2. HEALTH EFFECTS

2.1 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 of the toxicology of vanadium and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for vanadium based on toxicological studies and epidemiological investigations.

Elemental vanadium does not occur in nature; however, vanadium compounds exist in over 50 different mineral ores and in association with fossil fuels. It has six oxidation states (l-, 0, 2+, 3+, 4+, and 5+) of which 3+, 4+, and 5+ are the most common. 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. Information for the other vanadium compounds comes from oral studies in animals.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals 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, developmental,reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), 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 noobserved-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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious” effects. Public health officials and project managers 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 (LOAEL) or exposure

levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

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

Only one study was located regarding death in animals after inhalation exposure to vanadium. In this study designed to determine the LD_{50}, two of four rabbits died following an acute exposure to 114 mg vanadium/m^3 as vanadium pentoxide (Sjoeberg 1950). The NOAEL and LOAEL values are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. One experimental study utilizing two volunteers provided accurate exposure levels and showed that mucus formed and coughing occured following an acute exposure to 0.06 mg vanadium/m^3 as vanadium pentoxide (Zenz and Berg 1967). The onset of coughing and of mucus formation was delayed 7-24 hours. Pulmonary function tests were normal. This LOAEL was used to calculate the acute inhalation MRL of 0.0002 mg vanadium/m^3. Vanadium is used in making steel and is released from burning fuel oil, therefore, occupational exposure to vanadium pentoxide dusts stems mostly from metallurgy and boiler-cleaning. Workers exposed to a range of levels of vanadium pentoxide dusts 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 or more years

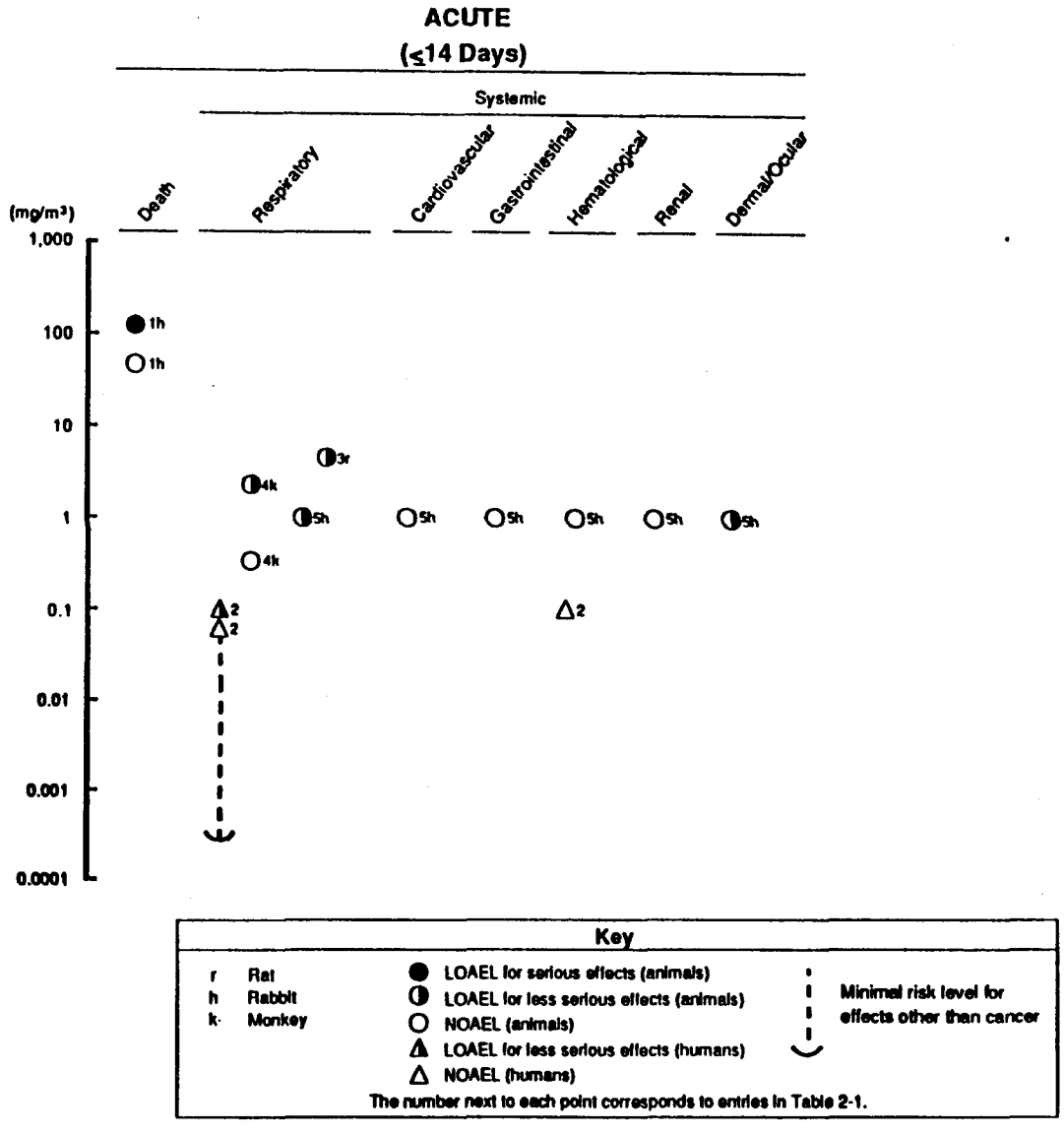
TABLE 2-1. Levels of Significant Exposure to Vanadium and Compounds - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mgV/m^3)	LOAEL (effect) Less serious (mgV/m^3)	LOAEL (effect) Serious (mgV/m^3)	Reference	Form
ACUTE EXPOSURE								
Death								
1	Rabbit	1 d 7 hr/d		43		114 (2/4 died)	Sjoeberg 1950	V_2O_5
Systemic								
2	Human	8 hr	Resp Hemato	1	0.06[b] (bronchial irritation)		Zenz and Berg 1967	V_2O_5
3	Rat	2 wk 5 d/wk 6 hr/d	Resp		4.7 (alveolar proteinosis)		Lee and Gillies 1986	$BiVO_4$
4	Monkey	2 wk 1 d/wk 6 hr/d	Resp	0.34	2.5 (less lung function)		Knecht et al. 1985	V_2O_5
INTERMEDIATE EXPOSURE								
Systemic								
5	Rabbit	8 mo 1 hr/d	Resp Derm/oc Renal Gastro Cardio Hemato	0.8 0.8 0.8 0.8	0.8 (dyspnea) 0.8 (eye irritation)		Sjoeberg 1950	V_2O_5

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 0.0002 mg vanadium/m^3. Concentration divided by uncertainty factor of 100 for human variability and use of a LOAEL and multiplied by 8/24 to extrapolate to a full day exposure.

$BiVO_4$ = bismuth orthovanadate; Cardio = cardiovascular; d = day(s); Derm/oc = Dermal/ocular; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; V = vanadium; V_2O_5 = vanadium pentoxide; wk = week(s)

FIGURE 2-1. Levels of Significant Exposure To Vanadium and Compounds - Inhalation



(Lewis 1959; Orris et al. 1983; Sjoeberg 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 et al. 1979, 1980, 1981. More severe pathology has not been reported. Symptoms are reversible within days or weeks after exposure ceases. Inhalation exposure is believed to predominate in occupational settings but oral (mucociliary clearance) could contribute to total exposure. 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.

