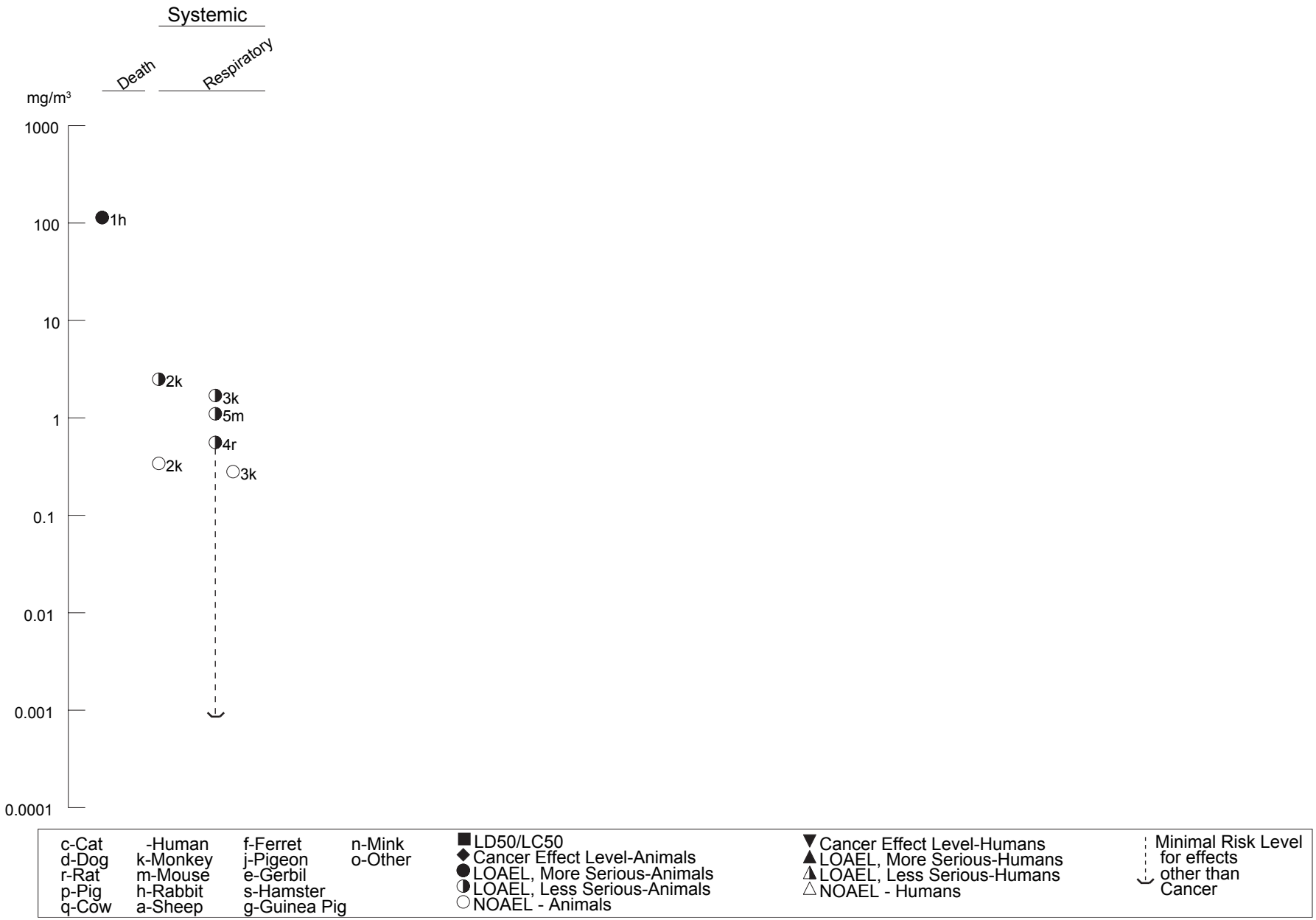


Figure 3-1 Levels of Significant Exposure to Vanadium - Inhalation *(Continued)*

Intermediate (15-364 days)

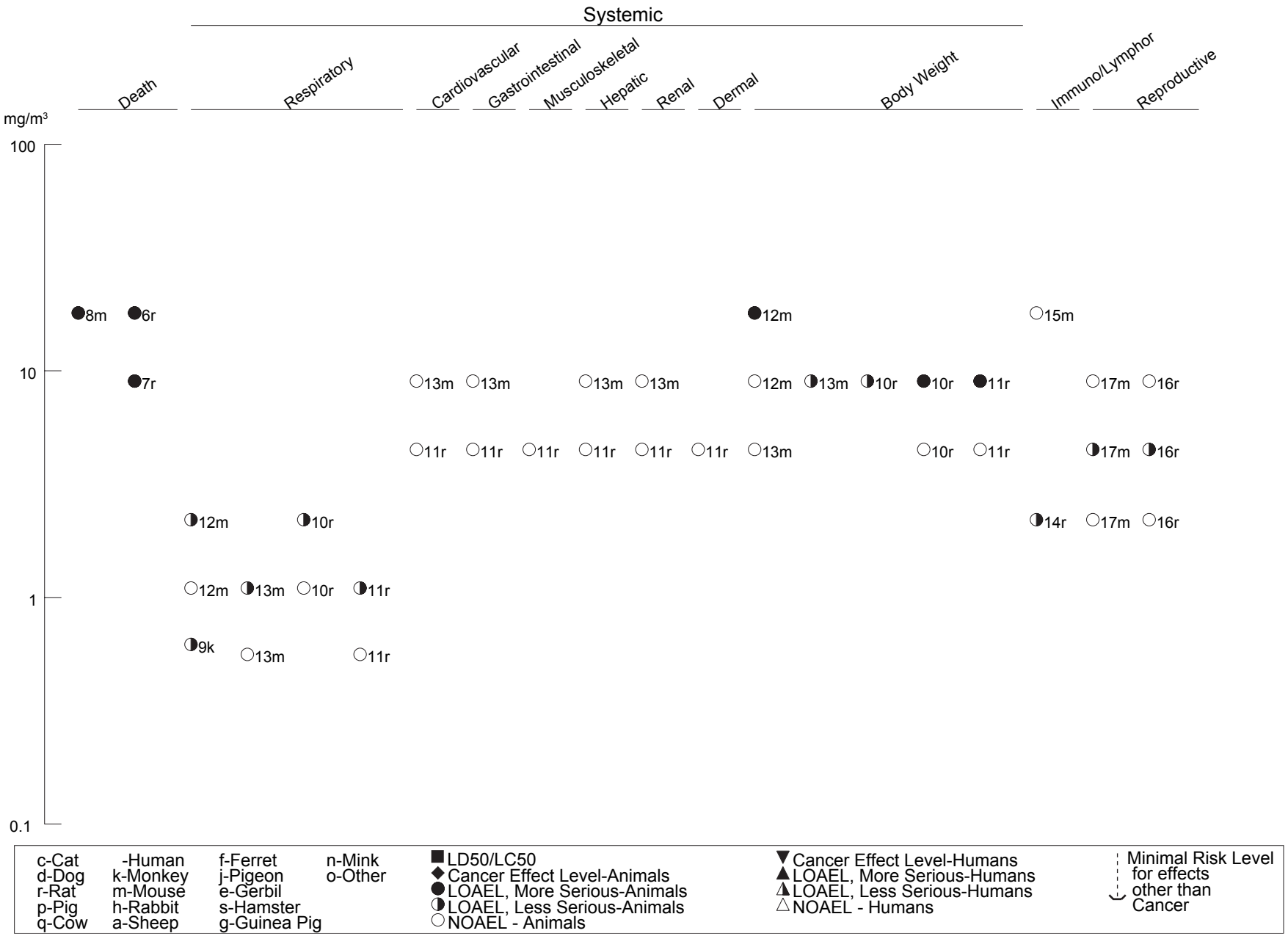
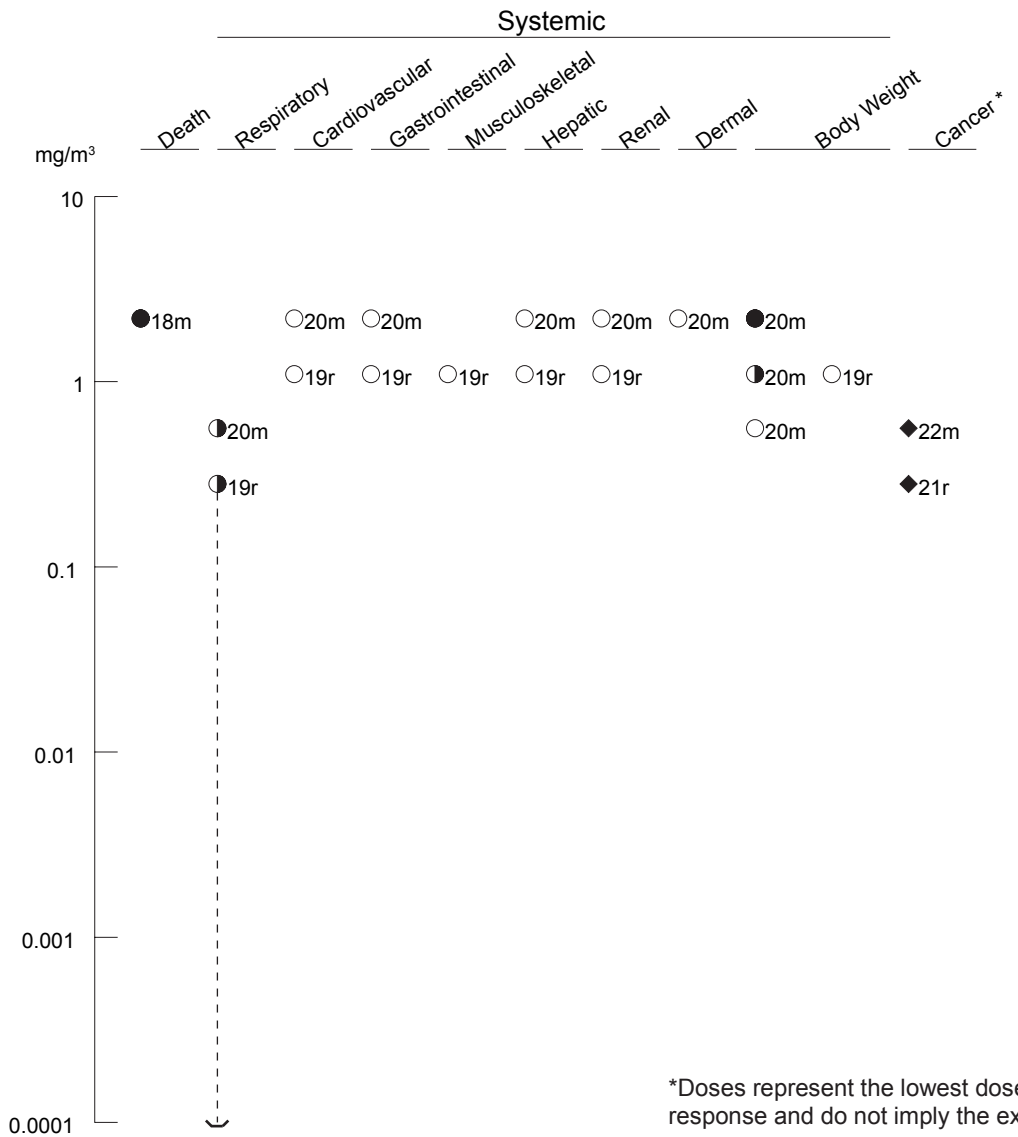


Figure 3-1 Levels of Significant Exposure to Vanadium - Inhalation *(Continued)*

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

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

■ LD50/LC50
◆ 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

Minimal Risk Level for effects other than Cancer

Animal data support the human findings and provide additional evidence that vanadium compounds are respiratory toxicants. Signs of respiratory distress, impaired lung function, increased pulmonary reactivity, and histological alterations in the lungs, larynx, and nasal cavity have been observed in laboratory animals. Rapid respiration during the exposure period was observed in rats exposed to 9.0 mg vanadium/m^3 as vanadium pentoxide for 16 days or 4.5 mg vanadium/m^3 for 4 weeks. In rats exposed to 9.0 mg vanadium/m^3 for 9 weeks, abnormal respiration was also observed during periods between vanadium exposures (NTP 2002). Audible wheezing and coughing were observed in monkeys exposed to 0.62 mg vanadium/m^3 for 6 hours; respiratory symptoms were not observed at 0.14 or 0.028 mg vanadium/m^3 as vanadium pentoxide (Knecht et al. 1992).

Decreases in pulmonary function were observed in rats exposed to ≥2.2 mg vanadium/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 2002). Exposure to 2.2 or 4.5 mg vanadium/m^3 resulted in alterations characterized as restrictive based on reduced lung compliance, changes in breathing measurements, impaired capacity to diffuse carbon monoxide, reduced static and dynamic lung volumes, and exaggerated airflow. The changes in breathing mechanics, static lung volumes, and forced expiratory maneuvers observed at 9.0 mg vanadium/m^3 were suggestive of an obstructive lung disease; however, the investigators noted that these alterations may have been due to the deteriorating condition of the rats rather than an obstructive disease. Increased pulmonary resistance was observed in monkeys 1 day after a 6-hour exposure to 2.8 mg vanadium/m^3 (Knecht et al. 1985). Pulmonary reactivity, as evidenced by an obstructive pattern of impaired pulmonary function, was also observed in monkeys following a 6-hour exposure to 1.7 mg vanadium/m^3 as vanadium pentoxide (Knecht et al. 1992); an increase in the total number of inflammatory cells present in the lungs was also observed. A similar degree of pulmonary reactivity was observed when the monkeys were re-challenged with methacholine following a 26-week exposure to 0.28 mg vanadium/m^3 (6 hours/day, 5 days/week). Pulmonary reactivity was not significantly affected by a provocation challenge with 0.28 mg vanadium/m^3 before or after the 26-week exposure (Knecht et al. 1992).

Histological alterations were observed in the lungs, larynx, and nose of rats and mice exposed to vanadium pentoxide 6 hours/day, 5 days/week for acute, intermediate, and chronic durations (NTP 2002). In the lungs, hyperplasia of alveolar and bronchiolar epithelium occurred at 1.1 mg vanadium/m^3 in rats and mice exposed for 6, 13, or 90 days, 0.28 mg vanadium/m^3 in rats exposed for 2 years, and 0.56 mg vanadium/m^3 in mice exposed for 2 years. Lung inflammation and histiocytic infiltration (alveolar macrophages) were observed at similar concentrations in the acute, intermediate, and chronic duration studies. Fibrosis was also observed in rats exposed to 2.2 mg vanadium/m^3 for 13 or 90 days or 0.28 mg

vanadium/m^3 for 2 years and in mice exposed to 1.1 mg vanadium/m^3 for 2 years. In both species, the severity of the lung lesions increased with increasing exposure duration and vanadium pentoxide exposure level. NTP (2002) also conducted several studies to examine the time course of the lung lesions. In rats exposed to 2.2 mg vanadium/m^3, histiocytic infiltrates and inflammation were observed after 2 days of exposure and alveolar and bronchiolar epithelial hyperplasia were first observed after 5 days of exposure to 1.1 or 2.2 mg vanadium/m^3. In rats exposed to 0.56 mg vanadium/m^3, hyperplasia was only observed in a few animals after 542 days of exposure; however, at the end of the 2-year study, there was a significant increase in the incidence at this exposure level. In mice, lung lesions were not observed after 1 or 2 days of exposure. Bronchiolar epithelial hyperplasia and inflammation were observed after 5 days of exposure to 2.2 mg vanadium/m^3. At the lower exposure levels, lung lesions were observed after 12 days of exposure to 1.1 mg vanadium/m^3 and 54 days of exposure to 0.56 mg vanadium/m^3. Severe lung inflammation and mucous cell metaplasia were observed in mice exposed to vanadium pentoxide via laryngeal aspiration (Rondini et al. 2010; Yu et al. 2011) and lung inflammation and interstitial fibrosis were observed in mice administered vanadium pentoxide via intranasal administration (Turpin et al. 2010). Bronchoalveolar lavage fluid from rats nose-only exposed to 2 mg vanadium/m^3 as ammonium metavanadate 8 hours/day for 4 days contained higher levels of neutrophils, small macrophages, and protein levels and increased lactate dehydrogenase activity than air-exposed controls (Cohen et al. 1996); these alterations are suggestive of lung inflammation. Vanadium exposure also resulted in alterations in the ability of pulmonary alveolar macrophages to respond to immunoregulating cytokines

The nasal effects observed in rats consisted of hyperplasia and squamous metaplasia of respiratory epithelium at 2.2 mg vanadium/m^3 for 13 weeks, inflammation at 9.0 mg vanadium/m^3 for 13 weeks, and goblet cell hyperplasia of the respiratory epithelium at 0.28 mg vanadium/m^3 for 2 years. In mice exposed to vanadium pentoxide for 2 years, the nasal effects included suppurative inflammation at 1.1 mg vanadium/m^3, olfactory epithelium atrophy at 0.56 mg vanadium/m^3, hyaline degeneration of olfactory and respiratory epithelium at 0.56 mg vanadium/m^3, and squamous metaplasia of respiratory epithelium at 0.56 mg vanadium/m^3. Chronic exposure also resulted in damage to the larynx; degeneration and hyperplasia of the epiglottis epithelium were observed in rats exposed to 0.28 mg vanadium/m^3 and squamous metaplasia of epiglottis epithelium was observed in rats exposed to 1.1 mg vanadium/m^3 and mice exposed to 0.56 mg vanadium/m^3.

Cardiovascular Effects. Workers exposed chronically to vanadium pentoxide dusts at incompletely documented exposure levels had normal blood pressure values (Vintinner et al. 1955). No other

cardiovascular parameters were investigated in this study, but another study revealed normal electrocardiograms in vanadium workers (Sjöberg 1950).

No significant alterations in heart rate, blood pressure, or electrocardiogram readings were observed in rats exposed to 4.5 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks (NTP 2002). Decreases in heart rate and blood pressure were found in rats exposed to 9.0 mg vanadium/m^3; however, this was attributed to the poor condition of the animals rather than a direct cardiotoxic effect. No histological alterations were observed in the hearts of rats exposed to 4.5 or 1.1 mg vanadium/m^3 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Gastrointestinal Effects. No gastrointestinal complaints were reported by subjects exposed to 0.6 or 0.1 mg vanadium/m^3 vanadium pentoxide dusts for 8 hours (Zenz and Berg 1967). Workers exposed to vanadium in oil-burner ashes also did not show gastrointestinal symptoms (Sjöberg 1950). One study found that workers exposed chronically to vanadium dusts in factories sometimes complained of nausea and vomiting (Levy et al. 1984), but these symptoms can have a number of causes (such as exposure to other substances) and cannot be directly attributed to the vanadium. No histological alterations were observed in the gastrointestinal tract of rats exposed to 4.5 or 1.1 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Hematological Effects. No hematological alterations were observed in humans following acute (Zenz and Berg 1967) or occupational exposure (Kiviluoto et al. 1981a; Sjöberg 1950; Vintinner et al. 1955) to vanadium dusts.