Animal data support the human findings and provide additional evidence that vanadium cornpounds are respiratory toxicants. Monkeys that breathed 2.8 mg vanadium/m^3 as vanadium pentoxide for 6 hours showed increased pulmonary resistance 1 day later which was not seen at 0.3 mg vanadium/m^3 (Knecht et al. 1985). They also had a dramatic increase in polymorphonuclear leucocytes in bronchioalveolar lavage, thus increasing total cell counts. Rats that breathed bismuth orthovanadate for 6 hours a day for 2 weeks showed increases in lung weight, and alveolar proteinosis as shown by an increased accumulation of alveolar macrophages, lung lipids, and type II pneumocytes (Lee and Gillies 1986). Rabbits that were exposed for one hour a day for 8 months had difficulty breathing (Sjoeberg 1950).

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 (Sjoeberg 1950).

Rabbits exposed one hour a day for 8 months to vanadium pentoxide did not show histopathological evidence of cardiovascular damage (Sjoeberg 1950), but this study does not provide a thorough investigation of cardiovascular function.

Gastrointestinal Effects. Volunteers exposed acutely to vanadium pentoxide dusts had no gastrointestinal complaints (Zenz and Berg 1967). People who were exposed to vanadium in oil-burner ashes also did not show gastrointestinal symptoms (Sjoeberg 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. These people probably also swallowed *some* of the dusts.

Rabbits exposed for 8 months to high levels (200 mg/m^3) of vanadium pentoxide dusts showed little histopathological damage to the gastrointestinal system (Sjoeberg 1950).

2. HEALTH EFFECTS

Hematological Effects. Volunteers exposed acutely (Zenz and Berg 1967),as well as workers exposed chronically to vanadium dusts, had normal hematological values (Kiviluoto et al. 1981a; Sjoeberg 1950; Vintinner et al. 1955).

Rabbits exposed acutely or chronically to vanadium pentoxide dusts showed no bone marrow changes upon histological examination (Sjoeberg 1950).

Musculoskeletal Effects. Muscular strength was not. altered in one study of workers exposed to vanadium pentoxide (Vintinner et al. 1955).

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to vanadium.

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 amino-transferase, aspartate aminotransferase, and lactate dehydrogenase) that are commonly used to detect possible liver damage (Kiviluoto et al. 1981a).

Rabbits exposed for 8 months to vanadium pentoxide dusts showed some fatty degeneration of the liver (Sjoeberg 1950). However, liver functidn was not tested, and the author stated, without explanation, that the liver changes were of no special significance.

Renal Effects. Workers exposed chronically to 0.01-0.5 mg/m^3 of vanadium dusts had normal serum levels of 18 enzymes and other substances commonly used to detect possible kidney damage (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) (Sjoeberg 1950; Vintinner et al. 1955).

Rabbits exposed acutely or chronically to vanadium pentoxide dusts showed fatty degeneration of the kidney, but the author, without explanation, did not attribute this to the vanadium (Sjoeberg 1950). No other studies were located regarding hepatic effects in animals following inhalation exposure to vanadium.

Dermal/Ocular Effects. Workers chronically exposed to vanadium dusts in factories had slight to moderate eye irritation in addition to respiratory distress (Levy et al. 1984; Lewis 1959; Sjoeberg 1950; Thomas and Stiebris 1956; Vintinner et al. 1955). Brief exposure to vanadium dust can also cause conjunctivitis (Zenz et al. 1962). The other significant peripheral finding in some workers was a green discoloration of the tongue attributed to direct deposition of vanadium. Workers had no increases in dermatitis as compared to controls (Vintinner et al. 1955), but some workers had skin rashes (Orris et al. 1983).

Rabbits exposed to vanadium pentoxide dusts also showed conjunctivitis (severity not specified) from acute or chronic exposures (Sjoeberg 1950).

Other Systemic Effects. Workers exposed to vanadium ore dust also reported weight loss (Vintinner et al. 1955).

2.2.1.3 Immunological Effects

The only human data located 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 (Sjoeberg 1950). .This, however, cannot be considered to be an adequate evaluation of immunological function.

Rabbits exposed acutely or chronically to vanadium pentoxide dusts did not show histopathological changes in the spleen (Sjoeberg 1950), but this is not a complete assessment of the immune system.

2.2.1.4 Neurological Effects

Volunteers exposed acutely had no neurological complaints (Zenz and Berg 1967). Most workers exposed to vanadium dusts did not report major adverse neurological signs (Sjoeberg 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.

Rabbits exposed to vanadium pentoxide for 8 months did not show pathological changes in the brain (Sjoeberg 1950). No other animal studies were located which tested neurological function.

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

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to vanadium.

2.2.2 Oral Exposure

2.2.2.1 Death

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

A gavage study has shown that 41 mg vanadium/kg as sodium metavanadate is the LD_{50} (14 days) for rats, and the value for mice is 31.2 mg/kg (Llobet and Domingo 1984). These values are recorded in Table 2-2 and plotted in Figure 2-2. Chronic exposures of up to 4.1 mg vanadium/kg as vanadyl sulfate in food or water did not affect mortality in rats or mice, respectively (Schroeder and Balassa 1967; Schroeder et al. 1970).

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for body weight changes in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

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 (Domingo et al. 1985).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to vanadium.

Rats fed 15 mg vanadium/kg as ammonium vanadate for 2 months showed increased right ventricular pressure and pulmonary hypertension, but no changes in systemic circulation (Susie and Kentera 1986). This laboratory also showed that sodium orthovanadate in the food for 6 months did not alter heart rate or blood pressure, but did induce vasoconstriction (Susic and Kentera 1988). Rats that had one kidney removed had increased systolic blood pressure within 7 weeks of consuming 5 mg/kg/day of vanadium in the diet (Steffen et al. 1981).

Gastrointestinal Effects. Very few data are available regarding gastrointestinal effects. Human volunteers (assumed body weight, 70 kg) given 0.47-1.3 mg vanadium/kg as ammonium vanadyl tartrate in capsules for 45-68 days had intestinal cramping and diarrhea (Dimond et al. 1963). Since vehicle and compound controls were not used, it is difficult to determine whether this effect was caused by the vanadium. Workers exposed to vanadium