During the first 23 days of a 13-week study, minimal erythrocyte microcytosis (as evidenced by decreases in hematocrit values, hemoglobin, mean cell volume, and mean cell hemoglobin) was observed in rats exposed to vanadium pentoxide 6 hours/day, 5 days/week (NTP 2002). The alterations in hematocrit and hemoglobin were observed after 4 days of exposure to 1.1 mg vanadium/m^3, mean cell volume and mean cell hemoglobin were decreased after 23 or 90 days of exposure to 2.2 mg vanadium/m^3. At 13 weeks, the microcytosis was replaced by erythrocytosis (as evidenced by increases in hemoglobin, hematocrit, nucleated erythrocytes, and reticulocytes) in rats exposed to 4.5 or 9.0 mg vanadium/m^3.

Musculoskeletal Effects. Muscular strength was not altered in one study of workers exposed to vanadium pentoxide (Vintinner et al. 1955). No significant histological alterations were observed in the bone or muscle following a 13-week or 2-year exposure of rats to 9.0 or 1.1 mg vanadium/m^3 as vanadium pentoxide, respectively, or mice to 9.0 or 2.2 mg vanadium/m^3, respectively.

Hepatic Effects. Workers exposed chronically to 0.01–0.5 mg/m^3 of vanadium dusts had normal serum levels of four enzymes (serum alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase) that are commonly used to detect possible liver damage (Kiviluoto et al. 1981a).

Significant increases in serum ALT levels were observed in rats exposed to 4.5 mg vanadium/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 2002). However, this alteration was not considered to be biologically relevant because it was not associated with histological alterations in the liver. No histological alterations were observed in the livers of rats exposed to 4.5 or 1.1 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Renal Effects. Workers exposed chronically to 0.01–0.5 mg/m^3 of vanadium dusts had normal serum levels of electrolytes, creatinine, and urea, suggesting no alterations in renal function (Kiviluoto et al. 1981b). Workers in other studies of chronic exposure to vanadium had normal urine levels of substances used to detect kidney disease (casts, protein levels, urea) (Sjöberg 1950; Vintinner et al. 1955).

Significant increases in serum urea nitrogen concentration were observed in male rats exposed to 4.5 mg vanadium/m^3 for 13 weeks and females exposed to 2.2 mg vanadium/m^3 for 23 days (but not after 13 weeks of exposure) (NTP 2002). However, because decreases in total protein and creatinine concentration were also observed, the urea nitrogen alteration was attributed to decreased body weight rather than an effect on renal clearance. A decrease in overnight urine volumes and increase in urine specific gravity were observed in rats exposed to 2.2 mg vanadium/m^3 for 13 weeks (NTP 2002). No alterations in urine volume or specific gravity were observed in urine samples collected after a 16-hour water deprivation period, suggesting that the alterations observed in the overnight urine sample were reflective of dehydration rather than altered kidney function. No histological alterations were observed in the kidneys of rats exposed to 4.5 or 1.1 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Dermal Effects. No increases in the occurrence of dermatitis were observed in vanadium pentoxide workers (Vintinner et al. 1955); increases in skin rashes were observed in some workers (NIOSH 1983). No histological alterations of the skin were observed in rats and mice following intermediate- or chronic-duration exposure to vanadium pentoxide (NTP 2002).

Ocular Effects. Workers chronically exposed to vanadium dusts in factories had slight to moderate eye irritation (Levy et al. 1984; Lewis 1959; Sjöberg 1950; Thomas and Stiebris 1956; Vintinner et al. 1955). Brief exposure to vanadium dust can also cause conjunctivitis (Zenz et al. 1962).

Body Weight Effects. Workers exposed to vanadium ore dust reported weight loss (Vintinner et al. 1955). Significant decreases in body weight gain have been observed in rats and mice exposed to vanadium pentoxide (6 hours/day, 5 days/week) for intermediate or chronic durations (NTP 2002). The LOAELs were 9.0 mg vanadium/m^3 for rats exposed for 16 or 90 days, 18 mg vanadium/m^3 for mice exposed for 16 days, 9.0 mg vanadium/m^3 for mice exposed for 90 days, and 1.1 mg vanadium/m^3 for mice exposed for 2 years. At lower concentrations, the decreases were within 10% of the controls. Marked decreases in body weight gain (approximately 30% or higher) were observed at lethal concentrations.

3.2.1.3 Immunological and Lymphoreticular Effects

There are limited human studies on the potential immunotoxicity of vanadium. One study found that workers chronically exposed to unspecified levels of vanadium dusts in factories showed no significant signs of allergic reactions on the skin or in the respiratory system (Sjöberg 1950). This, however, cannot be considered to be an adequate evaluation of immunological function. A study of children (10–12 years of age) living in the vicinity of a facility involved in hydrometallurgical processing of vanadium-rich slag found significant decreases in lymphocyte stimulation with phytohemagglutinin, Concanavalin A, and pokeweed mitogens and an increase in the incidence of viral and bacterial respiratory infections (Lener et al. 1998). Alterations in immunoglobulin A and G levels were also found; however, the effect was only observed in the children with moderate exposure and not in the high exposure group.

Systemic immunity was evaluated in rats and mice exposed to vanadium pentoxide 6 hours/day, 5 days/week for 16 days (NTP 2002). Significant decreases in *in vitro* phagocytosis and increases *in vivo* bactericidal activity were observed in rats exposed to ≥2.2 mg vanadium/m^3. No adverse effect on the

response to *Klebsiella pneumoniae* or to the influenza virus were observed in mice exposed to 18 mg vanadium/m^3.

3.2.1.4 Neurological Effects

Most workers exposed to vanadium dusts did not report major adverse neurological signs (Sjöberg 1956; Vintinner et al. 1955). However, some workers complained of dizziness, depression, headache, or tremors of the fingers and arms (Levy et al. 1984; Vintinner et al. 1955), which may or may not have been specifically due to vanadium exposure. No histological alterations were observed in the nervous system following a 13-week or 2-year exposure of rats to 4.5 or 1.1 mg vanadium/m^3, respectively, or mice to 9.0 or 2.2 mg vanadium/m^3, respectively (NTP 2002). Because the NTP (2002) study did not assess neurological function, these NOAELs are not listed in Table 3-1 or Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located regarding the reproductive effects in humans after inhalation exposure to vanadium. There are limited data on the potential reproductive toxicity of vanadium in animals following inhalation exposure. No histological alterations were observed in rats exposed to 9.0 mg vanadium/m^3 as vanadium pentoxide for 3 months or 1.1 mg vanadium/m^3 for 2 years or in mice exposed to 9.0 mg vanadium/m^3 for 3 months or 2.2 mg vanadium/m^3 for 2 years (NTP 2002). No significant alterations in sperm count, motility, or concentration were observed in rats exposed to 9.0 mg vanadium/m^3 for 3 months (NTP 2002). In females exposed to 4.5 mg vanadium/m^3 as vanadium pentoxide for 3 months, significant increases in estrous cycle length were observed (NTP 2002); at 9.0 mg vanadium/m^3, the number of cycling females was significantly reduced. No studies examined reproductive function.

3.2.1.6 Developmental Effects

No studies were located regarding the developmental effects in humans or animals after inhalation exposure to vanadium.

3.2.1.7 Cancer

No studies were located regarding the carcinogenicity in humans after inhalation exposure to vanadium. NTP (2002) examined the carcinogenic potential of vanadium in rats and mice exposed to vanadium pentoxide 6 hours/day, 5 days/week for 2 years. Increases in the incidence of alveolar/bronchiolar

adenoma, carcinoma, or the combined incidences of adenoma and carcinoma were observed in male rats. As indicated in Table 3-2, the incidences of these tumors were not statistically different from controls; however, the incidence of adenomas at 0.28 mg vanadium/m^3 and combined incidence of adenoma and carcinoma at 0.56 or 1.1 mg vanadium/m^3 were greater than historical control levels. Due to the rarity of these tumors, NTP considered the increases in adenoma and carcinoma observed in male rats to be related to vanadium pentoxide exposure. In female rats, no significant increases in lung tumors were observed. In the 0.28 mg vanadium/m^3 group, the incidence of alveolar/bronchiolar adenoma exceeded the historical control range. NTP (2002) noted that this may be related to vanadium pentoxide exposure; however, because it was only observed at the lowest vanadium pentoxide concentration, a clear relationship between lung neoplasms and vanadium pentoxide could not be determined in female rats. In male mice, significant increases in the incidence of alveolar/bronchiolar carcinoma and the combined incidence of alveolar/bronchiolar adenoma and carcinoma were observed at 0.56, 1.1, and 2.2 mg vanadium/m^3; an increased incidence of alveolar/bronchiolar adenoma was observed at 1.1 mg vanadium/m^3. In female mice, the incidences of alveolar/bronchiolar adenoma or carcinoma and the combined incidence of adenoma and carcinoma were significantly elevated in the 0.56, 1.1, and 2.2 mg vanadium/m^3 groups. As presented in Table 3-2, the tumor incidences in the male and female mice were not concentration-related. Based on vanadium lung burden studies in female rats and mice exposed to vanadium pentoxide, NTP (2002) estimated that the total vanadium lung "doses" were 130, 175, and 308 µg vanadium in rats exposed to 0.28, 0.56, or 1.1 mg vanadium/m^3 for 540 days and 153, 162, and 225 µg vanadium in mice exposed to 0.56, 1.1, or 2.2 mg vanadium/m^3 for 553 days. In both species, the similarity of the total dose at the two lower concentrations (total lung doses of 130 and 175 µg vanadium in rats exposed to 0.28 and 0.56 mg vanadium/m^3 and 153 and 162 µg vanadium in mice exposed to 0.56 and 1.1 mg vanadium/m^3) provides a partial explanation for the flat dose-response curve for lung tumors. NTP (2002) also suggested that the differences in lung tumor responses between the rats and mice may be due to finding that mice received considerably more vanadium on a body weight basis than rats.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans after oral exposure to vanadium.

Table 3-2. Incidence of Lung Tumors in Rats and Mice Exposed to Vanadium Pentoxide for 2 Years[a]

	Concentration (mg vanadium/m^3)			
	0	0.28	0.56	1.1
Rats				
Male				
Alveolar/bronchiolar adenoma, multiple	0/50	2/49	0/48	0/50
Alveolar/bronchiolar adenoma (includes multiple)[b]	4/50	8/49	5/48	6/50
Alveolar/bronchiolar carcinoma, multiple	0/50	1/49	0/48	0/50
Alveolar/bronchiolar carcinoma (includes multiple)[c]	0/50	3/49	1/48	3/50
Alveolar/bronchiolar adenoma or carcinoma[d]	4/50	10/49	6/48	9/50
Female				
Alveolar/bronchiolar adenoma	0/49	3/49	1/50	0/50
Alveolar/bronchiolar carcinoma	0/49	0/49	0/50	1/50
Alveolar/bronchiolar adenoma or carcinoma	0/49	3/49	1/50	1/50
Mice	0	0.56	1.1	2.2
Male				
Alveolar/bronchiolar adenoma, multiple	1/50	1/50	11/50[e]	5/50
Alveolar/bronchiolar adenoma (includes multiple)	13/50	16/50	26/50[e]	15/50
Alveolar/bronchiolar carcinoma, multiple	1/50	10/50[e]	16/50[e]	13/50[e]
Alveolar/bronchiolar carcinoma (includes multiple)	12/50	29/50	30/50	35/50
Alveolar/bronchiolar adenoma or carcinoma	22/50	42/50[e]	43/50[e]	43/50[e]
Female	0	0.28	0.56	1.1
Alveolar/bronchiolar adenoma, multiple	0/50	3/50	5/50[e]	6/50[e]
alveolar/bronchiolar adenoma (includes multiple)	1/50	17/50[e]	23/50[e]	19/50[e]
Alveolar/bronchiolar carcinoma, multiple	0/50	9/50[e]	5/50[e]	5/50[e]
Alveolar/bronchiolar carcinoma (includes multiple)	0/50	23/50[e]	18/50[e]	22/50[e]
Alveolar/bronchiolar adenoma or carcinoma	1/50	32/50[e]	35/50[e]	32/50[e]

[a]Animals were exposed for 6 hours/day, 5 days/week
[b]Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ±standard deviation): 4.2±3.5%, range 0–12%; with inhalation chamber controls given NIH-07 diet: 1.7±2.4%, range 0–10%
[c]Historical incidence for NTP-2000: diet 0.4±0.8%, range 0–2%; NIH-07 diet: 0.8±1.2%, range 0–10%
[d]Historical incidence for NTP-2000: diet 4.5±3.9%, range 0–14%; NIH-07 diet: 2.5±2.6%, range 0–10%
[e]$p \leq 0.01$

Source: NTP 2002

The 14-day LD_{50} values for sodium metavanadate are 41 mg vanadium/kg in rats and 31.2 mg vanadium/kg in mice (Llobet and Domingo 1984). Deaths have been reported in rat dams exposed to 17 mg vanadium/kg/day as sodium orthovanadate on gestation days 6–15 (Sanchez et al. 1991) and in rats exposed to 22.06 or 24.47 mg vanadium/kg/day as ammonium metavanadate for 4 weeks (Zaporowska and Wasilewski 1989, 1990). Although the cause of death was not determined, marked decreases in body weight, food intake, and water consumption and increases in the occurrence of diarrhea were observed in animals dying early. Chronic exposures of up to 19 mg vanadium/kg as vanadyl sulfate in food or water did not affect mortality in rats or mice (Dai et al. 1994a, 1994b; Schroeder and Balassa 1967; Schroeder et al. 1970).

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

No studies were located regarding musculoskeletal or dermal/ocular effects in humans or animals following oral exposure to vanadium.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to vanadium. Rats receiving sodium metavanadate in the drinking water for 3 months had mononuclear cell infiltration, mostly perivascular, in the lungs; the investigators noted that the effects were more evident at the highest dose level (3.5 mg vanadium/kg/day), but incidence data were not reported (Domingo et al. 1985).

Cardiovascular Effects. No significant alterations in systolic or diastolic blood pressure were observed in adults exposed to 0.12 mg vanadium/kg/day as vanadyl sulfate for 4, 8, or 12 weeks via capsules taken at mealtime (Fawcett et al. 1997).

Several studies have examined the effects of vanadium on blood pressure in laboratory animals. The results are inconsistent; however, differences in the methods used to measure blood pressure and the strains of rats tested complicate cross study comparisons. Significant increases in systolic, diastolic, and/or mean blood pressure were observed in Sprague-Dawley rats exposed to 0.12–12 mg vanadium/kg/day as sodium metavanadate in drinking water for 180–210 days (measured in femoral artery of anesthetized rats; Boscolo et al. 1994), in Sprague-Dawley rats exposed to 1.2–12 mg vanadium/kg/day as

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat	1 d 1 x/d (GW)				41 (LD50)	Llobet and Domingo 1984 SODIUM METAVANADATE	
2	Mouse	once (GW)				31 (LD50)	Llobet and Domingo 1984 SODIUM METAVANADATE	
3	Mouse (Swiss)	Gd 6-15 (G)				17 F (17/19 dams died)	Sanchez et al. 1991 SODIUM ORTHOVANADATE	
Systemic								
4	Rat (Wistar)	2 wk (W)	Hemato		27.72 M (increased reticulocytes, increased polychromatophilic erythroblasts in bone marrow)		Zaporowska and Wasilewski 1989 AMMONIUM METAVANADATE	
			Bd Wt	27.65 F				
5	Mouse (Swiss)	Gd 6-15 (G)	Bd Wt			7.5 F (46% decrease in maternal weight gain)	Paternain et al. 1990 VANADYL SULFATE	
Developmental								
6	Rat	Gd 6-14 (G)		4.2	8.4 (facial hemorrhages)		Paternain et al. 1987 SODIUM METAVANADATE	

Table 3-3 Levels of Significant Exposure to Vanadium - 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	Comments
7	Mouse (Swiss)	Gd 6-15 (G)			7.5 F (increased early resorptions, decreased fetal growth, increased soft tissue and skeletal defects)		Paternain et al. 1990 VANADYL SULFATE	
8	Mouse (Swiss)	Gd 6-15 (G)		4.2	8.3 (decreased number of ossified sacrococcygeal vertebrae)		Sanchez et al. 1991 SODIUM ORTHOVANADATE	
INTERMEDIATE EXPOSURE								
Death								
9	Rat (Wistar)	4 or 8 wk (W)				24.47 M (10/32 animals died by week 4)	Zaporowska and Wasilewski 1989 AMMONIUM METAVANADATE	
10	Rat (Wistar)	4 wk (W)				22.06 M (12/20 rats died)	Zaporowska and Wasilewski 1990 AMMONIUM METAVANADATE	
Systemic								
11	Human	45-68 d (C)	Hemato	0.19			Dimond et al. 1963 AMMONIUM VANADYL TARTRATE	
			Hepatic	0.19				
			Renal	0.19				

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
12	Human	daily 12 wk (C)	Cardio	0.12			Fawcett et al. 1997 VANADYL SULFATE	
			Hemato	0.12[b]				
			Hepatic	0.12				
			Bd Wt	0.12				
13	Rat (Wistar)	10 wk (F)	Hemato	1 F	2.1 F (decreased hemoglobin and hematocrit, increased reticulocyte)		Adachi et al. 2000 SODIUM METAVANADATE	
			Bd Wt	2.1 F				
14	Rat (Swiss)	60 d (G)	Cardio		31 M (decreased aorta diameter)		Akgun-Dar et al. 2007 VANADYL SULFATE	
			Metab	31 M				
15	Rat (Sprague-Dawley)	210 d (W)	Resp	4.7 M			Boscolo et al. 1994 SODIUM METAVANADATE	
			Cardio		0.12 M (increased blood pressure)			
			Hepatic	4.7 M				