TABLE 2-2. Levels of Significant Exposure to Vanadium and Compounds - Oral

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg V/kg/day)	LOAEL (effect) Less serious (mg V/kg/day)	LOAEL (effect) Serious (mg V/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Rat	(GW)	1 d 1 x/d		16		41 (LD_{50})	Llobet and Domingo 1984	$NaVO_3$
2	Mouse	(GW)	1 x		17		31 (LD_{50})	Llobet and Domingo 1984	$NaVO_3$
Developmental									
3	Rat	(G)	GD 6-14			8.4 (facial hemorrhage)		Paternain et al. 1987	$NaVO_3$
INTERMEDIATE EXPOSURE									
Systemic									
4	Human	(C)	45-68 d	Hepatic Hemato Renal	1.3 1.3 1.3			Dimond et al. 1963	
5	Rat	(W)	3 mo	Renal Resp Hepatic	0.3[b] 0.3 2.87	0.57 (hemorrhagic foci) 0.57 (vascular infiltration)	2.87 (effects increase)	Domingo et al. 1985	$NaVO_3$
6	Rat	(F)	100 d	Other	2	3.9 (decreased weight gain in females)		Franke and Moxon 1937	$NaVO_3$
7	Rat	(F)	75-103d	Hemato Other	6.6 6.6	30 (decreased weight) gain)		Mountain et al. 1953	V_2O_5
8	Rat	(F)	2 mo	Cardio		15 (increased ventricular pressure)		Susic and Kentera 1986	NH_4VO_3
Immunological									
9	Mouse	(W)	4-13 wk		6.5			Sharma et al. 1981	Na_3VO_4

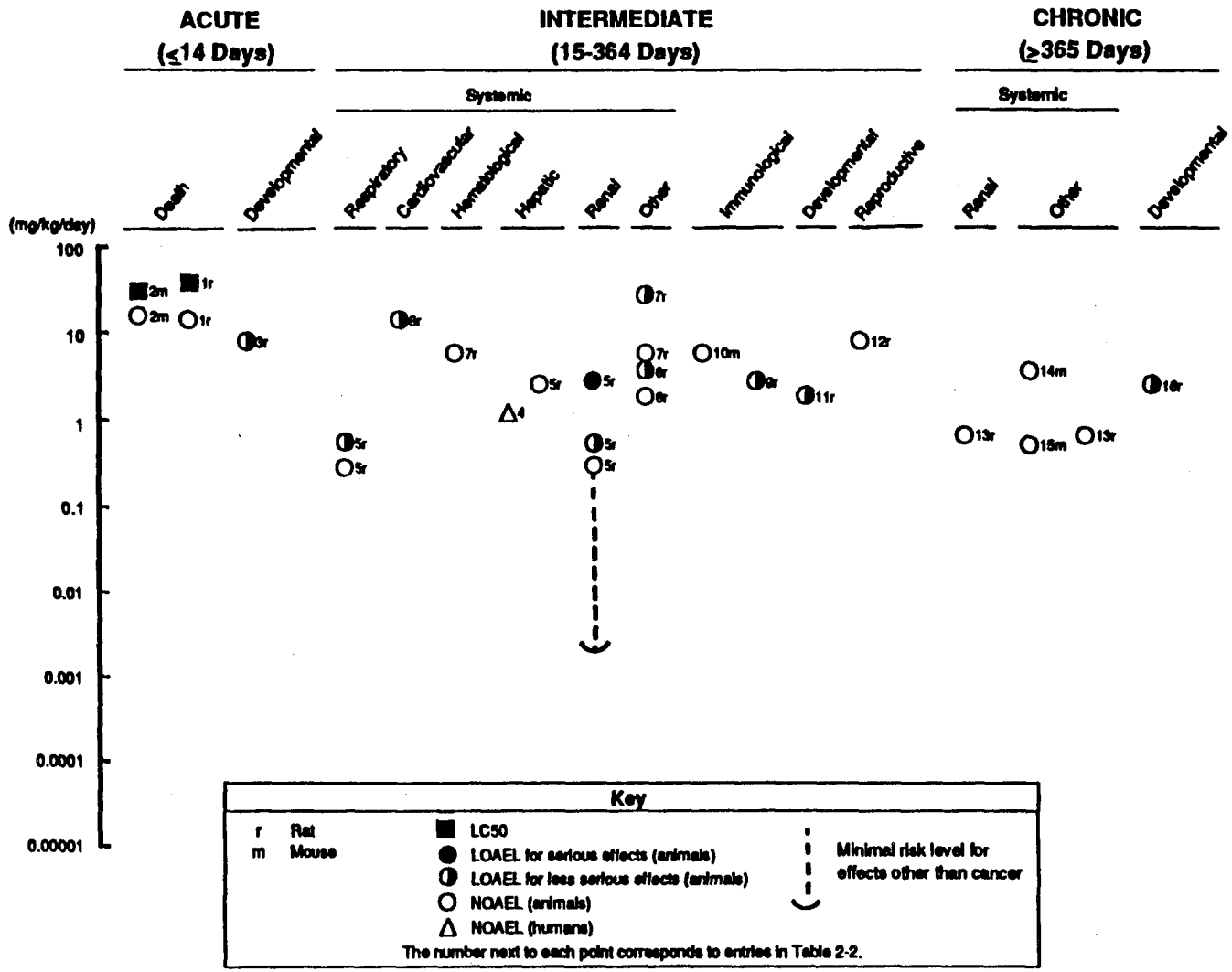
TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg V/kg/day)	LOAEL (effect) Less serious (mg V/kg/day)	LOAEL (effect) Serious (mg V/kg/day)	Reference	Form
Developmental									
10	Rat	(G)	60 d			2.1 (reduced pup weigh and length)		Domingo et al. 1986	$NaVO_3$
Reproductive									
11	Rat	(GW)	60 d		8.4			Domingo et al. 1986	$NaVO_3$
CHRONIC EXPOSURE									
Systemic									
12	Rat	(W)	2.5 yr	Renal Other	0.7 0.7			Schroeder et al. 1970	$VOSO_4$
13	Mouse	(F)	2 yr	Other Cardio Renal Resp Hemato	4.1 4.1 4.1 4.1 4.1			Schroeder and Balassa 1967	$VOSO_4$
14	Mouse	(W)	2.5 yr	Other	0.54			Schroeder and Mitchner 1975	$VOSO_4$
Developmental									
15	Rat	(W)	2 gen ad lib			2.8 (altered lung collagen)		Kowalska et al. 1988	$NaVO_3$

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.003 mg/kg/day. Dose divided by uncertainty factors of 10 for human variability and 10 for interspecies variability.

ad lib = ad libitum; AVT = ammonium vanadyl tartrate; (C) = capsule; Cardio = cardiovascular; d = day(s); (F) = food; (G) = gavage, vehicle not specified; (GW) = gavage in water; Gd = gestation day; gen = generation; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month(s); $NaVO_3$ = sodium metavanadate; Na_3VO_4 = sodium orthovanadate; NH_4VO_3 = ammonium metavanadate; NOAEL = no-observed-adverse-effect level; Resp = respiratory; V = vanadium; V_2O_5 = vanadium pentoxide; $VOSO_4$ = vanadyl sulfate; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

FIGURE 2-2. Levels of Significant Exposure To Vanadium and Compounds - Oral



dusts may have swallowed some of the dusts. Some experienced nausea and vomiting (Levy et al. 1984). A study designed to look at hematological changes noted that the rats exposed to the highest dietary dose of 50 ppm exhibited diarrhea throughout the experiment (Franke and Moxon 1937).

Hematological Effects. Human volunteers (assumed body weight, 70 kg) given 0.47-1.3 mg vanadium/kg as ammonium vanadyl tartrate in capsules for 45-68 days had no hematological abnormalities as measured by white blood cell count, differential count, platelets and reticulocytes (Dimond et al. 1963). Sodium metavanadate in food for 100 days had no effect on hemoglobin levels in rats (Franke and Moxon 1937).

Hepatic Effects. The one human study located showed no changes in serum glutamic oxaloacetic transferase, cholesterol, triglyceride, or phospholipid levels following exposure to 0.47-1.3 mg vanadium/kg as ammonium vanadyl tartrate in capsules for 45-68 days (Dimond et al. 1963). Rats given sodium metavanadate in the drinking water for 3 months also did not show enzyme activity levels, bilirubin levels, or cholesterol levels indicative of liver damage (Domingo et al. 1985).

Renal Effects. Humans given 0.47-1.3 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).

Minor renal effects (altered renal function, as indicated by increased plasma urea, and mild histological changes) were seen in rats after oral exposure to sodium metavanadate for 3 months at levels up to 10% of the oral LD_{50} (Domingo et al. 1985). The author reported a dose-related trend, but quantitative histopathological data were not provided. This study was used to calculate an oral MRL for intermediate exposure as indicated in the footnote in Table 2-2.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to vanadium.

Rats given sodium metavanadate in the food for an intermediate period of time showed a slight decrease in body weight (Franke and Moxon 1937; Mountain et al. 1953). Mice chronically exposed to vanadyl sulfate in the drinking water showed a slight, but not statistically significant, weight increase as compared to controls (Schroeder and Mitchener 1975), while experiments from the same laboratory under comparable exposure conditions showed no weight changes in other mice or rats (Schroeder and Balassa 1967; Schroeder et al. 1970), respectively.

2.2.2.3 Immunological 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 vanadium in the drinking water for 1-3 months showed a dose-related but nonsignificant decrease in the antibody-forming cells in the spleen when challenged with sheep erythrocytes (Sharma et al. 1981). Mild spleen hypertrophy and hyperplasia were seen in rats treated with vanadium in the drinking water for 3 months (Domingo et al. 1985), but further immunological tests were not performed. The human NOAEL and rat LOAEL are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after oral exposure to vanadium.

2.2.2.5 Developmental Effects

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

Oral exposure to sodium metavanadate had only very slight effects in the development of rats. One study showed no embryolethality, teratogenicity, or significant skeletal or visceral abnormalities in pups exposed during gestation (Paternain et al. 1987). There was an increase (but,not doserelated) in facial and dorsal hemorrhages. The toxicological significance of this finding is not known. Maternal toxicity was not described. A two-generation, one-dose study in rats showed altered lung collagen metabolism in fetuses of adults with life-time exposure (Kowalska 1988). The toxicological significance of this finding is also not known. When rat dams were given high doses of sodium metavanadate in a reproduction study, pup size (weight and length) was only slightly (but statistically significantly) reduced at birth and throughout lactation (Domingo et al. 1986). More severe developmental effects were not seen. The rat dams did not show toxicity. Reliable LOAEL values from these studies are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Reproductive Effects

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

Gavage doses of sodium metavanadate given to male and female rats before mating and to female rats during gestation and lactation did not affect fertility, reproduction, or parturition (Domingo et al. 1986). This NOAEL value is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to vanadium. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 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.

2.2.3 Dermal Exposure

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

2.2.3.1 Death

2.2.3.2 Systemic Effects

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

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

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 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 less than 1 ppm of vanadium (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; Orris et al. 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). There is a possibility that oral exposure (mucociliary clearance) contributed to vanadium levels in the serum. The rate and extent of vanadium absorption in humans is not known.

Indirect evidence of absorption after inhalation of vanadium in animals is indicated in studies in which vanadium was administered intratracheally. Soluble vanadium compounds that are inhaled and deposited are readily absorbed. 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, more than 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).

Intratracheal administration of vanadium in rats indicates that rapid absorption of vanadium in humans may occur following acute exposure. Indirect evidence from occupational studies suggests that absorption of vanadium after chronic exposure to vanadium pentoxide may also occur.

2.3.1.2 Oral Exposure

No studies were located regarding the rate and extent of absorption in humans after oral exposure to vanadium. No systemic toxic effects were observed in volunteers who consumed vanadium as ammonium vanadyl tartrate in capsules, suggesting that it may be poorly absorbed (Dimond et al. 1963).

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). Indirect evidence is also given from animal studies indicating that a portion of vanadium is absorbed following oral administration. 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). 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 intestinal barrier.

2.3.1.3 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). Because vanadium is a metal, absorption through the skin is thought to be quite minimal due to its low solubility.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No data have been located regarding the distribution of vanadium in humans immediately following exposure. At autopsy, 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 (Schroeder et al. 1963). This is probably accumulation from chronic breathing of vanadium from naturally occurring dusts or air contaminated with fuel oil combustion waste products. The amount detected in the intestines is probably from swallowing the dusts. The heart, aorta, brain, kidney, muscle, ovary, and testes were found to have no detectable vanadium concentrations. Bone was not tested. The study was limited because exposure levels were not determined and insensitive detection methods were used. Serum vanadium levels in occupationally exposed 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).

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 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). This indicates that the retention site of vanadium is the bones.

Limited information was located regarding the distribution of vanadium in humans following inhalation exposure. Acute animal studies suggest that there is an initial accumulation of vanadium in the lungs, kidneys, and liver of rats, as well as high levels in the blood. However, retention of vanadium occurs primarily in the bone. Though there were no animal data on longer exposure to vanadium via the inhalation route, it seems likely that experimental studies would show distribution patterns similar to these seen with chronic human exposures.

2.3.2.2 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 less than 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.

Oral exposure for an intermediate duration produced the highest accumulation of vanadium in the kidney. In young male rats at 3 weeks of age, the kidneys, heart, and lungs had the highest levels immediately following exposure (Edel et al. 1984). Vanadium in the kidney, liver, and lung decreased significantly at 115 days of age. There was an accumulation in muscle and fat, related to the growing mass of the tissues with age. The higher levels of vanadium in the young rat tissues may be due to the higher retention capacity of the undeveloped tissues, or a greater permeability of the intestinal wall. 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 3rd 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).

The distribution of vanadium in humans following oral exposure may be assessed from animal studies. In acute-duration exposures, vanadium is rapidly distributed, primarily in the bones. Following intermediate-duration exposure, it is apparent that vanadium concentrations reaching the tissues are low, with the kidney, bones, liver, and lungs showing the highest levels initially. Prolonged retention of vanadium occurs only in the skeleton. Placental transfer of vanadium is suggested by the increased incidence of fetal abnormalities from dams receiving sodium metavanadate (Paternain et al. 1987).

2.3.2.3 Dermal Exposure

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

2.3.2.4 Other Routes of Exposure

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

2.3.3 Metabolism

Vanadium is an element, and as such, is not metabolized. However, 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. These two factors may affect the biphasic clearance of vanadium that occurs in the blood. 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, NADPH, and NADH occurs within an hour after intraperitoneal injection of sodium vanadate in mice (Bruech et al. 1984). It is believed that vanadate requires these cytochrome P-450 components for oxidation to the vanadyl form. A consequence of this action is the diversion of electrons from the monooxygenase system resulting in the inhibition of drug dealkylation (Bruech et al. 1984).