Table 3-3 Levels of Significant Exposure to Vanadium - 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	Comments
16	Rat (Sabra)	4 wk (W)	Cardio	22 M			Bursztyn and Mekler 1993 SODIUM METAVANADATE	
			Metab	22 M				
17	Rat (Sprague-Dawley)	7 mo (W)	Cardio		12 M (increased blood pressure and heart rate)		Carmagnani et al. 1991 SODIUM METAVANADATE	
18	Rat (Sprague-Dawley)	7 mo (W)	Cardio		1.2 M (increased blood pressure)		Carmagnani et al. 1992 SODIUM METAVANADATE	
19	Rat (Wistar)	12 wk (W)	Hemato	9.7 M			Dai et al. 1995 AMMONIUM METAVANADATE	
			Bd Wt	9.7 M				
20	Rat (Wistar)	12 wk (W)	Hemato	7.6 M			Dai et al. 1995 VANADYL SULFATE	
			Bd Wt	7.6 M				
21	Rat (Sprague-Dawley)	Gd 0- Ld 21 (F)	Bd Wt		6 F (19% decrease in maternal body weight gain)		Elefant and Keen 1987 SODIUM METAVANADATE	
22	Rat (Wistar)	60 d (G)	Bd Wt	31 M			Jain et al. 2007 VANADYL SULFATE	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
23	Rat (Wistar)	75 or 103 d (F)	Hemato	6.6 M			Mountain et al. 1953 VANADIUM PENTOXIDE	
			Bd Wt	6.6 M		30 M (53% decrease in body weight gain)		
24	Rat (Sprague-Dawley)	8 wk (G)	Bd Wt	3.42 M	6.84 M (10% decrease in body weight gain)		Sanchez et al. 1998 SODIUM METAVANADATE	
25	Rat (Wistar)	6 wk (W)	Hemato		8.35 M (increased erythrocyte levels)		Scibior 2005 SODIUM METAVANADATE	
			Bd Wt	8.35 M				
26	Rat (Wistar)	6 wk (W)	Hemato		10.69 M (decreased erythrocyte and hemoglobin levels)		Scibior et al. 2006 SODIUM METAVANADATE	
27	Rat (Long- Evans)	2 mo (F)	Cardio		10 M (increased ventricular pressure)		Susic and Kentera 1986 AMMONIUM METAVANADATE	
28	Rat (Sprague-Dawley)	7.4 wk (W)	Metab	13 M			Yao et al. 1997 VANADYL SULFATE	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
29	Rat (Wistar)	4 or 8 wk (W)	Hemato		24.47 M (decreased erythroctyes, increased reticulocytes)		Zaporowska and Wasilewski 1989 AMMONIUM METAVANADATE	
30	Rat (Wistar)	4 wk (W)	Hemato		22.06 M (decreased erythrocyte, increased reticulocyte)		Zaporowska and Wasilewski 1990 AMMONIUM METAVANADATE	
31	Rat (Wistar)	4 wk (W)	Hemato		19.73 M (decreased hemoglobin and erythrocyte and increased reticulocyte)		Zaporowska and Wasilewski 1991 AMMONIUM METAVANADATE	
32	Rat (Wistar)	4 wk (W)	Gastro		19.73 (diarrhea)		Zaporowska and Wasilewski 1992a AMMONIUM METAVANADATE	
			Hemato		19.73 M (decreased hemoglobin and erythrocyte and increased reticulocyte)			
33	Rat (Wistar)	4 wk (W)	Hemato		12.99 M (decreased hemoglobin and erythrocyte and increased reticulocyte)		Zaporowska and Wasilewski 1992b AMMONIUM METAVANADATE	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
34	Rat (Wistar)	4 wk (W)	Hemato		1.18 M (decreased erythrocyte levels)		Zaporowska et al. 1993 AMMONIUM METAVANADATE	
			Bd Wt	4.93 M				
35	Rabbit (NS)	24, 129, or 171 d (W)	Hemato		1.8		Kasibhatla and Rai 1993 Not Reported	
Immuno/ Lymphoret								
36	Rat (Wistar)	10 wk (F)		1 F	2.1 F (decreased B-cell, IgG, and IgM levels)		Adachi et al. 2000 SODIUM METAVANADATE	
Neurological								
37	Rat (Sprague-Dawley)	8 wk (G)			1.72 M (impaired performance on neurobehavioral tests)		Sanchez et al. 1998 SODIUM METAVANADATE	
38	Rat (Sprague-Dawley)	daily 8 wk (GW)			6.84 M (impaired response in active avoidance tests)		Sanchez et al. 1999 SODIUM METAVANADATE	
Reproductive								
39	Rat (Sprague-Dawley)	60 d (GW)		8.4			Domingo et al. 1986 SODIUM METAVANADATE	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
40	Rat (Wistar)	60 d (G)			31 M (decreased fertility, sperm count, and motility)		Jain et al. 2007 VANADYL SULFATE	
41	Rat (Sprague-Dawley)	M: 70 d F:14 d premating, mating, gestation, lactation (W)			10 M (decreased fertility) 12 F (decreased fertility)		Morgan and El-Tawil 2003 AMMONIUM METAVANADATE	
42	Mouse (Swiss)	64 d (W)		17 M	25 M (decreased fertility and spermatozoa count)		Llobet et al. 1993 SODIUM METAVANADATE	
Developmental								
43	Rat (Sprague-Dawley)	60 d (G)			2.1 (reduced pup weight and length)		Domingo et al. 1986 SODIUM METAVANADATE	
44	Rat (Sprague-Dawley)	Gd 0- Ld 21 (F)				6 (decreased pup survival and body weight)	Elefant and Keen 1987 SODIUM METAVANADATE	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
45	Rat (Sprague-Dawley)	M: 70 d F:14 d premating, mating, gestation, lactation (W)			10 M (decreased viability, increased gross, skeletal and visceral anomalies, decreased pup body weight)		Morgan and El-Tawil 2003 AMMONIUM METAVANADATE	
					12 F (decreased viability, increased gross, skeletal and visceral anomalies, decreased pup body weight)			
46	Rat (Wistar)	Gd 19- Ld 25, pups exposed until pnd 100 (W)				10 (decreased pup survival)	Poggioli et al. 2001 VANADYL SULFATE	
CHRONIC EXPOSURE								
Death								
47	Rat	2.5 yr (W)		0.7			Schroeder et al. 1970 VANADYL SULFATE	
48	Mouse	2 yr (F)		4.1			Schroeder and Balassa 1967 VANADYL SULFATE	
49	Mouse	2.5 yr (W)		0.54			Schroeder and Mitchner 1975 VANADYL SULFATE	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
Systemic								
50	Rat (Wistar)	52 wk (W)	Resp	19 M			Dai and McNeill 1994; Dai et al. 1994a, 1994b VANADYL SULFATE	
			Cardio	19 M				
			Hemato	19 M				
			Hepatic	19 M				
			Renal	19 M				
			Bd Wt	17 M	28 M (20% decrease in body weight gain)			
			Metab	19 M				
51	Rat	2.5 yr (W)	Renal	0.7			Schroeder et al. 1970 VANADYL SULFATE	
			Bd Wt	0.7				
52	Mouse	2 yr (F)	Resp	4.1			Schroeder and Balassa 1967 VANADYL SULFATE	
			Cardio	4.1				
			Hemato	4.1				
			Renal	4.1				
			Bd Wt	4.1				
53	Mouse	2.5 yr (W)	Bd Wt	0.54			Schroeder and Mitchner 1975 VANADYL SULFATE	

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
54	Mouse	2 yr (F)		4.1			Schroeder and Balassa 1967 VANADYL SULFATE	

a The number corresponds to entries in Figure 3-2

b Used to derive an intermediate-duration oral MRL of 0.01 mg vanadium/kg/day; dose divided by an uncertainty factor of 10 for human variability.

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; pnd = post-natal day; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Vanadium - Oral

Acute (≤14 days)

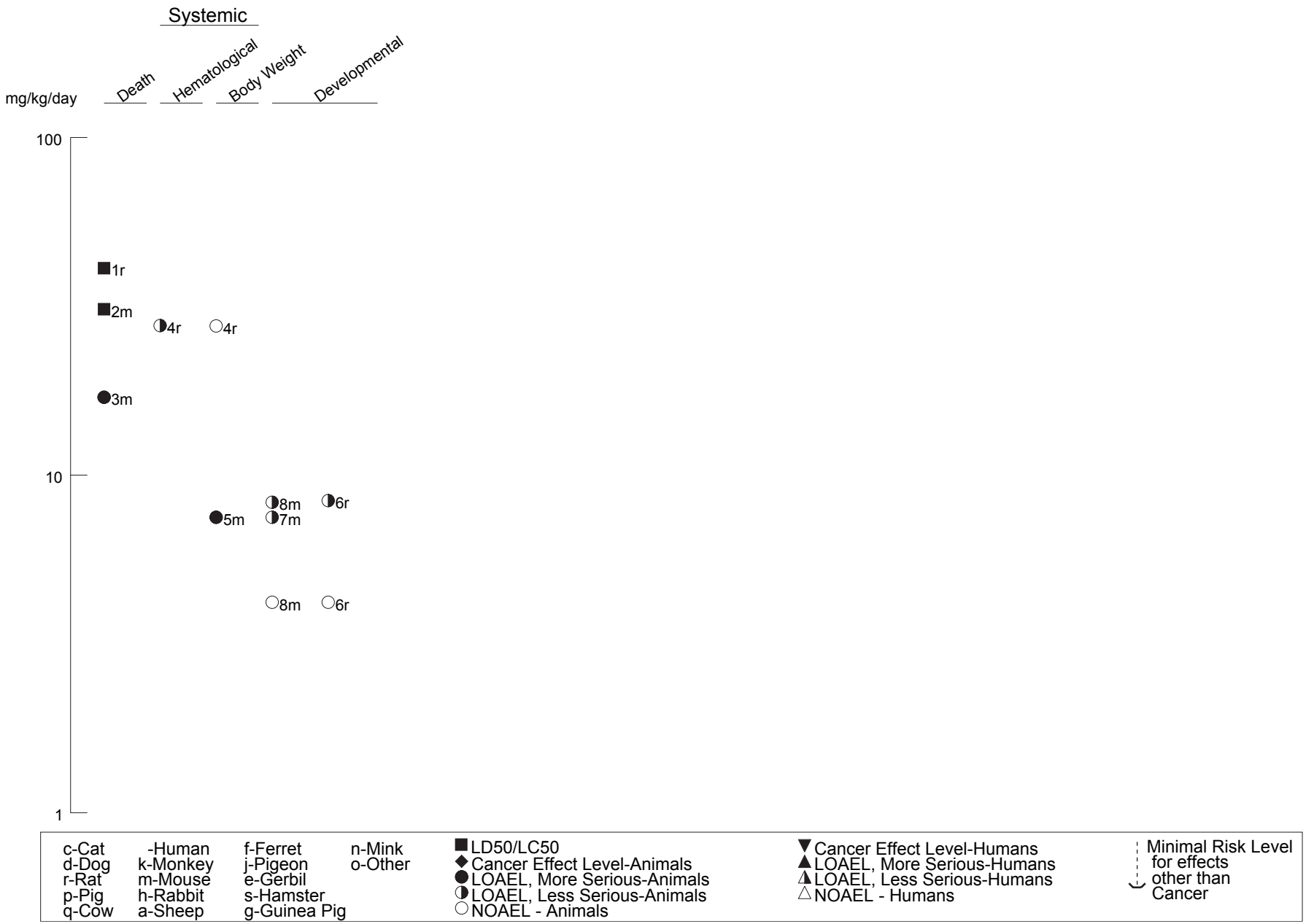
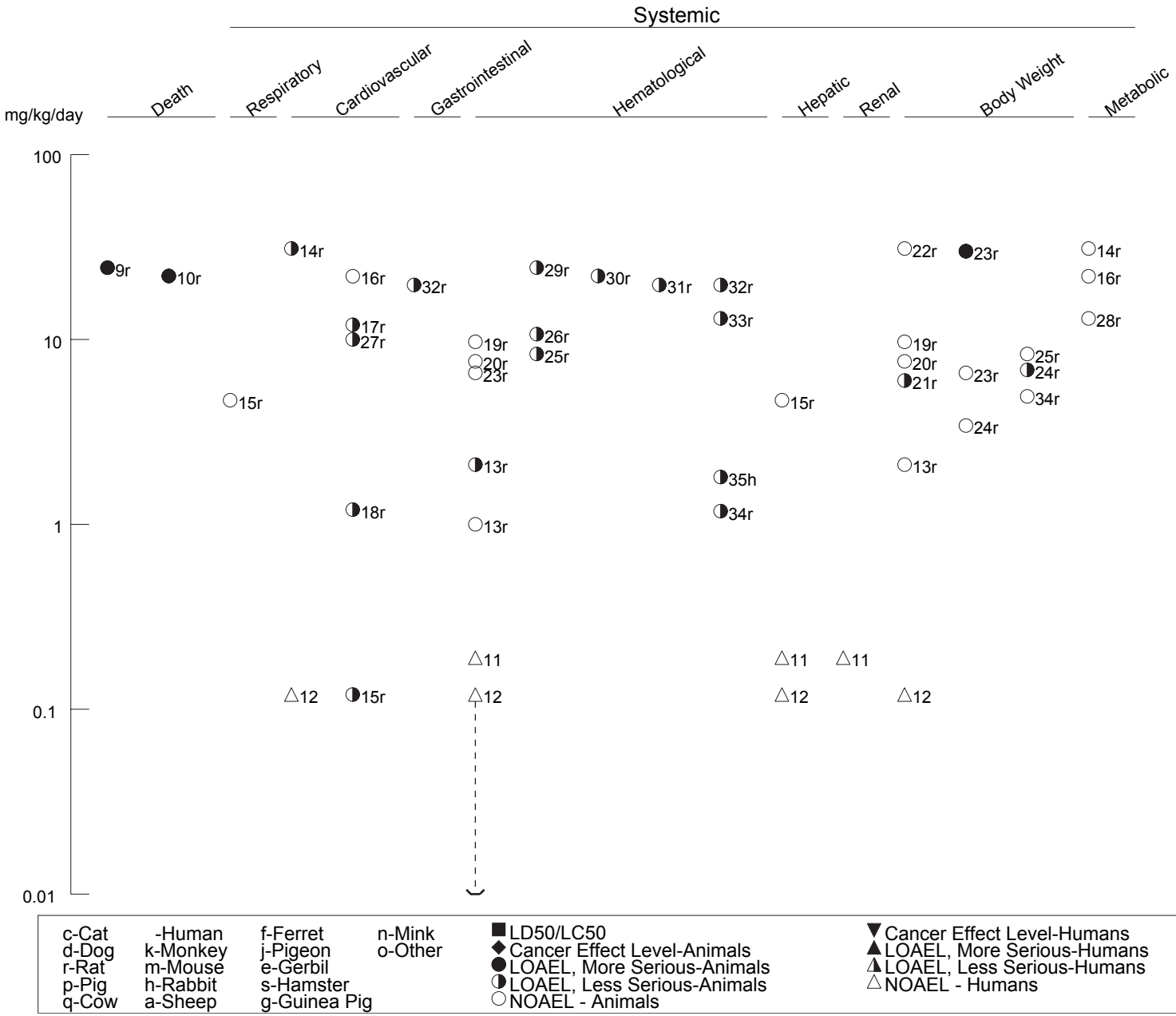


Figure 3-2 Levels of Significant Exposure to Vanadium - Oral *(Continued)*

Intermediate (15-364 days)



c-Cat	-Human	f-Ferret	n-Mink	■ LD50/LC50	▼ Cancer Effect Level-Humans	Minimal Risk Level for effects other than Cancer
d-Dog	k-Monkey	j-Pigeon	o-Other	◆ Cancer Effect Level-Animals	▲ LOAEL, More Serious-Humans	
r-Rat	m-Mouse	e-Gerbil		● LOAEL, More Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		◑ LOAEL, Less Serious-Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig		○ NOAEL - Animals		

Figure 3-2 Levels of Significant Exposure to Vanadium - Oral *(Continued)*

Intermediate (15-364 days)

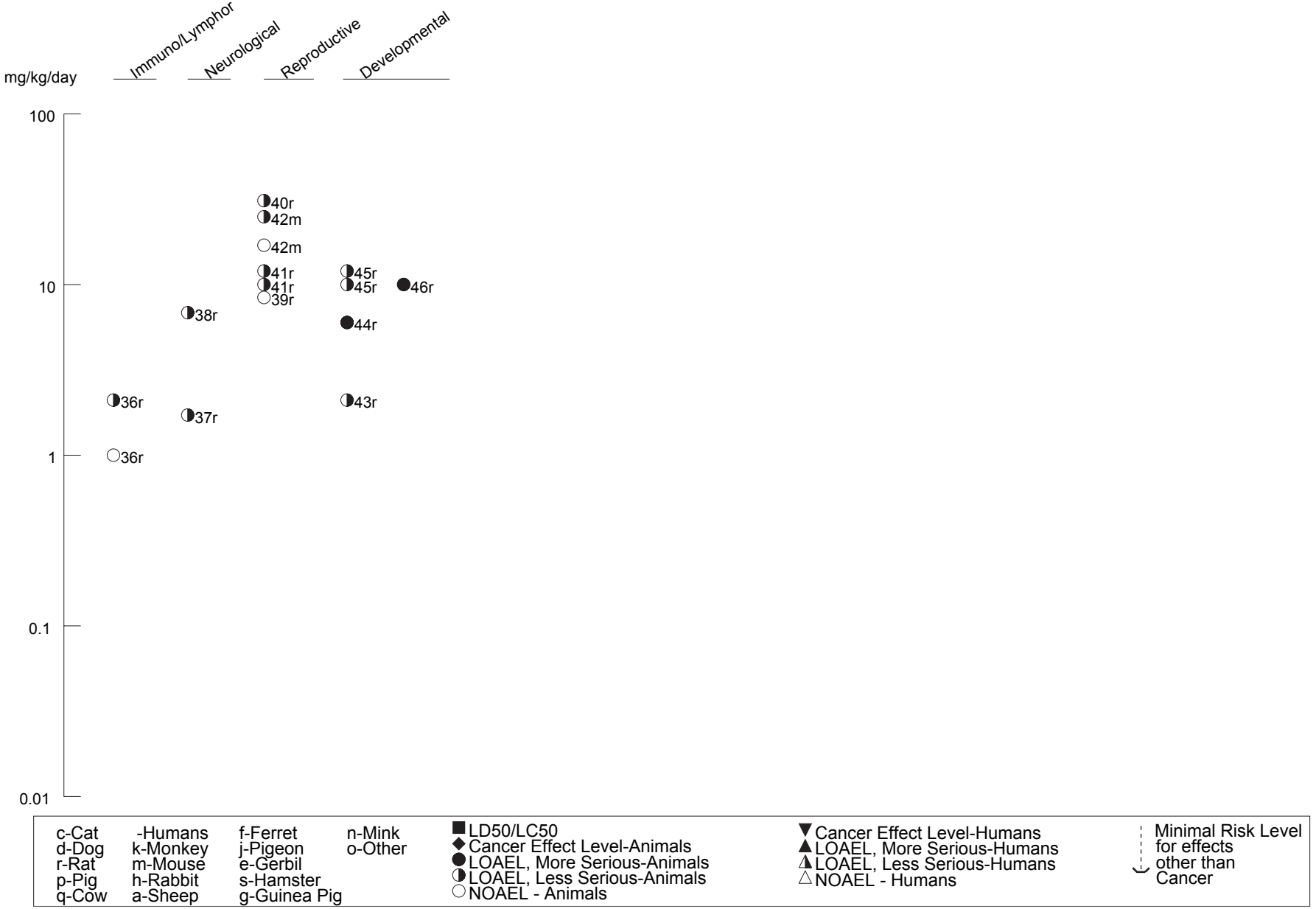
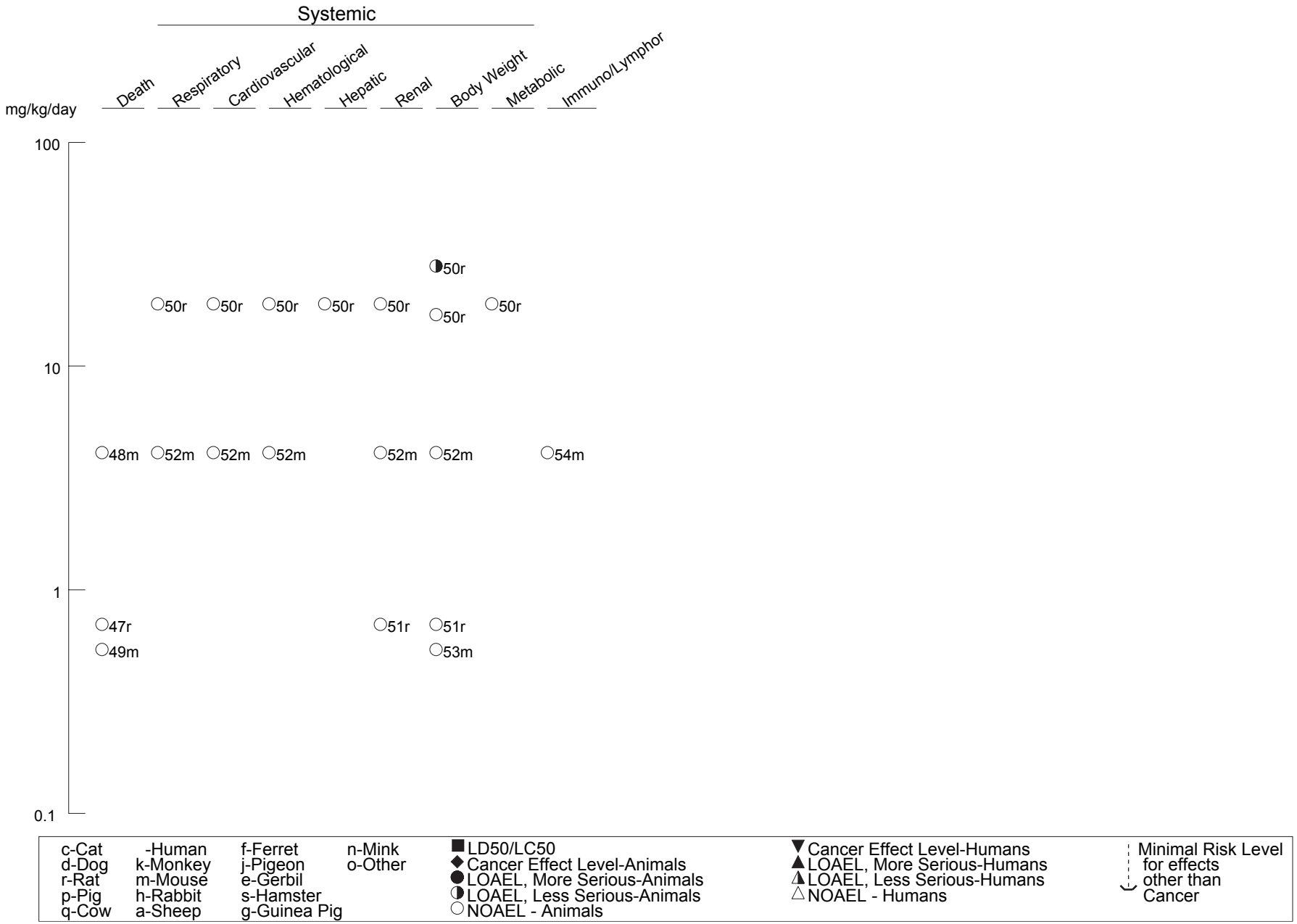


Figure 3-2 Levels of Significant Exposure to Vanadium - Oral *(Continued)*

Chronic (≥365 days)



sodium metavanadate in drinking water for 7 months (measured in the aorta of anesthetized rats; Carmagnani et al. 1991, 1992), and Long-Evans rats exposed to 10 mg vanadium/kg/day as ammonium vanadate in the diet for 60 days (measured in ventricle of anesthetized rats; Sušić and Kentera 1986). In contrast, no alterations in blood pressure were observed in rats exposed to 10 mg vanadium/kg/day as ammonium vanadate in the diet for 60 days (Long-Evans rats, measured in femoral artery; Sušić and Kentera 1986), 22 mg vanadium/kg/day as sodium metavanadate in drinking water for 4 weeks (Sabra rats, measured via tail cuff; Bursztyn and Mekler 1993), 32 mg vanadium/kg/day as vanadyl sulfate in drinking water for 52 weeks (Wistar rats, measured via tail cuff; Dai and McNeill 1994), or 63 mg vanadium/kg/day as sodium metavanadate in the diet for 24 weeks (Long-Evans rats, measured via tail cuff or femoral artery; Sušić and Kentera 1988). Studies in compromised animals have also found alterations in blood pressure. Increases in arterial blood pressure (measured via tail cuff) were observed in salt-induced hypertensive rats exposed to 22 mg vanadium/kg/day as sodium metavanadate in drinking water for 4 weeks compared to hypertensive controls (Bursztyn and Mekler 1993). Similar increases in blood pressure (measured via tail cuff) were observed in uninephrectomized rats exposed to 6 mg vanadium/kg/day as sodium metavanadate in the diet for 18 weeks (Sušić and Kentera 1988) or 5 mg vanadium/kg/day as sodium orthovanadate in the diet (Steffen et al. 1981). Alterations in the renin-angiotensin-aldosterone system and alterations in urinary excretion of electrolytes observed in the Boscolo et al. (1994) study provide suggestive evidence that altered renal function may play a role in vanadium-induced hypertension. Significant increases in plasma renin activity, plasma aldosterone levels, and increases in kallikrein (enzyme that releases vasodilating kinins from plasma proteins), and kininases I and II activities were observed in rats exposed to 1.2 or 4.7 mg vanadium/kg/day as sodium metavanadate in the drinking water for 7 months.

Other alterations in the cardiovascular system included significant decreases in aorta diameter and the aorta tunica intima thickness in rats administered 31 mg vanadium/kg/day as vanadyl sulfate via gavage for 60 days (Akgün-Dar et al. 2007) and an increase in heart rate in rats exposed to 12 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (Carmagnani et al. 1991, 1992), but not in rats exposed to ≤4.7 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (Boscolo et al. 1994; Carmagnani et al. 1992) or 10 mg vanadium/kg/day as ammonium vanadate in the diet for 2 months (Sušić and Kentera 1986).

Gastrointestinal Effects. The limited data available for assessing gastrointestinal effects suggest that exposure to vanadium may cause mild gastrointestinal irritation. Intestinal cramping and diarrhea were observed in subjects administered capsules containing 5 mg vanadium as ammonium vanadyl

tartrate administered 2–4 times/day for 45–68 days (Dimond et al. 1963). Several clinical studies investigating the efficacy and mechanism of action of sodium metavanadate and vanadyl sulfate for the treatment of diabetes mellitus have found mild gastrointestinal effects (Afkhami-Ardekani et al. 2008; Boden et al. 1996; Cohen et al. 1995; Cusi et al. 2001; Goldfine et al. 1995, 2000). Mild diarrhea was reported by 4/10 insulin- and noninsulin-dependent diabetes patients administered sodium metavanadate as capsules 3 times/day for 14 days; capsules taken at breakfast and lunch contained 21 mg vanadium and the capsule taken at dinner contained 10 mg vanadium (Goldfine et al. 1995); although the duration of the effects were not reported, the investigators noted that they "rapidly dissipated". One of the subjects reported nausea and vomiting that subsided when the dose was changed to 10 mg vanadium 3 times/day. In a subsequent study by this group (Goldfine et al. 2000), noninsulin-dependent diabetics were administered capsules containing 7.8, 16, or 31 mg vanadium as vanadyl sulfate administered 3 times/day. No gastrointestinal effects were observed in the subjects taking 7.8 mg capsules; in the subjects taking 16 mg capsules, "several subjects" had gastrointestinal complaints (no additional information provided). At the highest dose, 8/8 subjects reported cramping, abdominal discomfort, and/or diarrhea; the investigators noted that these subjects were treated with over-the-counter medication for the gastrointestinal effects. During the first week of a 3-week exposure, mild gastrointestinal symptoms (nausea in three subjects, mild diarrhea in four subjects, and abdominal cramps in three subjects) were reported by five of six noninsulin dependent diabetics administered twice daily capsules containing 14 mg vanadium as vanadyl sulfate hydrate (Cohen et al. 1995). In another study of eight noninsulin dependent diabetics administered capsules containing 16 mg vanadium as vanadyl sulfate as capsules 2 times/day for 4 weeks, diarrhea and abdominal cramps were reported during the first week of treatment, but not reported thereafter (in one subject, the effects persisted for 11 days) (Boden et al. 1996). In noninsulin-dependent diabetics administered via capsules containing 42 mg vanadium as sodium metavanadate (no additional dosing information was provided) for 6 weeks, vomiting was reported by 8/20 subjects (2 withdrew from the study due to the vomiting) and nausea during the first 3 weeks of the study was reported in 17/20 subjects (Afkhami-Ardekani et al. 2008). Similarly, 4/11 noninsulin-dependent diabetics reported gastrointestinal effects (4 reported diarrhea and 2 reported abdominal discomfort) during exposure to vanadyl sulfate; effects were only reported during the first 2 weeks of exposure in 3 of the 4 affected subjects (Cusi et al. 2001). Initially, the subjects were administered capsules containing 8 mg vanadium 2 times/day; the amount of vanadium in the capsule and frequency of ingestion was increased every 2–3 days and reached 16 mg vanadium/capsule administered 3 times per day by week 2. In a study examining the effect of vanadium on serum cholesterol levels in patients with ischemic heart disease (Somerville and Davies 1962), upper abdominal pain, anorexia, and nausea were reported in 5/12 patients administered 75 mg/day diammonium vanado-tartrate via capsule for 2 weeks and

125 mg/day for the next 5 months; doses were administered in three divided daily doses. Similarly, abdominal pain, nausea, vomiting, and multiple daily diarrhea were observed in a woman ingesting an unknown fatal dose of ammonium vanadate (Boulassel et al. 2011). Several animal studies have reported diarrhea in rats exposed to ≥8.35 mg vanadium/kg/day as sodium metavanadate or ammonium metavanadate (Ścibior 2005; Zaporowska and Wasilewski 1989, 1990, 1992a); the diarrhea was often observed at doses associated with marked decreases in food intake and water consumption.

Hematological Effects. No alterations in reticulocyte or platelet counts (Dimond et al. 1963) or erythrocyte, hemoglobin, hematocrit, or platelet levels (Fawcett et al. 1997) were observed in adults exposed to 0.19 mg vanadium/kg/day as ammonium vanadyl tartrate for 6–10 weeks or 0.12 mg vanadium/kg/day as vanadyl sulfate for 12 weeks, respectively.

A series of studies conducted by Zaporowska and associates examined the hematotoxicity of ammonium metavanadate administered in drinking water to rats for acute or intermediate durations. A 2-week exposure to 27.72 mg vanadium/kg/day resulted in significant increases in reticulocyte levels and increases in the percentage of polychromatophilic erythroblasts in the bone marrow in male rats (Zaporowska and Wasilewski 1989); a nonsignificant increase in erythrocytes was also observed at this dose level. Exposures to 12.99–24.47 mg vanadium/kg/day for 4 weeks resulted in decreases in erythrocyte levels and hemoglobin levels and increases in reticulocyte levels (Zaporowska and Wasilewski 1989, 1990, 1991, 1992a, 1992b). However, death and decreases in body weight gain, food intake, and water consumption were also observed at these dose levels. Similar effects were observed in rats exposed to 8.35 or 10.69 mg vanadium/kg/day as sodium metavanadate for 6 weeks (Ścibior 2005; Ścibior et al. 2006). One study in this series tested lower concentrations which did not result in frank toxicity. Significant decreases in erythrocyte and hematocrit levels were observed in rats exposed to 1.18 or 4.93 mg vanadium/kg/day as ammonium metavanadate for 4 weeks (Zaporowska et al. 1993); significant increases in reticulocyte levels were observed at 4.93 mg vanadium/kg/day. The decreases in erythrocyte levels were small (approximately 11% less than controls) and not dose-related. Decreases in hemoglobin and hematocrit and increases in reticulocytes were observed in rats exposed to 2.1 mg vanadium/kg/day as sodium metavanadate for 10 weeks (Adachi et al. 2000a) and decreases in erythrocyte counts were observed in rabbits exposed to 1.8 mg vanadium/kg/day of an unknown metavanadate compound for 24 days (Kasbhatla and Rai 1993). However, other investigators have not found hematological alterations in rats exposed to 19 mg vanadium/kg/day as vanadyl sulfate for 1 year (Dai and McNeill 1994), 9.7 mg vanadium/kg/day as ammonium metavanadate for 12 weeks (Dai et al. 1995), 7.6 mg vanadium/kg/day as vanadyl sulfate for 12 weeks (Dai et al. 1995), or 6.6 mg

vanadium/kg/day as vanadium pentoxide for 10–15 weeks (Mountain et al. 1953). As suggested by Ścibior et al. (2006), the differences may be due to the duration of exposure, compound administered, or age of the animals.

Hepatic Effects. No significant alterations in serum AST, cholesterol, triglyceride, phospholipid, and/or bilirubin levels were observed in humans administered, via capsules, 0.19 mg vanadium/kg as ammonium vanadyl tartrate for 45–68 days (Dimond et al. 1963), 0.12 mg vanadium/kg/day as vanadyl sulfate for 12 weeks (Fawcett et al. 1997), or 125 mg/day as diammonium oxy-tartratovanadate for 6 weeks (Curran et al. 1959).

Several studies in laboratory animals examining cholesterol and triglyceride levels (Adachi et al. 2000a; Dai et al. 1994a) or serum enzyme levels (ALT or AST) (Adachi et al. 2000a; Dai et al. 1994b; Yao et al. 1997) have not found biologically relevant alterations. The highest NOAEL values for these effects are 13 mg vanadium/kg/day (Yao et al. 1997) following intermediate-duration exposure and 19 mg vanadium/kg/day following chronic-duration exposure (Dai et al. 1994a, 1994b). No histological alterations were observed in the livers of rats exposed to 3.5 mg vanadium/kg/day as sodium metavanadate in drinking water for 3 months (Domingo et al. 1985), 4.7 mg vanadium/kg/day as sodium metavanadate in drinking water for 210 days (Boscolo et al. 1994), or 19 mg vanadium/kg/day as vandyl sulfate in drinking water for 1 year (Dai et al. 1994b).

Renal Effects. Humans given 0.19 mg vanadium/kg as ammonium vanadyl tartrate capsules for 45–68 days did not show any changes in urinalysis for albumin, hemoglobin, or formed elements. Blood urea nitrogen levels were also unchanged (Dimond et al. 1963). Similarly, no alterations in blood urea nitrogen levels were observed following a 6-week exposure to 125 mg/day as diammonium oxy-tartratovanadate administered in three divided daily doses (Curran et al. 1959)

There are limited data on the renal toxicity of vanadium compounds. Narrowing of the lumen of the proximal tubules was observed in rats exposed to 4.7 or 12 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (Boscolo et al. 1994; Carmagnani et al. 1991); however, neither study reported the incidence of the lesion or statistical significance. Similarly, corticomedullar micro-hemorrhagic foci were observed in the kidneys of rats exposed to sodium metavanadate in drinking water for 3 months (Domingo et al. 1985); the investigators noted that the effect was more evident at the highest dose (3.5 mg vanadium/kg/day), but incidence data or statistical analyses were not included in the paper. This study also found significant increases in serum total protein, urea, and uric acid levels in rats

exposed to 3.5 mg vanadium/kg/day. No statistically significant increases in the incidence of histological alterations were observed in rats exposed to 19 mg vanadium/kg/day as vanadyl sulfate in drinking water for 1 year (Dai et al. 1994b). No histological alterations were observed in the kidneys of rats exposed to 0.7 mg vanadium/kg/day (Schroeder et al. 1970) as vanadyl sulfate in drinking water for 2.5 years or in mice exposed to 4.1 mg vanadium/kg/day as vanadyl sulfate in the diet for 2 years (Schroeder and Balassa 1967).