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 metalbinding sites on the protein. With intravenous administration of vanadate or 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).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Occupational studies showed that urinary vanadium levels significantly increased in exposed workers (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; Orris et al. 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) (Orris et al. 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 (Khoads and Sanders 1985). Three days after exposure to vanadium pentoxide, 40% of the

recovered ^{48}V dose was cleared in the urine while 30% remained in the skeleton, and 2%-7% was in the lungs, liver, kidneys, or blood (Conklin et al. 1982).

Epidemiological studies and animal studies suggest that elimination of vanadium following inhalation exposure is primarily in the urine.

2.3.4.2 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 accumulated in the feces after 6 days (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 the small absorbed portion of vanadium is through the kidney in animals.

2.3.4.3 Dermal Exposure

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

2.4 RELEVANCE TO PUBLIC HEALTH

An acute-duration inhalation MRL of 0.0002 mg/m^3 was derived. Zenz and Berg (1967) exposed volunteers to vanadium pentoxide dust at levels of 0.06, 0.1, and 0.6 mg vanadium/m^3 for 8 hours. Subjects exposed at 0.06 mg vanadium/m^3 had increased mucus formation and slight coughing 1 day after exposure. These effects ceased within 4 days. At 0.1 mg vanadium/m^3, coughing was more persistent. Effects were more pronounced at higher concentration levels. There were no reports of fever, increased pulse, or other signs of irritation at any dose level. Pulmonary function tests were normal. The 0.06 mg vanadium/m^3 level was considered a LOAEL for coughing, which was regarded as a sign of respiratory irritation. The MRL value was calculated by dividing the actual administered dose of vanadium (0.06 mg/m^3) by an uncertainty factor of 100 (for human variability and the use of a LOAEL) and corrected for less than 24 hours of exposure (8/24), thus obtaining an MRL value of 0.0002 mg vanadium/m^3. The use of this study for the derivation of an MRL is supported by numerous epidemiological studies (Levey et al. 1984; Lewis 1959; Musk and Tees 1982; Orris et al. 1983; Sjoeberg 1956; Thomas and Stiebris 1956; Vintinner et al. 1955; Wyers 1946; Zenz et al. 1962) as well as animal studies (Knecht et al. 1985; Lee and Gillies 1986) that demonstrate that the target organ for inhaled vanadium compounds is the respiratory system.

Neither intermediate-duration nor chronic-duration inhalation MRLs were derived for vanadium because of a lack of quantitative exposure data.

An acute-duration oral MRL was not derived for vanadium because of a lack of quantitative exposure data. One acute-duration oral study reported an increase in facial and dorsal hemorrhages in rats exposed to sodium metavanadate, but these developmental effects were not dose related (Paternain et al. 1987), and the toxicological significance of this finding is unknown.

An intermediate-duration oral MRL value of 0.003 mg vanadium/kg/day was derived. Domingo et al. (1985) administered 0, 5, 10, or 50 ppm of sodium metavanadate in the drinking water of rats for 3 months. All treated groups showed mild histological changes in kidneys, lungs, and spleen, and the changes became progressively more severe with increased dosages. Serum cholesterol and glucose levels, liver function, organ weights, weight gain, and water consumption were unaffected at all exposure levels. Vanadium was not detected in organs of animals receiving 5 ppm but was found in the kidneys and spleen of animals exposed at 10 ppm and in all organs of animals exposed at 50 ppm. Based on these findings, a NOAEL at the 5-ppm exposure level was used for the derivation of an intermediate-duration oral MRL. The administered dose (5 ppm) was converted from ppm in water to a mg vanadium/kg weight dose as follows (assuming an intake of 0.14 L/kg/day): 5 ppm in water = 5 mg vanadium/L; 5 mg vanadium/L x 0.14 L/kg/day x 41% vanadium in sodium metavanadate = 0.287 mg vanadium/kg/day, which is rounded to 0.3 mg vanadium/kg/day

Since the study used animals and a NOAKL was used as the MRL end point, the MRL value is calculated by dividing the adjusted administered dose (0.3 mg vanadium/kg/day) by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability); thus obtaining an MRL value of 0.003 mg vanadium/kg/day. The use of this NOAEL for the derivation of an MRL is supported by other studies that reported adverse developmental effects (Domingo et al. 1986), cardiovascular effects (Susic and Kentera 1986, 1988), and gastrointestinal effects (Dimond et al. 1963; Franke and Moxon 1937) at levels greater than the NOAEL used for the MRL.

A chronic-duration oral MRL was not derived for vanadium because of a lack of quantitative exposure data. Several chronic-duration oral studies using mice and rats exposed to vanadyl sulfate reported no significant changes in body weight (Schroeder and Balassa 1967; Schroeder and Mitchener 1975; Schroeder et al. 1970). However, these were not used because data was not available to determine the most sensitive end point for the derivation of a chronic-duration oral MRL. A two-generation, one-dose study of rats exposed to sodium metavanadate reported altered lung collagen metabolism in fetuses of adults with life-time exposure (Kowalska 1988). However, the toxicological significance of this finding is unknown.

Acute-duration, intermediate-duration, and chronic-duration dermal MRLs were not derived for vanadium because of the lack of an appropriate methodology for the development of dermal MRLs.

The major adverse health effect in humans from vanadium has been seen in workers exposed to large amounts of vanadium pentoxide dusts. These people have coughs, chest pains, sore throats, and irritated eyes, but the symptoms disappear soon after exposure ceases. The response is similar to that of an upper respiratory tract infection. Data were not located to assess the relationship of exposure levels or duration to severity of response. No other significant health effects of vanadium have been found. Large amounts of vanadium dusts would need to occur near hazardous waste sites for most people to be at risk. People could also be exposed to vanadium in fly ash when coalburning boilers are used, cleaned or destroyed. It is possible that vanadium might leach into water supplies near hazardous waste sites, but since the gastrointestinal absorption is so low, the health implications for people drinking the water are not readily apparent. Likewise, dermal absorption is low, and the relevance of exposure to vanadium in soil surrounding waste sites would need to be evaluated on a case by case basis.

Death. There are no reports of death in humans following inhalation, oral, or dermal exposure to vanadium. Humans are unlikely to be in contact with large enough amounts of vanadium to cause death. Rabbits have died from breathing 60 mg vanadium/m^3 as vanadium pentoxide. The LD_{50} value for gavage administration of sodium vanadate in rats is 41 mg vanadium/kg. This is much higher than the LD_{50} values for intraperitoneal injections of sodium metavanadate, which are 11 mg vanadium/kg in rats and 13 mg vanadium/kg in mice (Chanh 1965).

Systemic Effects

Respiratory Effects. The only significant, clearly documented, effect in humans is mild to moderate respiratory distress and mucosal irritation from exposure to vanadium dusts. Vanadium workers may have coughs, wheezing, chest pain, sore throats, or eye irritation, which can last for several days after exposure. These effects are common to many types of dust exposures. The effects are no more severe than those experienced during a routine upper respiratory tract infection and can sometimes be delayed for several hours after exposure. Chronic effects are not reported with regularity. Chest xrays and urine and blood analyses in these people are normal. These workers often develop a green color on their tongues from direct accumulation of vanadium.