Body Weight Effects. No significant alterations in body weight were observed in adults exposed to 0.12 mg vanadium/kg/day as vanadyl sulfate administered via capsules for 12 weeks (Fawcett et al. 1997). Numerous studies have reported significant decreases in body weight gain in rats or mice exposed to vanadium compounds. In general, intermediate-duration exposure to <10 mg vanadium/kg/day did not result in >10% decreases in body weight gain (Adachi et al. 2000a; Dai et al. 1995; Sanchez et al. 1998; Ścibior 2005; Zaporwska et al. 1993). At higher concentrations, a considerable amount of variability in the magnitude of decreases in body weight gain was observed. Decreases of 12–15% were observed in rats or mice exposed to 10.69, 13, 20.93, 22.06, or 33 mg vanadium/kg/day as vanadyl sulfate, ammonium metavanadate, or sodium metavanadate in drinking water (Llobet et al. 1993; Ścibior et al. 2006; Yao et al. 1997; Zaporowski and Wasilewski 1989, 1990). However, decreases of ≥37% were observed in rats exposed to 12.99 or 19.73 mg vanadium/kg/day as ammonium vanadate in drinking water (Zaporowski and Wasilewski 1991, 1992a, 1992b); these decreases in body weight gain were accompanied by marked decreases in food intake and water consumption. A severe decrease in body weight gain (54%) and weight loss were observed in rats exposed to 30 or 55 mg vanadium/kg/day, respectively, as vanadium pentoxide for 75 days (Mountain et al. 1953). In contrast, no alterations in body weight gain were observed in rats exposed to 22 mg vanadium/kg/day as sodium metavanadate in drinking water (Bursztyn and Mekler 1993) or administered via gavage at 31 mg vanadium/kg/day as vanadyl sulfate (Akgün-Dar et al. 2007; Jain et al. 2007). Significant decreases in maternal weight gain have been observed in rats exposed to 6 mg vanadium/kg/day as sodium metavanadate (Elfant and Keen 1997) and mice administered 7.5 mg vanadium/kg/day as vanadyl sulfate (Paternain et al. 1990). Following chronic exposure, a 20% decrease in body weight gain was observed in rats exposed to vanadyl sulfate in drinking water for 1 year (Dai et al. 1994a). No alterations in body weight gain were observed in mice exposed to 4.1 or 0.54 mg vanadium/kg/day as vanadyl sulfate (Schroeder and Balassa 1967; Schroeder and Mitchener 1975) or rats exposed to 0.7 mg vanadium/kg/day as vanadyl sulfate (Schroeder et al. 1970).

It is likely that the decreases in body weight in a number of these studies are secondary to decreases in water consumption (possibly due to palatability). Decreases in food intake and body weight gain have been observed in rats placed on a water restricted diet (Crampton and Lloyd 1954); young rats were particularly sensitive to the effect (2-month-old rats were used in the Zaporowski and Wasilewski studies). Thus, LOAELs for decreases in body weight gain in drinking water studies reporting decreases in water consumption (possibly due to palatability) are not presented in Table 3-3 or Figure 3-2; similarly, LOAELs were not listed for studies that did not report whether there was an effect on drinking water consumption.

Metabolic Effects. No studies were located regarding metabolic effects in healthy humans after oral exposure to vanadium. No significant alterations in blood glucose or insulin levels were observed in rats exposed to 22 mg vanadium/kg/day as sodium metavanadate in drinking water for 4 weeks (Bursztyn and Mekler 1993), rats administered 31 mg vanadium/kg/day as vanadyl sulfate for 60 days (Akgün-Dar et al. 2007), or rats exposed to 19 mg vanadium/kg/day as vanadyl sulfate in drinking water for 1 year (Dai et al. 1994a). Additionally, no alterations in the response to an oral glucose tolerance test were observed in rats exposed to 13 mg vanadium/kg/day as vanadyl sulfate in drinking water for 7.4 weeks (Yao et al. 1997).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to vanadium. Minimal information on immunological effects in animals was located. Mice exposed to 0.13, 1.3, or 6.5 mg vanadium/kg/day as sodium orthovanadate in the drinking water for 6 weeks showed a dose-related, but nonsignificant, decrease in the antibody-forming cells in the spleen when challenged with sheep erythrocytes (Sharma et al. 1981). The number of plaques formed was 46, 69, and 78%, respectively, lower than the response in the controls; the investigators noted that statistical significance was not achieved due to the large variation in the control group. Decreases in B-cell levels and IgG and IgM levels were observed in rats exposed to 2.1 mg vanadium/kg/day as sodium metavanadate in the diet for 10 weeks (Adachi et al. 2000a). Mild spleen hypertrophy and hyperplasia were seen in rats exposed to sodium metavanadate in the drinking water for 3 months (Domingo et al. 1985); the investigators noted that the effects were more evident at the highest dose (3.5 mg vanadium/kg/day), but incidence data were not reported. Increases in the responsiveness to the phytohemagglutinin and Con A mitogens was observed in rats exposed to 0.13 mg vanadium/kg/day as vanadium pentoxide in drinking water for 6 months; this was not observed in rats similar exposed to 13 mg vanadium/kg/day (Mravcová et al.

1993). At the 13 mg vanadium/kg/day dose level, there was an increase in spleen weight and a decrease in pokeweed mitogen responsiveness. Mravcová et al. (1993) also reported increases in spleen weight, decreases in spleen cellularity, increases in peripheral blood leukocytes, increases in responsiveness to phytohemagglutinin and Con A mitogens, and an increased response to sheep red blood cells in mice administered via gavage 6 mg vanadium/kg as vanadium pentoxide in deionized water 5 days/week for 6 weeks. The significance of these findings in the rat and mouse studies is difficult to evaluate because the investigators only reported the statistically significance of increase in peripheral blood leukocytes in mice. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to vanadium. Data on the neurotoxicity of vanadium are limited to two studies in rats. In one study, decreases in travelling distance and horizontal movement in an open field test and poorer avoidance performance and higher latency period in an active avoidance test were observed in rats administered 1.72 mg vanadium/kg/day as sodium metavanadate for 8 weeks (Sanchez et al. 1998). In the second study, no alterations in travelling distance or vertical movements were observed in an open field test in rats administered 6.84 mg vanadium/kg/day as sodium metavanadate for 8 weeks (Sanchez et al. 1999). A decrease in the number of avoidance responses to conditioned stimuli and increases in the latency period were also observed in these rats. These LOAEL values are recorded in Table 3-3 and Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to vanadium. Decreases in fertility have been observed in female rats mated to unexposed males (Ganguli et al. 1994b; Morgan and El-Tawil 2003) and in male rats or mice mated with unexposed females (Jain et al. 2007; Llobet et al. 1993; Morgan and El-Tawil 2003). The lowest LOAEL values for decreased fertility are 12 and 10 mg vanadium/kg/day for females and males, respectively (Morgan and El-Tawil 2003). No alterations in fertility were observed in male and female rats administered 8.4 mg vanadium/kg/day as sodium metavanadate (Domingo et al. 1986). Decreases in sperm count and motility have also been observed in rats administered 31 mg vanadium/kg/day as vanadyl sulfate for 60 days (Jain et al. 2007). This NOAEL value and reliable LOAEL values are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to vanadium. A variety of fetal malformations/anomalies have been observed in animals following gestational exposure to vanadium. Exposure on gestation days 6–14 or 6–15 resulted in increases in facial hemorrhages (Paternain et al. 1987), hematomas in facial, neck, and dorsal areas (Paternain et al. 1990), and delayed ossification (Paternain et al. 1990; Sanchez et al. 1991); the rat and mouse dams were administered 7.5–8.3 mg vanadium/kg/day as vanadyl sulfate, sodium metavanadate, or sodium orthovanadate. One study also reported increases in early resorptions and decreases in fetal growth in the offspring of mice administered 7.5 mg vanadium/kg/day as vanadyl sulfate (Paternain et al. 1990); marked decreases in maternal body weight were also observed at this dose level. Vanadium exposure throughout gestation and lactation resulted in decreases in pup body weight and length at ≥2.1 mg vanadium/kg/day (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003). Increases in stillbirths and decreases in pup survival were observed at 6 mg vanadium/kg/day (Elfant and Keen 1987); this dose level was associated with decreases in maternal food intake and body weight. Increases in gross, skeletal, and visceral anomalies were observed in the offspring of rats exposed to 12 mg vanadium/kg/day as ammonium metavanadate (Morgan and El-Tawil 2003); similar effects were observed in unexposed dams mated with males exposed to 10 mg vanadium/kg/day (Morgan and El-Tawil 2003). In rats exposed to 10 mg vanadium/kg/day as vanadyl sulfate in drinking water during gestation and lactation and exposed until postnatal day 100, significant decreases in survival were observed (Poggioli et al. 2001). This study also found significant decreases in the number of rearings in an open field test and no alterations in locomotor activity or working memory. A two-generation, one-dose study in rats showed altered lung collagen metabolism in fetuses of adults with lifetime exposure (Kowalska 1988). The toxicological significance of this finding is also not known. Reliable LOAEL values from these studies are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located that specifically studied cancer in humans or animals after oral exposure to vanadium. However, some studies designed to test other end points noted no increase in tumor frequency in rats and mice chronically exposed to 0.5–4.1 mg vanadium/kg as vanadyl sulfate in drinking water (Schroeder and Balassa 1967; Schroeder and Mitchener 1975; Schroeder et al. 1970). Although results of these oral studies were negative for carcinogenicity, they were inadequate for evaluating carcinogenic effects because insufficient numbers of animals were used, it was not determined whether or not a

maximum tolerated dose was achieved, a complete histological examination was not performed, and only one exposure dose per study was evaluated.

3.2.3 Dermal Exposure

No studies were located regarding the following health effects in humans or animals after dermal exposure to vanadium:

3.2.3.1 Death

3.2.3.2 Systemic Effects

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

3.3 GENOTOXICITY

The *in vitro* and *in vivo* data on the genotoxicity of vanadium compounds are summarized in Tables 3-4 and 3-5, respectively. In workers exposed to vanadium pentoxide, no alterations in the occurrence of sister chromatid exchange (Ivancsits et al. 2002) or deoxyribonucleic acid (DNA) strand breaks (Ehrlich et al. 2008; Ivancsits et al. 2002) were observed; however, an increase in micronuclei formation was observed in lymphocytes (Ehrlich et al. 2008). Similarly, increases in the micronuclei formation were observed in mouse bone marrow cells following oral exposure to vanadyl sulfate (Ciranni et al. 1995; Villani et al. 2007), sodium orthovanadate (Ciranni et al. 1995), or ammonium metavanadate (Ciranni et al. 1995); however no increases in micronuclei formation were observed in mouse erythrocytes following intermediate duration inhalation exposure to vanadium pentoxide (NTP 2002). Increases in chromosomal aberrations were also observed in mouse bone marrow following a single gavage exposure to vanadyl sulfate, sodium orthovanadate, or ammonium metavanadate (Ciranni et al. 1995). As with the vanadium workers, DNA damage was not observed in mouse bone marrow or testis cells following intermediate duration exposure to vanadyl sulfate in drinking water.

Conflicting results have been found for genotoxicity tests in prokaryote assays. Impaired recombination repair were found in *Bacillus subtilis* following exposure to vanadium pentoxide, vanadyl dichloride, or

Table 3-4. Genotoxicity of Vanadium and Compounds *In Vitro*

Species (test system)	End point	Results		Reference	Form
		With activation	Without activation		
Bacillus subtilis	Recombination repair	No data	+	Kada et al. 1980	V_2O_5
			+		$VOCl_2$
			+		NH_4VO_3
B. subtilis	Recombination repair	No data	+	Kanematsu et al. 1980	V_2O_5
			+		$VOCl_2$
			+		NH_4VO_3
Escherichia coli	Gene mutation	No data	–	Kanematsu et al. 1980	V_2O_5
			–		NH_4VO_3
Salmonella typhimurium	Gene mutation	No data	–	Kanematsu et al. 1980	V_2O_5
			–		NH_4VO
S. typhimurium	Gene mutation	–	–	NTP 2002	V_2O_5
Saccharomyces cerevisiae	Induction of diploid spores	No data	+	Sora et al. 1986	$VOSO_4$
S. cerevisiae	Reverse point mutation	+	+	Bronzetti et al. 1990	NH_4VO_3
S. cerevisiae	Mitotic gene conversion	+	+	Bronzetti et al. 1990	NH_4VO_3
Mouse erythroleukemia cells	DNA repair	No data	+	Foresti et al. 2001	$NaVO_3$
Mouse 3T3 and 3T6 cells	DNA synthesis	No data	+	Smith 1983	Na_3VO_4
					$VOSO_4$
Chinese hamster ovary cells	DNA protein crosslinks	No data	+	Cohen et al. 1992	NH_4VO_3
Hamster V79 fetal lung fibroblasts	*hprt* mutation frequency	No data	+	Cohen et al. 1992	NH_4VO_3
Chinese hamster V79 cells	*hprt* mutation frequency	No data	+	Klein et al. 1994	NH_4VO_3
Chinese hamster V79 cells	*gpt* mutation frequency	No data	–	Klein et al. 1994	NH_4VO_3
Chinese hamster V79 cells	*hprt* mutation frequency	No data	–	Zhong et al. 1994	V_2O_5
Syrian hamster ovary cells	Micronuclei formation	No data	–	Gibson et al. 1997	V_2O_5
Chinese hamster V79 cells	Micronuclei formation	No data	+	Zhong et al. 1994	V_2O_5
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Owusu-Yaw et al. 1990	$VOSO_4$
		+	+		V_2O_3
		+	+		NH_4VO_3
Chinese hamster V79 cells	Sister chromatid exchange	No data	–	Zhong et al. 1994	V_2O_5

Table 3-4. Genotoxicity of Vanadium and Compounds *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Zhong et al. 1994	V_2O_5
Chinese hamster ovary cells	Chromosomal aberrations	+ + +	+ + +	Owusu-Yaw et al. 1990	$VOSO_4$ V_2O_3 NH_4VO_3
Human tumor cells	Colony formation	No data	+	Hanauske et al. 1987	<0.1 pM V
Human tumor cells	Colony formation	No data	–	Hanauske et al. 1987	>0.1 pM V
Human leukocytes	DNA strand break	No data	+	Birnboim 1988	Na_3VO_4
Human fibroblasts	DNA strand break	No data	+	Ivancsits et al. 2002	V_2O_5
Human erythrocytes, lymphocytes	DNA strand break	No data	–	Ivancsits et al. 2002	V_2O_5
Human nasal epithelial cells	DNA strand break	No data	–	Kleinsasser et al. 2003	V_2O_5
Human lymphocytes	DNA strand break	No data	+	Kleinsasser et al. 2003	V_2O_5
Human lymphocytes	DNA strand break	No data	+	Wozniak and Blasiak 2004	$VOSO_4$
Human cervical cancer cells (HeLa)	DNA strand break	No data	+	Wozniak and Blasiak 2004	$VOSO_4$
Human lymphocytes	DNA strand break	No data	±	Rojas et al. 1996	V_2O_5
Human leukocytes	DNA strand break	No data	+	Rojas et al. 1996	V_2O_5
Human leukocytes	DNA double strand breaks	No data	+	Rodríguez-Mercado et al. 2011	V_2O_4
Human leukocytes	DNA double strand breaks	No data	–	Rodríguez-Mercado et al. 2011	V_2O_3, V_2O_5
Human leukocytes	DNA damage	No data	+	Rodríguez-Mercado et al. 2011	V_2O_3, V_2O_4, V_2O_5
Human leukocytes	Impaired DNA repair	No data	+	Rodríguez-Mercado et al. 2011	V_2O_3, V_2O_4, V_2O_5
Human lymphocytes	Chromosomal aberrations	No data	+ + + +	Migliore et al. 1993	NH_4VO_3, $NaVO_3$, Na_3VO_4, $VOSO_4$
Human lymphocytes	Structural chromosomal aberrations	No data	–	Roldán and Altamirano 1990	V_2O_5

Table 3-4. Genotoxicity of Vanadium and Compounds *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Human lymphocytes	Numerical chromosomal aberrations	No data	+	Roldán and Altamirano 1990	V_2O_5
Human lymphocytes	Sister chromatid exchange	No data	—	Roldán and Altamirano 1990	V_2O_5
Human lymphocytes	Sister chromatid exchange	No data	— — — —	Migliore et al. 1993	NH_4VO_3, $NaVO_3$, Na_3VO_4, $VOSO_4$
Human lymphocytes	Micronuclei formation	No data	+ +	Migliore et al. 1995	Na_3VO_4, $VOSO_4$
Human lymphocytes	Micronuclei formation	No data	+ + + +	Migliore et al. 1993	NH_4VO_3, $NaVO_3$, Na_3VO_4, $VOSO_4$

— = negative result; + = positive result; ± = weakly positive; DNA = deoxyribonucleic acid; hprt = hypoxanthine phosphoribosyltransferase; $NaVO_3$= sodium metavanadate; Na_3VO_4 = sodium orthovanadate; NH_4VO_3 = ammonium metavanadate; V_2O_5 = vanadium pentoxide; V_2O_3 = vanadium trioxide; V_2O_4 = vanadium tetraoxide; $VOSO_4$ = vanadyl sulfate; $VOCl_2$ = vanadyl dichloride

Table 3-5. Genotoxicity of Vanadium and Compounds *In Vivo*

Species (test system)	End point	Exposure Route	Result	Reference	Form
Human leukocytes	Sister chromatid exchange	Inhalation (occupational)	−	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	Sister chromatid exchange	Inhalation (occupational)	−	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	Micronuclei formation	Inhalation (occupational)	+	Ehrlich et al. 2008	V_2O_5
Human leukocytes	DNA strand breaks	Inhalation (occupational)	−	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	DNA strand breaks	Inhalation (occupational)	−	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	DNA strand breaks	Inhalation (occupational)	−	Ehrlich et al. 2008	V_2O_5
CD-1 mouse bone marrow	Micronuclei formation	Drinking water	−	Villani et al. 2007	$VOSO_4$
CD-1 mouse blood reticulocytes	Micronuclei formation	Drinking water	±	Villani et al. 2007	$VOSO_4$
CD-1 mouse bone marrow	Micronuclei formation	Gavage	+ + +	Ciranni et al. 1995	$VOSO_4$ Na_3VO_4 NH_4VO_3
B6C3F1 mouse erythrocytes	Micronuclei formation	Inhalation	−	NTP 2002	V_2O_5
CD-1 mouse bone marrow	Chromosome aberrations	Gavage	+ + +	Ciranni et al. 1995	$VOSO_4$ Na_3VO_4 NH_4VO_3
CD-1 mouse bone marrow	DNA damage	Drinking water	−	Villani et al. 2007	$VOSO_4$
CD-1 mouse testis cells	DNA damage	Drinking water	−	Villani et al. 2007	$VOSO_4$

— = negative result; + = positive result; ± = weakly positive; DNA = deoxyribonucleic acid; V_2O_5 = vanadium pentoxide; $VOSO_4$ = vanadyl sulfate; Na_3VO_4 = sodium orthovanadate; NH_4VO_3 = ammonium metavanadate

ammonium metavanadate (Kada et al. 1980; Kanematsu et al. 1980). No alterations in gene mutation frequency were found in *Escherichia coli* or *Salmonella typhimurium* for vanadium pentoxide (Kanematsu et al. 1980; NTP 2002) or ammonium metavanadate (Kanematsu et al. 1980). In nonmammalian eukaryotes, increases in reverse point mutations and mitotic gene conversion were found in *Saccharomyces cerevisiae* (Bronzetti et al. 1990). In general, alterations in DNA repair, synthesis, formation of cross links or strand breaks, and gene mutation frequency were observed in mammalian cells for vanadium trioxide, vanadium tetraoxide, vanadium pentoxide, ammonium metavanadate, vanadyl sulfate, and sodium orthovanadate (Birnboim 1988; Cohen et al. 1992; Foresti et al. 2001; Ivancsits et al. 2002; Klein et al. 1994; Kleinsasser et al. 2003; Rodríguez-Mercado et al. 2011; Rojas et al. 1996; Smith 1983; Wozniak and Blasiak 2004; Zhong et al. 1994). *In vitro* human data suggest cell-specific differences in the ability of vanadium compounds to induce DNA strand breaks. DNA strand breaks were found in fibroblasts and lymphocytes (Ivancsits et al. 2002; Kleinsasser et al. 2003; Wozniak and Blasiak 2004) but not in erythrocytes or nasal epithelial cells (Ivancsits et al. 2002; Kleinsasser et al. 2003). In a study comparing the ability of several vanadium compounds to induce double DNA strand breaks, significant increases in DNA double strand breaks were found in human leukocytes exposed to vanadium tetraoxide, but no alterations were found for vanadium trioxide and vanadium pentaoxide (Rodríguez-Mercado et al. 2011). Increases in the occurrence of chromosomal aberrations were observed in Chinese hamster V79 cells exposed to vanadium pentoxide (Zhong et al. 1994), Chinese hamster ovary cells exposed to vanadyl sulfate, vanadium trioxide, or ammonium metavanadate (Owusu-Yaw et al. 1990), and human lymphocytes exposed to ammonium metavanadate, sodium metavanadate, sodium orthovanadate, vanadium pentoxide, or vanadyl sulfate (Migliore et al. 1993; Roldán and Altamirano 1990). An increase in sister chromatid exchange was found in Chinese hamster ovary cells exposed to vanadyl sulfate, vanadium trioxide, or ammonium metavanadate (Owusu-Yaw et al. 1990), but not in Chinese hamster V79 cells exposed to vanadium pentoxide (Zhong et al. 1994) or human lymphocytes exposed to vanadium pentoxide, ammonium metavanadate, sodium metavanadate, sodium orthovanadate, or vanadyl sulfate (Migliore et al. 1993; Roldán and Altamirano 1990). Increases in micronuclei formation were also found in Chinese hamster V79 cells exposed to vanadium pentoxide (Zhong et al. 1994) and in human lymphocytes exposed to sodium orthovanadate, vanadyl sulfate, ammonium metavanadate, or sodium metavanadate (Migliore et al. 1993, 1995), but not in Syrian hamster ovary cells exposed to vanadium pentoxide (Gibson et al. 1997). Thus, the available data provide evidence that vanadium compounds are genotoxic, both clastogenic effects and DNA damage have been observed in *in vitro* and *in vivo* studies.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Several occupational studies indicate that absorption can occur in humans following inhalation exposure. An increase in urinary vanadium levels was found in workers exposed to <1 ppm of vanadium (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983). The vanadium concentration in serum was also reported to be higher than the nonoccupationally exposed controls following exposure to vanadium pentoxide dust (Kiviluoto et al. 1981b).

Indirect evidence of absorption after inhalation of vanadium in animals is indicated in studies involving inhalation exposure or intratracheal administration. In rats and mice exposed to 0.28–2.2 mg vanadium/m^3 as vanadium pentoxide for 14 days or 2 years (6 hours/day, 5 days/week), marginal increases in blood vanadium levels were observed, suggesting that vanadium pentoxide was poorly absorbed or rapidly cleared from the blood (NTP 2002); in the 2-year studies, the increase in blood vanadium levels were somewhat concentration-related. Intratracheal studies suggest that soluble vanadium compounds are readily absorbed through the lungs. Initial pulmonary clearance is rapid in rats. There was rapid 100% absorption of vanadium in rats receiving radiolabeled vanadyl chloride (Conklin et al. 1982). The greatest absorption of a radioactive dose, ^{48}V, was found to occur 5 minutes after administration (Roshchin et al. 1980). Most of the vanadium, 80 and 85% of the tetravalent (V4+) and pentavalent (V5+) forms of vanadium, respectively, cleared from the lungs 3 hours after intratracheal exposure (Edel and Sabbioni 1988). After 24 hours, >50% of vanadyl oxychloride was cleared from the lungs of male rats (Oberg et al. 1978), and at 3 days, 90% of vanadium pentoxide was eliminated from the lungs of female rats (Conklin et al. 1982). In another study 50% was cleared in 18 minutes, and the rest within a few days (Rhoads and Sanders 1985).

3.4.1.2 Oral Exposure

No studies were located regarding the rate and extent of absorption in humans after oral exposure to vanadium.

The absorption of vanadium through the gastrointestinal tract of animals is low. Less than 0.1% of an intragastric dose was detectable in the blood of rats at 15 minutes postexposure, and less than 1% at

1 hour (Roshchin et al. 1980). Similarly, only 2.6% of an orally administered radiolabeled dose of vanadium pentoxide was absorbed 3 days after exposure in rats (Conklin et al. 1982). In contrast, 16.5% of vanadium was absorbed in rats exposed to sodium metavanadate in the diet for 7 days (Adachi et al. 2000b). Vanadium was reported in tissues and urine within hours after a single (Edel and Sabbioni 1988) and repeated oral exposure in rats (Bogden et al. 1982; Parker and Sharma 1978), suggesting that it is rapidly absorbed. Young rats that consumed vanadium in the drinking water and feed were found to have higher tissue vanadium levels 21 days after birth than they did 115 days after birth (Edel et al. 1984). The data suggest that there is a higher absorption of vanadium in these young animals due to a greater nonselective permeability of the undeveloped gastrointestinal barrier.

3.4.1.3 Dermal Exposure

No specific studies were located regarding absorption in humans or animals after dermal exposure to vanadium, although absorption by this route is generally considered to be very low (WHO 1988). Absorption through the skin is thought to be quite minimal due to its low lipid/water solubility.

3.4.2 Distribution

Vanadium has been detected in the lungs (in 52% of the cases) and intestines (in 16% of the cases) of humans with no known occupational exposure, collected from autopsy data (Schroeder et al. 1963). In the gastrointestinal tract, it was primarily found in the ileum (37%), cecum (45.1%), sigmoid colon (15.9%), and rectum (26.2%). The heart, aorta, brain, kidney, muscle, ovary, and testes were found to have no detectable vanadium concentrations. Bone was not tested.

3.4.2.1 Inhalation Exposure

There are limited data on the distribution of vanadium in workers; serum vanadium levels in workers were highest within a day after exposure followed by a rapid decline in levels upon cessation of exposure (Gylseth et al. 1979; Kiviluoto et al. 1981b). Analytical studies have shown low levels of vanadium in human kidneys and liver, with even less in brain, heart, and milk. Higher levels were detected in hair, bone, and teeth (Byrne and Kosta 1978).

Inhalation exposure and intratracheal administration studies in laboratory animals have examined the distribution of vanadium. Following nose-only exposure of rats to ammonium metavanadate (2 mg vanadium/m^3, 8 hours/day), lung vanadium levels increased by 44% after 2 days of exposure and rapidly

decreased by 39% after exposure termination on day 4 (Cohen et al. 1996). In rats chronically exposed to 0.56 or 1.1 mg vanadium/m^3 as vanadium pentoxide (6 hours/day, 5 days/week), vanadium lung burdens peaked after 173 days of exposure and declined for the remainder of the study (day 542); lung burden levels never reached steady state (NTP 2002). In contrast, lung burdens appeared to reach steady state by exposure day 173 in rats exposed to 0.28 mg vanadium/m^3 (NTP 2002). Similarly, lung burdens did not reach steady state in mice exposed to 1.1 or 2.2 mg vanadium/m^3 as vanadium pentoxide, 6 hours/day, 5 days/week for 542 days (NTP 2002). Rather, lung burdens peaked near day 54 and declined through day 535. Steady state was achieved in mice exposed to 0.56 mg vanadium/m^3 during the first 26 days of exposure. These data suggest that vanadium is cleared more rapidly from the lungs of mice compared to rats.

Vanadium is rapidly distributed in tissues of rats after acute intratracheal administration. Within 15 minutes after exposure to 0.36 mg/kg vanadium oxychloride, radiolabeled vanadium was detectable in all organs except the brain. The highest concentration was in the lungs, followed by the heart and kidney. The other organs had low levels. Maximum concentrations were reached in most tissues between 4 and 24 hours (Oberg et al. 1978). Vanadium is found to have a two-phase lung clearance after a single acute exposure (Oberg et al. 1978; Rhoads and Sanders 1985). The initial phase is rapid with a large percentage of the absorbed dose distributed to most organs and blood 24 hours postexposure, followed by a slower clearance phase. Vanadium is transported mainly in the plasma. It is found in appreciable amounts in the blood initially and only at trace levels 2 days after exposure (Roshchin et al. 1980). The pentavalent and tetravalent forms of vanadium compounds were found to have similar distribution patterns (Edel and Sabbioni 1988). Three hours after intratracheal exposure to the pentavalent or tetravalent form, 15–17% of the absorbed dose was found in the lung, 2.8% in the liver, and 2% in the kidney (Edel and Sabbioni 1988). Although levels in the kidney are high after exposure, the bone had greater retention of vanadium.

Skeletal levels of vanadium peaked 1–3 days postexposure (Conklin et al. 1982; Rhoads and Sanders 1985; Roshchin et al. 1980) and have been reported to persist after 63 days (Oberg et al. 1978).

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to vanadium.

Acute studies with rats showed the highest vanadium concentration to be located in the skeleton. Male rats had approximately 0.05% of the administered ^{48}V in bones, 0.01% in the liver, and <0.01% in the

kidney, blood, testis, or spleen after 24 hours (Edel and Sabbioni 1988). Similar findings were noted by other authors who found that the bone had the greatest concentration of radiolabeled vanadium, followed by the kidney (Roshchin et al. 1980). Conklin et al. (1982) reported that after 3 days, 25% of the absorbed vanadium pentoxide was detectable in the skeleton and blood of female rats. In female rats exposed to sodium metavanadate in the diet for 7 days, the highest concentrations of vanadium were found in bone, followed by the spleen and kidney (Adachi et al. 2000b); the lowest concentration was found in the brain. As summarized in Table 3-6, vanadium elimination half-times in various tissues were 3.57–15.95 or 3.18–13.50 days following a 1-week exposure to 8.2 mg vanadium/kg/day as sodium metavanadate or vanadyl sulfate, respectively, administered in a liquid diet (Hamel and Duckworth 1995). Although the elimination half-times were longer in rats administered sodium metavanadate compared to vanadyl sulfate, no statistical comparisons were made.

Oral exposure for an intermediate duration produced the highest accumulation of vanadium in the kidney. Adult rats exposed to 5 or 50 ppm vanadium in the drinking water for 3 months had the highest vanadium levels in the kidney, followed by bone, liver, and muscle (Parker and Sharma 1978). The retention in bone may have been due to phosphate displacement. All tissue levels plateaued at the third week of exposure. A possible explanation for the initially higher levels in the kidney during intermediate-duration exposure is the daily excretion of vanadium in the urine. When the treatment is stopped, levels decrease in the kidney. At the cessation of treatment, vanadium mobilized rapidly from the liver and slowly from the bones. Other tissue levels decreased rapidly after oral exposure was discontinued. Thus, retention of vanadium was much longer in the bones (Edel et al. 1984; Parker and Sharma 1978).

In rats exposed to approximately 100 mg/L vanadium in drinking water as vanadyl sulfate or ammonium metavanadate for 12 weeks, significant increases, as compared to controls, in bone, kidney, and liver vanadium levels were observed; no alterations in vanadium muscle levels were found (Thompson et al. 2002). The highest concentration of vanadium was found in the bone, followed by the kidney and liver. Tissue vanadium concentrations were significantly higher in rats exposed to ammonium metavanadate as compared to animals exposed to vanadyl sulfate.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans and animals after dermal exposure to vanadium.

Table 3-6. Vanadium Elimination Half-Times in Various Organs in Rats Exposed to 8.2 mg Vanadium/kg/day for 1 Week

	Half-time (days)	
Organ	Sodium metavanadate	Vanadyl sulfate
Liver	3.57	3.18
Kidney	3.92	3.27
Fat	4.06	5.04
Lung	5.52	4.45
Muscle	6.11	4.49
Heart	7.03	5.05
Spleen	9.13	5.15
Brain	11.17	9.17
Testes	15.95	13.50

Source: Hamel and Duckworth 1995

3.4.2.4 Other Routes of Exposure

After intraperitoneal administration to rats, vanadium is distributed to all organs. After 24 hours, the highest concentrations were found in the bones and kidney, although initial levels were highest in the kidney (Roshchin et al. 1980; Sharma et al. 1980). This is similar to the distribution seen following inhalation and oral exposure.

3.4.3 Metabolism

Vanadium is an element, and as such, is not metabolized. In the oxygenated blood, it circulates as a polyvanadate (isopolyanions containing pentavalent vanadium) but in tissues, it is retained mainly as the vanadyl cation (cationic form of tetravalent vanadium). Depending on the availability of reducing equivalents (such as reduced glutathione-SH, NADPH, NADH) and oxygen, vanadium may be reduced, reoxidized, and/or undergo redox cycling (Byczkowski and Kulkarni 1998).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Occupational studies showed that urinary vanadium levels significantly increased in exposed workers (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983; Zenz et al. 1962). Male and female workers exposed to 0.1–0.19 mg/m^3 vanadium in a manufacturing company, had significantly higher urinary levels (20.6 µg/L) than the nonoccupationally exposed control subjects (2.7 µg/L) (NIOSH 1983). The correlation between ambient vanadium levels and urinary levels of vanadium is difficult to determine from these epidemiological studies (Kiviluoto et al. 1981b). In most instances, no other excretion routes were monitored. Analytical studies have shown very low levels in human milk (Byrne and Kosta 1978). Evidence from animal studies supports the occupational findings. Vanadium administered intratracheally to rats was reported to be excreted predominantly in the urine (Oberg et al. 1978) at levels twice that found in the feces (Rhoads and Sanders 1985). Three days after exposure to vanadium pentoxide, 40% of the ^{48}V dose was excreted, mostly in the urine while 30% remained in the skeleton (5 days after exposure) (Conklin et al. 1982).

In female rats exposed to 0.56 or 1.1 mg vanadium/m^3 as vanadium pentoxide for 16 days (6 hours/day, 5 days/week), lung clearance half-times during an 8-day recovery period were 4.42 and 4.96 days,

respectively (NTP 2002). In mice similarly exposed to 1.1 or 2.2 mg vanadium/m^3, lung clearance half-times were 2.55 and 2.40 days, respectively (NTP 2002). In contrast to the 16-day exposure data, the lung clearance half-times in female rats exposed to 0.28, 0.56, or 1.1 mg vanadium/m^3 for 2 years (6 hours/day, 5 days/week) were 37.3, 58.6, and 61.4 days, respectively (NTP 2002). In mice, the half-times were 6.26, 10.7, and 13.9 days at 0.56, 1.1, and 2.2 mg vanadium/m^3 exposure levels (NTP 2002). These data suggest that vanadium is more rapidly cleared from the lungs following a short exposure period compared to longer periods.

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to vanadium.

Since vanadium is poorly absorbed in the gastrointestinal tract, a large percentage of vanadium is excreted unabsorbed in the feces in rats following oral exposure. More than 80% of the administered dose of ammonium metavanadate or sodium metavanadate accumulated in the feces after 6 or 7 days (Adachi et al. 2000b; Patterson et al. 1986). After 2 weeks of exposure, 59.1±18.8% of sodium metavanadate was found in the feces (Bogden et al. 1982). However, the principal route of excretion of absorbed vanadium is through the kidney in animals. Approximately 0.9% of ingested vanadium was excreted in the urine of rats exposed to sodium metavanadate in the diet for 7 days (Adachi et al. 2000b). An elimination half-time of 11.7 days was estimated in rats exposed to vanadyl sulfate in drinking water for 3 weeks (Ramanadham et al. 1991).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to vanadium.

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 and Krishnan 1994; Andersen et al. 1987). 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 parameterization, (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 vanadium 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.

No PBPK models for vanadium were located.