Studies in animals support the findings that vanadium primarily effects the respiratory system. The respiratory system responds to the particulate matter by increasing the number of leukocytes which are used to clear away the foreign matter. Respiratory distress lead to death in rats following intraperitoneal injections of sodium metavanadate (Donaldson et al. 1985).

The mechanism of vanadium's effect on the respiratory system is similar to that of other metals. In vitro tests show that vanadium damages alveolar macrophages (Castranova et al. 1984; Sheridan et al. 1978; Waters et al. 1974; Wei and Misra 1982). It does this by decreasing the macrophage membrane integrity, thus impairing the cells' phagocytotic ability and viability. Without macrophages, the respiratory system's ability to clear itself of many other particles normally found in the air is diminished.

Renal Effects. Minor renal effects (altered renal function, as indicated by increased plasma urea, and mild histological changes) were seen in rats after oral exposure to sodium metavanadate for 3 months at levels up to 10% of the oral LD_{50} (Domingo et al. 1985). A few animal studies have shown renal effects from parenteral injections of vanadium. These include increased lipid peroxidation (Donaldson et al. 1985) and decreased tubular reabsorption (Westenfelder et al. 1981). Vanadium, like most metals, has also been shown to accumulate transiently in the kidneys following parenteral injections (Roshchin et al. 1980), or oral exposure (Bogden et al. 1982; Conklin et al. 1982; Edel and Sabbioni 1988; Parker and Sharma 1978). However, it is difficult to determine the potential for toxicity in humans. However, renal effects have not been observed upon urinalysis in occupationally exposed workers (Kiviluoto et al. 1981b; Sjoeberg 1950; Vintinner et al. 1955).

Other Systemic Effects. Other minor systemic effects (weight loss) have been seen in animals, but there are not enough collaborative data to indicate that vanadium poses significant risks to any other organ system. A study in mice fed vanadium chronically showed a lack of histopathological effects in unspecified tissues (Schroeder and Balassa 1967).

In vitro experiments have shown that vanadium as vanadate inhibits sodium-potassium ATPase activity and thus inhibits the sodium potassium pump (Nechay and Saunders 1978). This pump is necessary for proper transport of materials across cell membranes. The kidney (Higashino et al. 1983; Phillips et al. 1983), heart (Aiton and Cramb 1985; Akera et al. 1983), red blood cells (Beauge et al. 1980; Siemon et al. 1982), and brain (Keller and Sharma 1985) are affected in vitro.

Immunological Effects. Very few data are available on the immunological effects of vanadium in humans or animals. One intermediate-duration oral mouse study of sodium orthovanadate showed no immunological damage as measured by a response to sheep erythrocytes (Sharma et al. 1981). Intraperitoneal injections of ammonia metavanadate into mice have caused impairment in response to bacterial challenges also decreased peritoneal macrophage phagocytic ability (Cohen et al. 1986). These authors have suggested that the decreased macrophage response may explain why vanadium workers have increased susceptibility to respiratory disease.

Neurological Effects. Humans who have been exposed to vanadium dusts in the workplace have generally not reported significant effects related to the nervous system. Nonspecific effects such as dizziness or headaches have been reported by some workers. It is possible that the effects that vanadium has in inhibiting the sodium-potassium pump would adversely affect the nervous system, but this has not been tested and/or reported. Rats given intraperitoneal injections of vanadium showed lethargy and ataxia (Haider and Kashyap 1989), but the relevance of this to humans exposed by expected routes is not known. Vanadium does not accumulate in the brain of humans or animals. In the absence of animal data via relevant routes, the neurotoxicity of vanadium could not be fully assessed.

Developmental Effects. No direct information is available on developmental effects of vanadium in humans. Offspring of animals that have had oral exposure to vanadium have shown slight defects, including increases in visible hemorrhages (Paternain et al. 1987), altered lung collagen metabolism (Kowalska 1988), and slight decreases in fetal length and weight (Domingo et al. 1986). Minor skeletal abnormalities have been noted in the offspring of animals that have been injected with vanadium (Carlton et al. 1982; Wide 1984). These included supernumary ribs and delayed skeletal ossification. Maternal toxicity was not observed at the doses producing these developmental effects in these two studies. Because these effects were so minor and do have correlations to human development, the relevance of these animal findings to developmental effects in humans is not known.

Reproductive Effects. Autopsy data have not provided detectable levels of vanadium in human reproductive organs. It is unlikely that the reproductive system is a sensitive indicator for vanadium toxicity in humans. Only one animal study was located that specifically tests the effects of vanadium on reproduction. In this well-conducted rat study, no adverse effects on fertility, reproduction, or parturition were noted when male and female rats were exposed to sodium metavanadate and then mated.

Genotoxic Effects. The only information on genotoxicity of vanadium is from in vitro studies, as shown in Table 2-3. The majority of these studies show positive effects in test systems using bacteria, yeast, and mouse cells in culture for end points such as recombination repair, gene mutation, or DNA synthesis. None of these studies showed any indication of a cytotoxic effect. Human leukocytes have been shown to have DNA strand breaks from exposure to vanadate (Birnboim 1988). These in vitro data indicate that vanadium has the potential for genotoxicity in humans. The application of vanadium salts at low concentrations (<0.1 pM) stimulated colony formation in fresh human tumor cells, but high concentrations (>0.1 pM) inhibited growth (Hanauske et al. 1987). The mechanism for this action is not clear. The authors suggest that vanadium be further tested for its antitumor activity in animals.

TABLE 2-3. Genotoxicity of Vanadium and Compounds In Vitro

Species	End point	Results: With activation	Results: Without activation	Reference	Form
Bacillus subtilis	Recombination repair	+	+	Kada et al. 1980	V_2O_5
Escherichia coli	Gene mutation	No data	+	Kanematsu et al. 1980	V_2O_5
Salmonella typhimurium	Gene mutation	No data	-	Kanematsu et al. 1980	V_2O_5
Saccharomyces cerevisiae	Induction of diploid spores	No data	+	Sora et al. 1986	$VOSO_4$
Mouse 3T3 and 3T6 cells	DNA synthesis	No data	+	Smith 1983	Na_3VO_4, $VOSO_4$
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

+ = positive; - = negative; Na_3VO_4 = sodium metavanadate; pM = picomol; V_2O_5 = vanadium pentoxide; V = vanadium; $VOSO_4$ = vanadyl sulfate

Cancer. No studies regarding the carcinogenicity of vanadium in humans were located. Workers who have been exposed to vanadium dusts did not show an increased number of cancer deaths (Orris et al. 1983; Sjoeberg 1950; Vintinner et al. 1955), although detailed studies were not performed. Studies designed to test effects other than cancer in animals have not noted any increases in tumors resulting from inhalation (Sjoeberg 1950) or oral (Schroeder and Balassa 1967) exposure to vanadium. 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. Therefore an acceptable assessment of carcinogenic potential in humans cannot be made.

2.5 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 or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic 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 2.5.1.

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 often not 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 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/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. Vanadium is found in the urine of exposed workers. This measurement is specific for vanadium. 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 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. No other commonly measured cellular changes have been identified with vanadium exposure.

2.5.2 Biomarkers Used to Characterize Effects Caused by Vanadium

The primary effects of 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.

2.6 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 l-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).

2.7 POPULATIONS THAT ABE UNUSUALLY SUSCEPTIBLE

No unusually susceptible populations have been identified, but persons with pre-existing respiratory disorders such as asthma may be expected to have increased adverse effects from breathing vanadium dusts.

2.8 MITIGATION OF 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.

There are two main objectives for treating internal vanadium exposure: decreasing absorption and increasing excretion. There is no known treatment to decrease absorption or increase elimination after inhaling vanadium and/or its compounds. Following oral exposure, dilution with water or milk is one way to decrease overall absorption (Stutz and Janus.2 1988). To decrease gastrointestinal absorption, especially for organic vanadium compounds, it has been suggested that activated charcoal be given to the patient. Emesis induced immediately after an acute oral exposure may remove part of the ingested dose from the stomach. Gastric lavage has been suggested as being effective if performed soon after ingestion or in patients who are unconscious or at risk of convulsing (HSDB 1992). Two methods have been discussed in the literature for increasing excretion of the chemical after it has been ingested. One method is to administer calcium disodium edentate as a chelating agent (Haddad and Winchester 1990; Stutz and Janusz 1988). The other method is to give cathartic medication such as magnesium sulfate (Stutz and Janusz 1988). 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).

After acute inhalation exposure to high concentrations of vanadium and/or compounds, pulmonary edema may result. If so, oxygen administration may be necessary. Experimental evidence suggests that the administration of steroids such as prednisolone succinate or phthalate may prevent the development of a chemical lung edema (Stutz and Janusz 1988).

Enhanced excretion of vanadium was achieved with chelation therapy provided by deferoxamine mesylate (DFOA) (Gomez et al. 1988). 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

of ethylene diamine tetraacetate (EDTA) reduced vanadium-induced morbidity in mice and rats (Jones and Basinger 1983; Mitchell and Floyd 1954).

2.9 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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

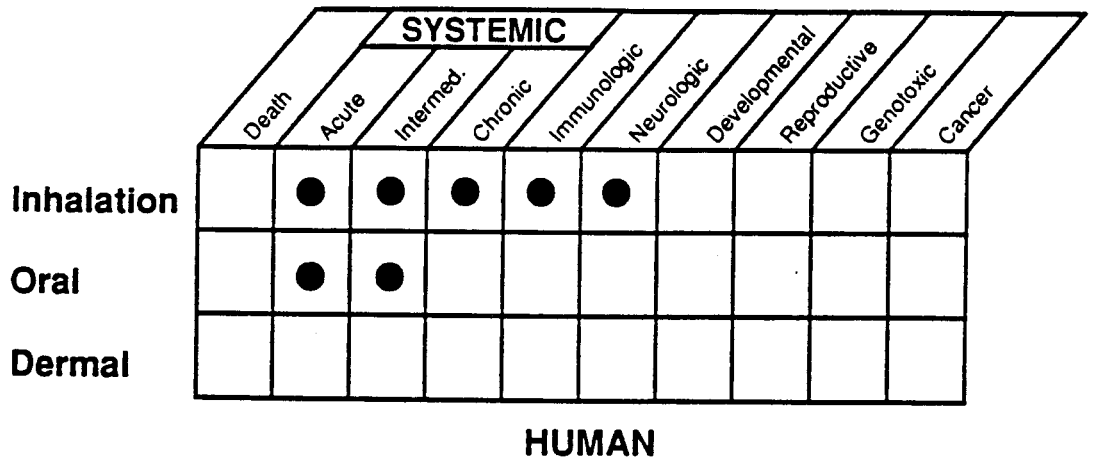
2.9.1 Existing Information on Health Effects of Vanadium

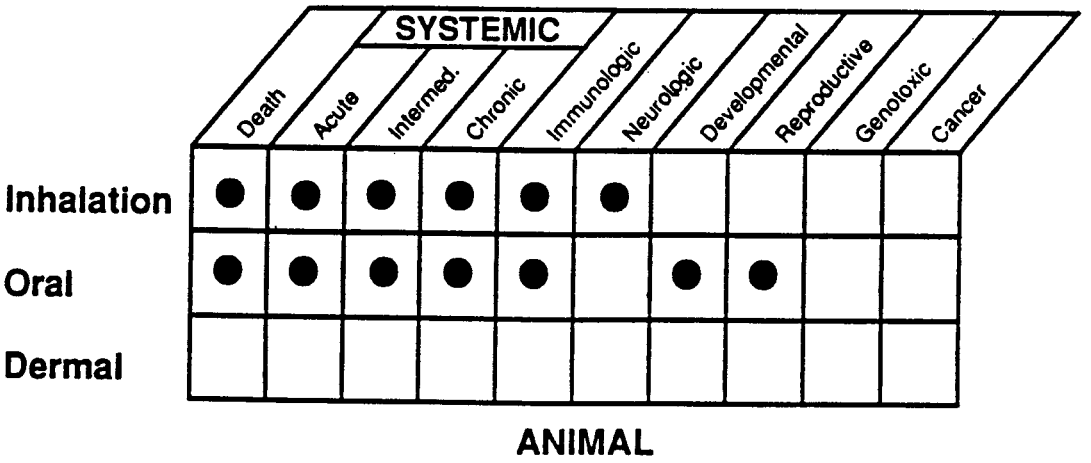
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to vanadium are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of vanadium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

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 bismuth orthovanadate in rats and vanadium pentoxide in monkeys following acute and intermediate exposures. Data are available following acute, intermediate, and chronic oral exposures in animals, including information on death (from sodium metavanadate or vanadyl sulfate), immunological (from sodium orthovanadate), neurological (from vanadium pentoxide), developmental, and reproductive effects (from sodium metavanadate). No animal dermal data were located.

FIGURE 2-3. Existing Information on Health Effects of Vanadium and Compounds





● Existing Studies

2.9.2 Data Needs

Acute-Duration Exposure. Sufficient information is available from occupationally exposed humans to identify the respiratory system as a target organ following acute inhalation exposure (Levy et al. 1984; Musk and Tees 1982; Thomas and Stiebris 1956; Zenz and Berg 1967; Zenz et al. 1962). The mechanism is known to be interference with alveolar macrophages (Castranova et al. 1984; Sheridan et al. 1978; Waters et al. 1974; Wei and Misra 1982). Data are not available to determine target organs in humans from acute oral or dermal exposure. Vanadium is very poorly absorbed from the gastrointestinal system (Conklin et al. 1982; Roschin et al. 1980) or skin (WHO 1988), so it is unlikely to result in a significant internal dose by these routes. However, since children are known to absorb some metals (such as lead) more readily than adults, they may be more susceptible to vanadium poisoning. Data were sufficient to derive an MRL for inhalation exposure (Zenz and Berg 1967). Further, animal studies designed to determine the level of vanadium in the air that would cause respiratory distress would be helpful in determining the relationship between the exposure level or duration and the severity of the response. This would be useful to determine possible toxic effects on humans exposed for an acute period near a hazardous waste site.