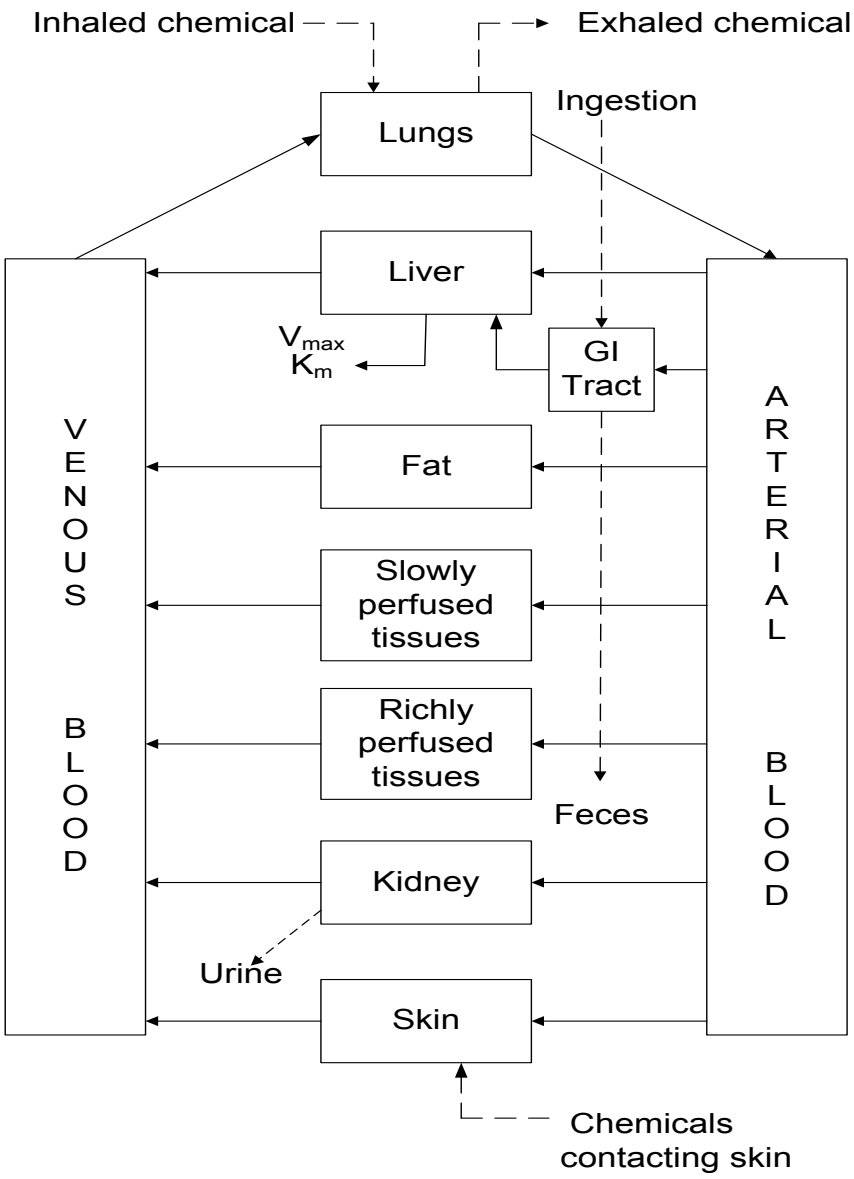
3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

In the body, there is an interconversion of two oxidation states of vanadium, the tetravalent form, vanadyl (V^{+4}), and the pentavalent form, vanadate (V^{+5}). Vanadium can reversibly bind to transferrin protein in the blood and then be taken up into erythrocytes. Vanadate is considered more toxic than vanadyl because vanadate is reactive with a number of enzymes and is a potent inhibitor of the Na+K+-ATPase of plasma membranes (Harris et al. 1984; Patterson et al. 1986). There is a slower uptake of vanadyl into erythrocytes compared to the vanadate form. Five minutes after an intravenous administration of radiolabeled vanadate or vanadyl in dogs, 30% of the vanadate dose and 12% of the vanadyl dose is found in erythrocytes (Harris et al. 1984). It is suggested that this difference in uptake is due to the time required for the vanadyl form to be oxidized to vanadate. When V^{+4} or V^{+5} is administered intravenously, a balance is reached in which vanadium moves in and out of the cells at a rate that is comparable to the rate of vanadium removal from the blood (Harris et al. 1984). Initially, vanadyl leaves the blood more rapidly than vanadate, possibly due to the slower uptake of vanadyl into cells (Harris et al. 1984). Five hours after administration, blood clearance is essentially identical for the two forms. A decrease in glutathione-SH, NADPH, and NADH occurs within an hour after intraperitoneal injection of sodium vanadate in mice (Bruech et al. 1984). It is believed that the redox cycling of vanadium V^{+5}/V^{+4}, depending on the local availability of oxygen in tissues, depletes reducing equivalents that are necessary for activity of cytochrome P-450.

Vanadium in the plasma can exist in a bound or unbound form (Bruech et al. 1984). Vanadium as vanadyl (Patterson et al. 1986) or vanadate (Harris and Carrano 1984) reversibly binds to human serum transferrin at two metal-binding sites on the protein. With intravenous administration of vanadate or

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



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.

Source: adapted from Krishnan and Andersen 1994

vanadyl, there is a short lag time for vanadate binding to transferrin, but at 30 hours, the association is identical for the two vanadium forms (Harris et al. 1984). The vanadium-transferrin binding is most likely to occur with the vanadyl form as this complex is more stable (Harris et al. 1984). The transferrin-bound vanadium is cleared from the blood at a slower rate than unbound vanadium in rats, which explains a biphasic clearance pattern (Sabbioni and Marafante 1978). The metabolic pathway appears to be independent of route of exposure (Edel and Sabbioni 1988).

3.5.2 Mechanisms of Toxicity

In vitro studies (as reviewed by Barceloux 1999; Etcheverry and Cortizo 1998; Harland and Harden-Williams 1994; Léonard and Gerber 1994; Mukherjee et al. 2004) have shown that vanadium acts as a phosphate analog and, as such, interferes with various ATPases, phosphatases, and phosphate-transfer enzymes. Vanadium has been shown to inhibit Na+K+ATPase, Ca2+ATPase, H+K+ATPase, K+ATPase, Ca+Mg+ATPase, dynein ATPase, actomyosin ATPase, acid and alkaline phosphatases, glucose-6-phosphatase, ribonuclease, phosphodiesterase, and phosphotryosyl-phosphatase. It has also been shown to stimulate tyrosine kinase phosphorylase, NADPH oxidase, and adenylate cyclase. Additionally, vanadium has been shown to have insulin-mimetic properties, particularly the ability to stimulate glucose uptake and oxidation and glycogen synthesis, and the ability to induce cell proliferation. The effect of vanadium on various enzymes may be responsible for the diverse effects observed in animals exposed to vanadium. However, little information is available regarding the mechanism of vanadium toxicity *in vivo*.

Although the respiratory tract is a sensitive target following inhalation exposure to vanadium, little information is available on the mode of action. Yu et al. (2011) showed that vanadium pentoxide induced mucin production in mouse airway epithelial cells; however, the mucin production was induced via EGFR- and MAPK-independent pathways. Vanadium pentoxide-induced mucin production did appear to be dependent on a RAF1-1KK-NF-κB pathway. Results of studies by Turpin et al. (2010) found that the vanadium pentoxide-induced airway fibrosis was associated with increased collagen and/or fibroblasts around the airways. Vanadium increased mRNA levels encoding several pro-fibrogenic growth factors (e.g., TGF-β1, CTGF, and PDGF-C) and chemokines (e.g., IFN-α, IFN-β, CXCL9, and CXCL10); collagen mRNA levels were also increased in the vanadium-exposed mice. Wang et al. (2003) showed that aspiration of sodium metavanadate resulted in inflammation and an increase in apoptosis, with a minimal amount of lung cell necrosis. The inflammatory cell influx and lung cell apoptosis were likely due to the generation of reactive oxygen species, particularly hydrogen peroxide.

3.5.3 Animal-to-Human Extrapolations

There are little data available to evaluate potential toxicokinetic differences between humans and laboratory animals. Similar effects have been reported in humans and animals following inhalation or oral exposure to vanadium; however, this conclusion is based on the limited human toxicity data. In absence of data to the contrary, rats or mice appear to be valid models for extrapolation to humans.

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 Thomas and Colborn (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 1997b). 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 *in vivo* or *in vitro* studies were located regarding endocrine disruption in humans and/or animals after exposure to vanadium.

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).

There are limited data on the toxicity of vanadium in children. A study in rats examined the influence of age on the renal toxicity of vanadium. Male rats were administered 10 mg/kg/day sodium orthovanadate via intraperitoneal injection for 8 days. Similar morphological effects were observed in the kidneys of 22-day-old rats and 62-day-old rats; however, the effects were more severe in the older rats (de la Torre et al. 1999). The difference in lesion severity is likely due to the significantly lower renal vanadium concentration in the young rats.

Edel et al. (1984) examined age-related changes in the distribution of vanadium in rats exposed to background levels of vanadium. At 21 days of age, the highest concentrations of vanadium (ng vanadium/g wet weight) were found in the kidney, heart, lung, brain, and liver. By 115 days of age, the highest concentration was in the femur; levels in the heart, lung, brain, spleen, and muscle were approximately 3–4 times lower. The concentrations of vanadium in the kidney, liver, and lungs significantly decreased with increasing age of the rat. The investigators suggested several mechanisms that may be responsible for the age-related changes in vanadium tissue concentration, including higher gastrointestinal absorption of vanadium in young rats, which may be due to increased bioavailability of vanadium in breast milk compared to the diet, or a higher vanadium retention capacity in undeveloped tissue due to a greater affinity or lower elimination rate.

As discussed in Section 3.2, a number of developmental effects including decreases in growth, increases in malformation and anomalies, and death have been observed in developmental toxicity studies (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003; Paternain et al. 1990); however most of these effects occurred at doses associated with significant maternal toxicity.

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).

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, 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 vanadium 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 vanadium 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 Vanadium

Several biomarkers of exposure have been identified for vanadium but none of them can be used to quantitatively determine exposure levels. Elevated levels of vanadium have been found in the serum (Gylseth et al. 1979; Kiviluoto et al. 1981b), blood (Kučera et al. 1998), and urine (Gylseth et al. 1979; Kiviluoto et al. 1981b; Kučera et al. 1998; Lewis 1959; NIOSH 1983; Zenz et al. 1962) of exposed workers. Elevated levels of vanadium have also been detected in children accidentally exposed to high levels of vanadium in drinking water (Kučera et al. 1992). Although elevated vanadium levels have been detected in vanadium-exposed individuals and a significant correlation between serum vanadium levels and urinary vanadium levels have been found (Kiviluoto et al. 1981b), relationships between exposure levels and blood/serum or urine vanadium levels have not been established. Some vanadium workers develop a characteristic green tongue, as a result of direct accumulation of the vanadium dusts on the tongue (Lewis 1959). One report from the 1950s states that vanadium exposure was associated with decreased cystine content in the fingernails of vanadium workers (Mountain et al. 1955). However, alterations in cystine levels can also be associated with dietary changes and with other disease states, so this is not specific for vanadium exposure. Another occupational exposure study did not find significant alterations in cysteine levels in fingernails (Kučera et al. 1998). Analytical methods have been developed to measure vanadium levels in hair (Fernandes et al. 2007; Kučera et al. 1992, 1998); however, a relationship between exposure levels and hair levels has not been established. Kučera et al. (1992) did not find a significant increase in hair vanadium levels in children exposed to elevated vanadium drinking water levels; however, significant increases in blood vanadium levels were found in this group. In an occupational exposure study, elevated hair vanadium levels were found (Kučera et al. 1998).

3.8.2 Biomarkers Used to Characterize Effects Caused by Vanadium

The primary effects of inhalation exposure to vanadium dusts are coughing, wheezing, and other respiratory difficulties. These effects, however, are not specific to vanadium and can be found following inhalation of many types of dusts.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Vanadium in the drinking water of mice had no influence on tumor induction by the known carcinogen 1,2-dimethylhydrazine given by subcutaneous injection (Kingsnorth et al. 1986), but dietary vanadium did decrease mammary tumors in mice caused by 1-methyl-1-nitrosourea administered concurrently (Thompson et al. 1984). The latter effect may have been due to interaction with DNA.

The combination of manganese and vanadium or of nickel and vanadium administered to pregnant mice caused some alterations in behavioral development of the pups as compared to either element administered alone (Hoshishima et al. 1983). Oral administration of vanadium in rats interfered with copper metabolism, probably by inhibiting the intestinal absorption of copper (Witkowska et al. 1988).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to vanadium than will most persons exposed to the same level of vanadium 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 vanadium, or compromised function of organs affected by vanadium. Populations who are at greater risk due to their unusually high exposure to vanadium are discussed in Section 6.7, Populations with Potentially High Exposures.

No unusually susceptible populations have been identified, but persons with pre-existing respiratory disorders such as asthma or chronic obstructive pulmonary disease (COPD) may be expected to have increased adverse effects from breathing vanadium dusts. Due to the insulin-mimetic effects of vanadium, individuals with hypoglycemia may be unusually susceptible to exposure to high levels of vanadium.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to vanadium. 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 vanadium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted

for medical advice. The following texts provide specific information about treatment following exposures to vanadium:

Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Company, 1033.

Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 406-407.

3.11.1 Reducing Peak Absorption Following Exposure

There is no known treatment to decrease absorption after inhaling or ingesting vanadium and/or its compounds. If vanadium gets onto the skin, washing the contaminated area with soapy water has been advised. For ocular exposure, it is suggested that the eyes be flushed with large amounts of saline or water (Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

Several studies have evaluated the effectiveness of chelating agents in reducing vanadium body burden. Significant increases in urinary excretion of vanadium were observed in rodents treated with ascorbic acid (Domingo et al. 1990), tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) (Domingo et al. 1990; Gomez et al. 1991), deferoxamine mesylate (Gomez et al. 1988, 1991), 2-mercaptosuccinic (Domingo et al. 1990), deferrioxamine (Tubafard et al. 2010), or deferiprone (Tubafard et al. 2010) following intramuscular injection of vanadyl sulfate (Domingo et al. 1990), 6-week oral exposure to sodium metavanadate or vanadyl sulfate (Gomez et al. 1991), or 60-day exposure to vanadium (specific compound and route of exposure not reported (Tubafard et al. 2010). Administration of ethylene diamine tetraacetate (EDTA), 2-mercaptosuccinic or tiron also significantly reduced kidney vanadium levels (Domingo et al. 1990) and tiron reduced spleen and kidney vanadium levels (Gomez et al. 1991). Administration of calcium disodium EDTA resulted in increases in urinary excretion of vanadium in calves exposed to high levels of dietary vanadium (Gummow et al. 2006); however, no difference in vanadium excretion was observed after vanadium exposure was terminated. Other studies have examined the potential of chelating agents to reduce toxicity. Humans or animals with vanadium poisoning have not been helped by the chelating agent dimercaprol (BAL), which is often effective in lessening the toxicity of other metals (Lusky et al. 1949). Intraperitoneal injections of ascorbic acid and EDTA reduced vanadium-induced morbidity in mice and rats (Jones and Basinger 1983; Mitchell and Floyd 1954). Decreased mortality was also observed in mice following intraperitoneal injection of D-pencillamine,

tiron, and deferoxamine mesylate (Jones and Basinger 1983). Administration of tiron 0, 24, 48, or 72 hours after pregnant mice received a 25 mg/kg sodium metavanadate intraperitoneal injection on gestation day 12 resulted in significant reductions in vanadium-induced abortions, early deliveries, fetal deaths, and incidence of reduced ossification (Domingo et al. 1993a). Administration of tiron after a 6-week exposure to sodium metavanadate reverted the vanadium-induced impairment in performance on neurobehavioral tests (Sanchez et al. 1999). Co-exposure to calcium disodium EDTA did not significantly alter the toxicity of ingested vanadium in calves (Gummow et al. 2006).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There are limited data on treatments which interfere with the mechanism of action for vanadium toxicity. Moderate to severe morphological alterations (average severity score of 3.0) were observed in the kidneys 25 days after rats were administered 1 mg vanadium/kg/day as ammonium metavanadate via subcutaneous injection (Al-Bayati et al. 2002). Administration of the antifibrotic agent, pirfenidone, for 41 days after exposure termination resulted in a decrease in the severity of the kidney lesions; the lesions were scored as very mild with a severity score of 1.42. Although the mechanism associated with the reduction in toxicity was not determined, it is possible that the pirfenidone-induced reduction in collagen-deposition in the kidney may have contributed to the diminished toxicity. Chandra et al. (2007a) demonstrated a reduction in testes toxicity in rats administered 0.4 mg vanadium/kg/day as sodium metavanadate via intraperitoneal injection for 26 days and 50 or 100 mg/kg vitamin E acetate simultaneously in the diet compared to rats administered vanadium only. The likely mechanism is that vitamin E interrupts the chain reactions of lipid peroxidation and scavenges ROS generated during the univalent reduction of molecular oxygen and normal activity of oxidative enzymes; thus its prevents the detrimental effect of vanadium on testis by inhibiting the oxidative stress.

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 vanadium 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 vanadium.

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.

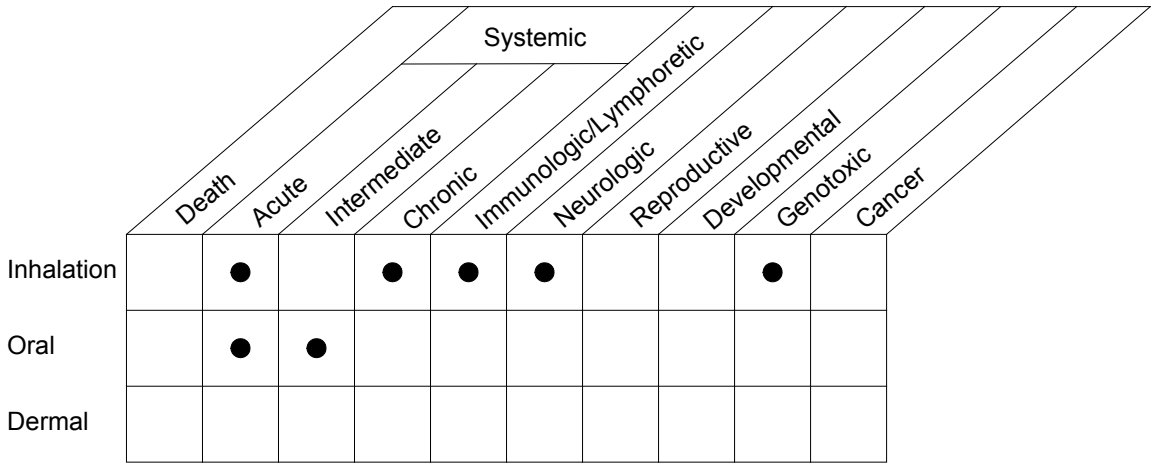
3.12.1 Existing Information on Health Effects of Vanadium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to vanadium are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of vanadium. 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 comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

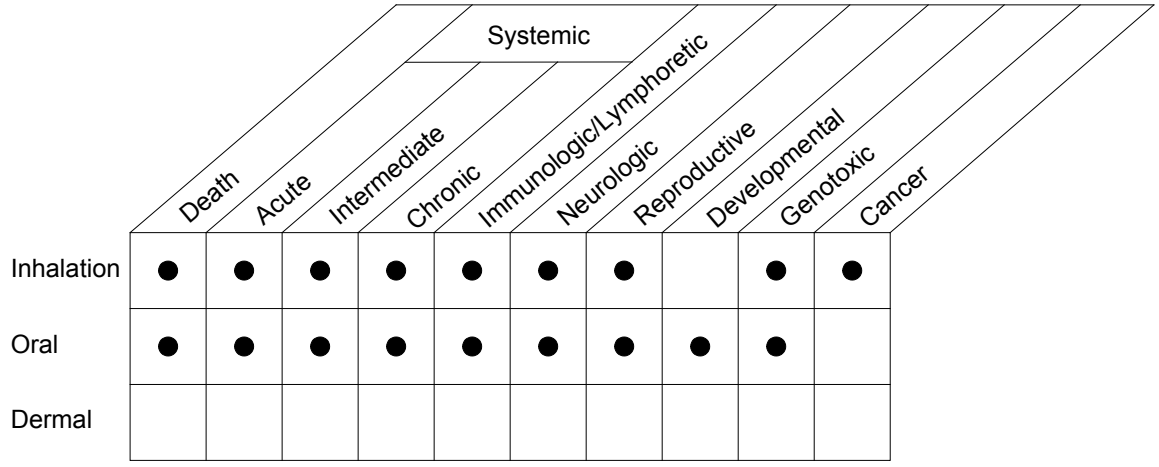
Data are available from humans regarding acute, intermediate, and chronic inhalation exposure to vanadium pentoxide and on immunologic and neurologic effects, primarily from case studies of factory workers. Data regarding acute effects are available from volunteers who ingested ammonium vanadyl tartrate in capsules for intermediate periods. No human dermal data were located.