Intermediate-Duration Exposure. Sufficient information is available from intermediate-duration studies in animals to identify the respiratory system as a target organ following inhalation exposure (Domingo et al. 1985; Sjoeberg 1950). An intermediate MRL could not be derived for inhalation exposure due to a lack of quantitative exposure data. An intermediate MRL was derived for oral exposure from an animal study showing slight toxic effects in kidneys, lungs, and spleen (Domingo et al. 1985). Lethality data are not available for intermediate-duration inhalation or dermal exposure, but these data are unlikely to help in assessing effects from low-level exposure. Animal studies using a number of concentration levels designed to test the level of vanadium in the air that would cause respiratory distress would be helpful in determining an intermediate MRL. These studies should include tests that could be used to predict the relationship between the exposure level or duration and the severity of the response which may be seen in people exposed for an intermediate duration near a hazardous was site.

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; Orris et al. 1983; Sjoeberg 1956; Vintinner et al. 1955; Wyers 1946). Data are not available to determine target organs in humans from chronic oral or dermal exposure. Vanadium is very poorly absorbed from the gastrointestinal system (Conklin et al. 1982; Roschin et al. 1980) or skin (WHO 1988), so it is unlikely to result in a significant internal dose by these routes. Quantitative exposure data were not sufficient to derive a chronic MRL for any exposure route. Lethality data are not available for chronic inhalation,

oral, or dermal exposure, but these data would be unlikely to help in assessing effects from low-level exposure. Animal studies designed to test the level of vanadium in the air that would cause respiratory distress would be helpful in determining a chronic MRL. These studies should include tests that could be used to predict the relationship between the exposure level or duration and the severity of the response for people exposed near hazardous waste sites.

Specific tests for carcinogenicity have not been performed in humans or animals by any route. Available occupational data using the inhalation route and chronic animal studies in two species using the oral route have not indicated any tumor increases. Although vanadium is not suspected of being a carcinogen, a definitive cancer assay would be necessary to show this.

Genotoxicity. There are no in vivo studies in humans or animals by any route investigating the genotoxicity of vanadium. The few in vitro studies located generally show positive effects in cultured bacteria (Kada et al. 1980; Kanematsu et al. 1980), yeast (Sora et al. 1986), and mouse cells (Smith 1983). The results of one study showing DNA strand breaks in human leukocytes suggest that further studies using human cells would be helpful in determining if vanadium is genotoxic in people (Birnboim 1988).

Reproductive Toxicity. No data exist on reproductive effects on humans from exposure to vanadium by any exposure route. One animal study shows that vanadium did not affect reproductive parameters in rats following oral exposure (Domingo et al. 1986). Since vanadium is poorly.absorbed from the gastrointestinal tract (Conklin et al. 1982; Roschin et al. 1980) and skin (WHO 1988), exposure by these routes is unlikely to be a health risk in humans. Toxicokinetic studies in humans (Schroeder et al. 1963) and reliable studies in animals (Edel and Sabbioni 1988) do not indicate that the reproductive system accumulates vanadium. Humans are most likely to be exposed to vanadium in the air, but the reproductive system does not appear to be a sensitive target of vanadium toxicity. Further studies would not appear to be particularly useful.

Developmental Toxicity. No human data were located on developmental effects of vanadium exposure by any exposure route. Since vanadium is poorly absorbed by the gastrointestinal tract (Conklin et al. 1982; Roschin et al. 1980) or skin (WHO 1988), exposure by these routes would be unlikely to result in a significant internal dose. Animal toxicokinetic studies do not indicate that the fetus accumulates vanadium. The lack of developmental studies decreases the confidence in the MRL.

Some animal studies have shown slight developmental effects following oral exposure to vanadium (Paternain et al. 1987). These studies were flawed since results from the same laboratory were not consistent across the studies. The likelihood of adverse effects occurring in humans if they were exposed to

sufficient quantities of vanadium is not known. Further animal studies would be unlikely to reveal human risk from vanadium.

Immunotoxicity. Effects on lymphoid tissue or peripheral lymphocytes have not been noted in the occupational studies in humans (Sjoeberg 1950) or in the animal studies (Sharma et al. 1981; Sjoeberg 1950). However, this system may still be affected since vanadium has been shown to have adverse effects on macrophages in vivo and in vitro (Cohen et al. 1986). Few workers have shown allergic responses or contact dermatitis from vanadium exposure (Sjoeberg 1950), so further work in this area is probably not critical.

Neurotoxicity. Very little information exists on the neurotoxicity of vanadium to humans or animals. Since numerous workers have been exposed to vanadium dusts and fumes in the workplace and have not reported or shown significant adverse neurological signs, it is unlikely that the neurological system is a sensitive target of vanadium exposure (Sjoeberg 1956; Vintinner et al. 1955; Zenz and Berg 1967). However, it is possible that modern tests of subtle neurological effects in humans and animals may be more sensitive in revealing neurotoxicity caused by vanadium.

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; Orris et al. 1983; Sjoeberg 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. Although vanadium can be found in foods, it is very poorly absorbed through the gastrointestinal tract (Conklin et al. 1982; Roshchin et al. 1980) or skin (WHO 1988) and is unlikely to pose a significant health threat by these routes. It is possible however, that children may absorb vanadium better than adults do.

Biomarkers of Exposure and Effect. Biomarkers specific for exposure to vanadium include the presence of vanadium in the urine (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; Orris et al. 1983; Zenze et al. 1962) 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 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 1955). However, this is not specific for vanadium since other factors, such as diet or disease, can also affect cystine content.

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). No animal studies were located that test absorption after inhalation exposure, although information is available from intratracheal exposures (Conklin et al. 1982; Edel and Sabbioni 1988; Oberg et al. 1978; Rhoads and Sanders 1985) Since inhalation is most likely to result in a significant exposure for humans, more data on the rate and extent of absorption may be useful. More data on kinetics following oral or dermal exposure would not be helpful, since it is believed that absorption in humans and animals is low by these routes. It is possible however, that children may absorb vanadium better than adults do.

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. No particular data needs are apparent.

Mitigation of Effects. Information is available regarding treatment of cases of acute oral exposure to vanadium, including traditional methods of decreasing absorption and increasing elimination (Stutz and Janusz 1988). Washing the skin or eyes following acute dermal exposure has also been recommended (Stutz and Janusz 1988). Treatment for acute inhalation exposure is limited to supportive treatment for pulmonary edema (Stutz and Janusz 1988). One chelation method has been suggested for mitigating the actions of vanadium once it has entered the bloodstream (Haddad and Winchester 1990; Stutz and Janusz 1988). Information regarding treatment or mitigation following intermediate or chronic exposures is lacking. 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.

2.9.3 On-going Studies

Vanadium pentoxide is cited for mutagenicity, genetic, and pulmonary sensitization testing by the NTP as of April 9, 1990. The NTP Chemical Manager is William J. Moorman. This will include a repeated dose inhalation study in rats and mice, and a test in Salmonella. Vanadium is not cited for on-going research by the International Agency for Research on Cancer (IARC) as of 1987.

Current federal research in progress includes the following studies:

Investigator	Affiliation	Research Description
Knect, E.	NIOSH	Inhalation studies
Mittag, T.W.	Mt. Sinai School of medecine	Effects on enzymes and intraocular pressure in animals
Reid, J.	SRI International	Prechronic toxicity of vanadium pentoxide
Wei, C.I.	University of Florida	Immunotoxicity in mouse peritoneal macrophages