Data are available regarding the effects of inhalation of vanadium pentoxide in rats, mice, and monkeys following acute, intermediate, and chronic exposures. Data are available in humans orally exposed to vanadyl sulfate or ammonium metavanadate. Data are available following acute, intermediate, and chronic oral exposures in animals, including information on death (from ammonium metavanadate, sodium metavanadate, or vanadyl sulfate), systemic toxicity (from vanadyl sulfate, sodium metavanadate, sodium orthovanadate, or ammonium metavanadate), immunological (from sodium orthovanadate), neurological (from vanadium pentoxide), developmental (from vandyl sulfate, sodium orthovanadate, ammonium metavanadate, or sodium metavanadate), and reproductive effects (from sodium metavanadate, ammonium metavanadate, or vanadyl sulfate). No animal dermal data were located.

Figure 3-4. Existing Information on Health Effects of Vanadium and Compounds



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information on the acute toxicity of inhaled vanadium in humans is limited to the finding of symptoms of respiratory irritation (persistent coughing) in a small number of subjects exposed to vanadium pentoxide dust for 8 hours (Zenz and Berg 1967). Several animal studies confirm that the respiratory tract is the most sensitive target of vanadium toxicity (Knecht et al. 1985, 1992; NTP 2002). These studies only examined the respiratory tract; however, longer duration studies have confirmed the respiratory tract as the most sensitive target following inhalation exposure. At lower concentrations, the observed effects included lung inflammation and alveolar and bronchiolar epithelial hyperplasia in rats and mice exposed to vanadium pentoxide for 6 or 13 days (NTP 2002); the severity of the lung effects increased with increasing vanadium concentrations. Impaired lung function was reported in monkeys exposed to fairly low concentrations of vanadium pentoxide for 6 hours (Knecht et al. 1985, 1992). The animal data were sufficient to derive an acute-duration inhalation MRL for vanadium based on lung inflammation in rats (NTP 2002).

There are limited data on human toxicity following ingestion of vanadium; gastrointestinal effects (diarrhea, cramps, nausea, vomiting) have been reported in patients given vanadium supplement as part of a diabetes treatment plan (Boden et al. 1996; Cusi et al. 2001; Goldfine et al. 1995). However, these studies are limited by the small number of subjects and the lack of control groups. A small number of studies in laboratory animals have examined the acute toxicity of vanadium following oral exposure. At the lowest doses tested, marked developmental toxicity (decreases in fetal growth, increases in resorptions and gross, visceral, and skeletal malformations and anomalies) was observed in rat and mouse offspring (Paternain et al. 1987, 1990; Sanchez et al. 1991). In adult rats, hematological effects (including increases in reticulocyte levels and polychromatophilic erythroblasts in bone marrow) were observed at higher doses than the developmental effects (Zaporowska and Wasilewski 1989). The database was considered inadequate for derivation of an acute-duration oral MRL due to the limitations in the human studies and the serious effects observed at the lowest animal dose tested. At the lowest adverse effect level, a 46% decrease in weight gain (considered a serious health effect) was observed in the rat dams (Paternain et al. 1990); it is ATSDR policy to not use serious LOAELs as the basis of an MRL. Additional studies which examine a variety of end points are needed to identify the most sensitive effect following acute oral exposure. These additional studies might provide a suitable basis for an acute-duration oral MRL.

No dermal exposure studies were identified in humans or animals. Studies are needed to establish the potential toxicity of vanadium compounds applied to the skin.

Intermediate-Duration Exposure. No human studies examined the toxicity of vanadium following intermediate-duration inhalation exposure. Animal data come from 16-day and 13-week exposure studies in rats and mice (NTP 2002). These studies clearly identify the respiratory tract as the most sensitive target of toxicity. At low concentrations of vanadium pentoxide, alveolar and bronchiolar epithelial hyperplasia were observed in both species. At higher concentrations, nasal effects were also observed. Although the NTP (2002) study is a high quality study which identified NOAEL and LOAEL values for a sensitive end point, an intermediate-duration inhalation MRL was not derived because the NOAEL value was the same as the LOAEL for lung inflammation in rats exposed to vanadium pentoxide for 13 days (NTP 2002). An explanation for the inconsistent findings is not apparent from the available data. An additional study designed to examine respiratory effects after various exposure durations may provide insight into the inconsistent findings of the NTP study and may be useful for derivation of an MRL.

Data on the toxicity of vanadium following intermediate-duration oral exposure come from two human studies and a number of animal studies. The human studies examined a number of potential end points in subjects exposed to relatively low doses of vanadium for 6–12 weeks; no adverse effects were observed (Dimond et al. 1963; Fawcett et al. 1997). Animal studies have identified several sensitive effects including hematological alterations (decreased erythrocyte levels and increased reticulocyte levels) (Ścibior 2005; Ścibior et al. 2006; Zaporowska and Wasilewski 1990, 1991, 1992a, 1992b; Zaporowska et al. 1993), increased blood pressure (Boscolo et al. 1994; Carmagnani et al. 1991, 1992), alterations in neurobehavioral performance tests (Sanchez et al. 1998), and developmental toxicity (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003; Poggioli et al. 2001). However, the findings are inconsistent and a cause of the conflicting results has not been identified. Additional animal studies examining hematological, blood pressure, and neurological end points are needed to support the findings of the animal studies. An intermediate-duration oral MRL based on the NOAEL identified in one of the human studies (Fawcett et al. 1997) was derived.

No dermal exposure studies were identified in humans or animals. Studies utilizing several vanadium compounds would be useful for assessing the potential dermal toxicity of vanadium.

Chronic-Duration Exposure and Cancer. Sufficient information is available in occupationally exposed humans to identify the respiratory system as a target organ following chronic inhalation exposure

(Lewis 1959; NIOSH 1983; Sjöberg 1956; Vintinner et al. 1955; Wyers 1946). Two-year rat and mouse studies (NTP 2002) confirm the identification of the respiratory tract as the most sensitive target of inhaled vanadium pentoxide. At the lowest concentrations tested, histological alterations in the lungs (alveolar and bronchiolar epithelial hyperplasia), larynx (degeneration and hyperplasia of epiglottis epithelium), and nasal cavity (goblet cell hyperplasia) were observed. The NTP (2002) rat study was used as the basis of a chronic-duration inhalation MRL for vanadium.

No studies examining the chronic oral toxicity of vanadium in humans were identified. Several studies have examined chronic oral toxicity in rats and mice (Dai and McNeill 1994; Dai et al. 1994a, 1994b; Schroeder and Balassa 1967; Schroeder et al. 1970); however, the doses tested did not result in adverse effects, with the exception of a decrease in body weight gain, and the most sensitive targets of vanadium toxicity following chronic exposure have not been identified. Additional studies examining a variety of end points, including potential hematological and cardiovascular effects (sensitive targets following intermediate-duration exposure), are needed to identify sensitive targets and establish dose-response relationships.

Data are not available to determine target organs in humans from chronic dermal exposure. Dermal exposure studies which could be used to identify targets of toxicity and dose-response relationships are needed.

No studies were located regarding the carcinogenicity in humans after inhalation, oral, or dermal exposure to vanadium. Significant increases in the incidence of lung tumors (alveolar/bronchiolar adenoma and/or carcinoma) were observed in mice exposed to airborne vanadium pentoxide for 2 years (NTP 2002). Suggestive evidence of lung carcinogenicity was also observed in male rats chronically exposed to vanadium pentoxide (NTP 2002). Although several oral studies did not find increases in tumor frequency in rats or mice exposed to vanadyl sulfate in drinking water (Schroeder and Balassa 1967; Schroeder and Mitchener 1975; Schroeder et al. 1970), these studies were considered inadequate for carcinogenicity assessment due to the small number of animals tested, low doses (maximum tolerated dose was not achieved), incomplete histological examination, and the use of one exposure dose per study. No studies examined the potential carcinogenicity of vanadium following dermal exposure. Additional studies are needed to evaluate the potential carcinogenicity of vanadium following oral and dermal exposure.

Genotoxicity. *In vivo* genotoxicity assays have been conducted in vanadium pentoxide workers (Ehrlich et al. 2008; Ivancsits et al. 2002), in mice exposed to airborne vanadium pentoxide (NTP 2002),

in mice exposed to vanadyl sulfate in drinking water (Villani et al. 2007), and in mice administered a gavage dose of vanadyl sulfate, ammonium metavanadate, or sodium orthovanadate (Ciranni et al. 1995). Most of the *in vitro* genotoxicity assays have been conducted in mammalian systems, although there are also mutagenicity assays in cultured bacteria (Kada et al. 1980; Kanematsu et al. 1980; NTP 2002) and yeast (Bronzetti et al. 1990; Sora et al. 1986). In mammalian systems, mutagenicity (Cohen et al. 1992), DNA damage (Birnboim 1988; Foresti et al. 2001; Ivancsits et al. 2002; Kleinsasser et al. 2003; Rojas et al. 1996; Smith 1983; Wozniak and Blasiak 2004), and clastogenicity (Gibson et al. 1997; Migliore et al. 1993, 1995; Owusu-Yaw et al. 1990; Roldán and Altamirano 1990; Zhong et al. 1994) have been observed. In general these studies provide evidence that vanadium compounds damage DNA and induce clastogenic alterations. However, there are a number of inconsistencies in the results and additional studies are needed.

Reproductive Toxicity. No studies were located regarding the reproductive effects in humans after inhalation, oral, or dermal exposure to vanadium. Following inhalation exposure, alterations in estrous cycle were observed in female rats exposed to vanadium pentoxide for 3 months (NTP 2002); no alterations in sperm characteristics were observed. Studies examining reproductive function are needed to evaluate whether the alterations observed in female rats would result in impaired fertility. Decreases in male and/or female fertility were observed in rats and mice orally exposed to vanadium (Ganguli et al. 1994b; Jain et al. 2007; Llobet et al. 1993; Morgan and El-Tawil 2003). Dermal exposure studies are needed to evaluate whether the reproductive system is also a target of toxicity for this route.

Developmental Toxicity. The potential developmental toxicity of vanadium has not been assessed in humans. Oral exposure studies in animals provide evidence that developmental toxicity is a sensitive end point. The observed effects include decreases in fetal/pup growth, increased mortality, and increases in gross, skeletal, and visceral malformations and anomalies (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003; Paternain et al. 1987, 1990; Poggioli et al. 2001). Most of these effects occurred at doses associated with decreases in maternal food intake and body weight. Additional studies utilizing doses not associated with maternal toxicity would be useful in determining whether the observed effects are secondary to maternal toxicity or whether the developing organism is a primary target. No studies were located regarding the developmental effects in animals after inhalation or dermal exposure to vanadium. Studies are needed to determine whether developmental toxicity would also be a sensitive target following inhalation or dermal exposure.

Immunotoxicity. Data regarding the immunotoxicity of vanadium in humans are limited to a study of vanadium workers which did not find signs of allergic reactions on the skin or in the respiratory tract (Sjöberg 1950). No alterations in immune response to bacteria and/or viruses were observed in mice exposed to airborne vanadium pentoxide for 16 days (NTP 2002); an altered response was observed in rats. An altered response to sheep red blood cells in mice exposed to sodium orthovanadate in drinking water for 6 weeks (Sharma et al. 1981) and decreases in B-cell, IgG, and IgM levels in rats exposed to sodium metavanadate in the diet for 10 weeks (Adachi et al. 2000a) were observed. No dermal exposure studies examining immunological end points were identified. Although the animal data provide some suggestive evidence of immunotoxicity, additional inhalation and oral exposure studies testing a full immunology battery are needed to establish the potential of vanadium to induce immunotoxicity.

Neurotoxicity. Some workers exposed to vanadium dust complained of dizziness, depression, headache, or tremors of the fingers and arms (Levy et al. 1984; Vintinner et al. 1955); however, these effects may not have been specifically due to vanadium exposure. Neurotoxicity was not evaluated in humans following oral or dermal exposure. In animals, alterations in performance on neurobehavioral tests were observed in rats orally exposed to sodium metavanadate (Sanchez et al. 1998, 1999). No histological alterations in the nervous system were observed in rats or mice exposed to airborne vanadium pentoxide (NTP 2002). Neurotoxicity potential was not assessed in animals following dermal exposure. Additional studies performing a complete neurological battery of tests are needed to fully evaluate the potential of vanadium to induce neurotoxicity, particularly since the Sanchez et al. (1998) study provides suggestive evidence that this may be a sensitive target following oral exposure.

Epidemiological and Human Dosimetry Studies. Studies of health effects on people who have inhaled vanadium in the workplace clearly show that the target organ is the respiratory system (Domingo et al. 1985; Levy et al. 1984; Lewis 1959; Musk and Tees 1982; NIOSH 1983; Sjöberg 1950, 1956; Thomas and Stiebris 1956; Vintinner et al. 1955; Wyers 1946; Zenz and Berg 1967; Zenz et al. 1962). The dose-response relationship is not known, because exposure levels are not well quantified. Further information on exposure levels associated with respiratory effects would be useful. However, people living near hazardous waste sites are unlikely to come in contact with amounts of vanadium dusts large enough to cause adverse health effects. Further epidemiological studies may be useful in revealing adverse health effects in people living near boiler ash dumps. Additional information on potentially susceptible populations, such as those people with asthma or other respiratory problems, would be useful. There are limited data regarding the oral toxicity of vanadium in humans. Studies in diabetics have shown that bolus administration can result in symptoms of gastrointestinal irritation (Boden et al. 1996;

Cusi et al. 2001; Goldfine et al. 1995). Two studies in healthy individuals (Dimond et al. 1963; Fawcett et al. 1997) examined a wide variety of potential targets of vanadium toxicity. However, both studies used a small number of subjects and additional studies are needed to evaluate the long-term toxicity of vanadium in humans, particularly since vanadium is present in a number of nutritional supplements and there is a potential for human exposure. An intermediate-duration oral study (Fawcett et al. 1997) which found no adverse effects in subjects administered vanadyl sulfate via capsules was used as the basis of an MRL.

Biomarkers of Exposure and Effect.

Exposure. Biomarkers specific for exposure to vanadium include the presence of vanadium in the urine (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983; Zenz et al. 1962) and serum (Gylseth et al. 1979) and a green discoloration of the tongue (Lewis 1959), the latter resulting from the direct accumulation of vanadium pentoxide. Further studies would be helpful in correlating urinary or serum vanadium levels with exposure levels. Vanadium can also be measured in the hair (Stokinger et al. 1953), and studies could be performed to determine if a correlation exists between levels of vanadium in hair and exposure levels. In the 1950s, decreased cystine content of the hair or fingernails was described as a possible biomarker of exposure (Mountain et al. 1955). However, this is not specific for vanadium since other factors, such as diet or disease, can also affect cystine content.

Effect. There are no specific biomarkers of effects. It is possible that further biochemical studies might show specific effects. For example, it is possible that specific effects may be seen on lung cells, which can be examined by lavage.

Absorption, Distribution, Metabolism, and Excretion. Data are available from human and animal studies regarding the kinetics of vanadium following inhalation and oral exposure. Specific data from dermal exposure are lacking; although significant absorption of vanadium by this route in humans is unlikely (WHO 1988), data are needed to confirm this hypothesis. No animal studies were located that evaluated absorption efficiency following inhalation exposure, although NTP (2002) reported marginal, but concentration-related, increases in blood vanadium in rats exposed to vanadium pentoxide for 14 days or 2 years. Additionally, information is available from intratracheal exposures (Conklin et al. 1982; Edel and Sabbioni 1988; Oberg et al. 1978; Rhoads and Sanders 1985). Oral exposure studies suggest that approximately 3–17% of ingested vanadium is absorbed and that absorption efficiency may vary among vanadium compounds (Adachi et al. 2000b; Conklin et al. 1982). Intratracheal administration and oral

exposure suggest similar patterns of distribution and excretion (Adachi et al. 2000b; Conklin et al. 1982; Ramanadham et al. 1991; Rhoads and Sanders 1985) for the two routes of exposure. Additional studies are needed to provide information on the toxicokinetic properties of vanadium following inhalation and dermal exposure. Additionally, there are limited data comparing the absorption and distribution of various vanadium compounds; inhalation, oral, and dermal exposure studies are needed to evaluate whether there are compound-specific differences.

Comparative Toxicokinetics. Animal data (Conklin et al. 1982; Oberg et al. 1978; Rhoads and Sanders 1985; Roshchin et al. 1980) and limited human (Dimond et al. 1963; Gylseth et al. 1979; Schroeder et al. 1963) data are available on the kinetics of vanadium. There is little reason to believe that vanadium toxicokinetics would differ between animals and humans. The data indicate that the kinetics are similar in both. However, as with any particulate substance, extrapolations on inhalation absorption rates from animals to humans would be difficult. Studies are available in humans, rats, mice, and dogs.

Methods for Reducing Toxic Effects. No vanadium-specific information on reducing the absorption of vanadium following inhalation, oral, or dermal exposure were identified; such information would be useful in the treatment of persons who may have been exposed to vanadium and/or its compounds near hazardous waste sites. Several animal studies have explored the use of chelating agents for reducing the vanadium body burden. Administration of ascorbic acid, tiron, deferoxamine mesylate, or 2-mercaptosuccinic have been shown to increase urinary excretion of vanadium or reduce kidney levels (Domingo et al. 1990; Gomez et al. 1988, 1991), and EDTA and tiron have been shown to reduce toxicity (Domingo et al. 1993a; Jones and Basinger 1983; Mitchell and Floyd 1954; Sanchez et al. 1999), presumably by reducing the body burden. There is some evidence that pirfenidone (an antifibrotic agent) (Al-Bayati et al. 2002) and vitamin E (Chandra et al. 2007a) may interfere with the mechanism of vanadium toxicity. Additional data are needed, particularly studies examining methods for reducing the toxicity of inhaled vanadium.

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.

There are limited data on the susceptibility of children to vanadium toxicity. No human or animal studies examined possible age-related differences in toxicity following inhalation, oral, or dermal exposure. An intraperitoneal study found decreases in the severity of renal lesions in young rats (22 days of age)

compared to older rats (62 days of age) (de la Torre et al. 1999). Additional studies are needed to evaluate if there are age-related differences in vanadium toxicity or toxicokinetic properties.

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

The National Institute of Environmental Health Sciences is sponsoring research studies by James Bonner and Daniel Morgan to examine the mechanisms through which vanadium pentoxide induces lung fibrosis (FEDRIP 2012).