2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO VANADIUM IN THE UNITED STATES

Vanadium is the 22nd most abundant element in the earth's crust with an average concentration of 100 ppm. It exists in oxidation states ranging from 2- to 5+ with 3+, 4+, and 5+ being the most common oxidation states. Vanadium is primarily used in the production of rust-resistant, spring, and high-speed tool steels; vanadium pentoxide is used in ceramics. Vanadium is released to the environment by continental dust, marine aerosols, volcanic emissions, and the combustion of coal and petroleum crude oils. It is naturally released into water and soil as a result of weathering of rock and soil erosion. Ambient air concentrations of vanadium are low, with urban areas having higher concentrations. Average vanadium concentrations were 3.0–3.7 ng/m^3 in urban areas of Illinois; in rural areas, the vanadium concentrations were 0.8–1.2 ng/m^3. Higher vanadium levels have been measured in the eastern United States due to the high density of oil fired power plants using vanadium-rich residual fuel oil. An average vanadium air concentration of 620 ng/m^3 was measured in Eastern cities compared to 11 ng/m^3 in cities throughout the United States. Vanadium residence time in the environment is inversely related to the particle size. In water, vanadium is converted from trivalent forms to pentavalent forms. The levels of vanadium in surface water range from 0.04 to 104 µg/L. Vanadium levels of 1.2–1.0 µg/L were measured in tap water samples collected in several U.S. states.

Food is the primary route of exposure for the general population; foods with the highest vanadium content include ground parsley, freeze-dried spinach, wild mushrooms, and oysters. Vanadium in food is mainly ingested as VO^{2+} (vanadyl, V^{4+}) or HVO_4^{2} (vanadate, V^{5+}). Estimates of dietary vanadium intake range from 0.09 to 0.34 µg/kg/day in adults. Humans are potentially exposed to a variety of vanadium compounds, the most common being vanadium pentoxide, sodium metavanadate, sodium orthovanadate, vanadyl sulfate, and ammonium metavanadate. Organic anthropogenic vanadium compounds, such as bis(maltolato)oxyvanadium (IV) or vanadyl acetyl acetonate, are used in the treatment of diabetes and cancer; these compounds have different toxicokinetic properties than inorganic vanadium compounds and are not discussed in this toxicological profile.

Although there is some evidence to suggest that vanadium is an essential nutrient, a functional role for vanadium in humans has not been established; increases in abortion rates and decreased milk production have been observed in vanadium-deprived goats. Vanadium mimics insulin and stimulates cell proliferation and differentiation. In animal models, particularly streptozotoxin-induced diabetes in rats,

vanadium has been shown to normalize blood glucose and lipid levels, improve insulin sensitivity, and prevent or reverse secondary complications such as cardiomyopathy, cataract development, and impaired antioxidant status.

2.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to vanadium primarily through oral (ingestion of vanadium in food) and inhalation routes of exposure. Based on occupational exposure studies, human experimental studies, and studies in laboratory animals, the respiratory tract following inhalation exposure and the gastrointestinal tract, hematological system, and developing organism following oral exposure are the primary targets of toxicity.

Adverse respiratory effects have been reported in humans and animals exposed to vanadium compounds at concentrations much higher than those typically found in the environment. Although the available data in humans are limited, signs of airway irritation (e.g., coughing, wheezing, sore throat) have been reported in subjects acutely exposed to 0.6 mg vanadium/m^3 and in workers exposed to vanadium pentoxide dust. These effects have persisted for days to weeks after exposure termination and are often not associated with alterations in lung function. Studies in laboratory animals provide strong support that the respiratory tract is the most sensitive target following inhalation exposure to vanadium. A variety of lung lesions including alveolar/bronchiolar hyperplasia, inflammation, and fibrosis have been observed in rats and mice exposed to vanadium pentoxide; the severity of the lesions is related to concentration and duration. The lung effects have been observed following acute exposure to 0.56 mg vanadium/m^3 and chronic exposures to 0.28 mg vanadium/m^3 and have been observed after 2 days of exposure. Longer duration exposures also result in inflammation and hyperplasia in the larynx and hyperplasia in nasal goblet cells. These histological alterations result in restrictive impairments in lung function; respiratory distress is observed at vanadium pentoxide concentrations of $\geq$4.5 mg vanadium/m^3.

Other sensitive targets of vanadium toxicity include the gastrointestinal system following oral exposure and hematological system following inhalation or oral exposure. Symptoms of gastrointestinal irritation (diarrhea, cramps, nausea) have been observed in humans following bolus administration of sodium metavanadate, vanadyl sulfate, ammonium vanadyl tartrate, or diammonium vanado-tartrate as a treatment in noninsulin-dependent diabetics or patients with ischemic heart disease. The gastrointestinal effects occurred following ingestion of $\geq$14 mg vanadium and no effects were observed in subjects ingesting capsules containing 7.8 mg vanadium. In most studies, the gastrointestinal effects only

occurred during the first week or two of the study suggesting that with repeated exposure, humans develop a tolerance to these effects. Diarrhea has also been observed in rats and mice orally exposed to lethal doses of vanadium. Microcytic erythrocytosis (evidenced by decreases in hematocrit, hemoglobin, and mean cell volume and increases in reticulocytes and nucleated erythrocytes) has been observed in rats exposed to 1.1 mg vanadium/m^3 as vanadium pentoxide for at least 4 days. Hematological effects, including decreases in erythrocyte levels, decreases in hemoglobin, and increases in reticulocytes have also been observed in rats orally exposed to 1.18 mg vanadium/kg/day as ammonium metavanadate for 4 weeks.

Information on the potential of vanadium to induce developmental effects in humans is limited, but developmental effects have been observed in laboratory animals. Decreases in pup growth have been observed at maternal doses of ≥2.1 mg vanadium/kg/day. At higher doses, decreases in pup survival and gross, skeletal, and visceral malformations and anomalies have been reported; marked decreases in maternal body weight are also observed at these dose levels.

No studies have examined the carcinogenic potential of vanadium in humans. An increase in lung carcinoma incidence has been observed in mice chronically exposed to vanadium pentoxide; there is also marginal evidence for lung cancer in male rats (incidence of carcinoma was higher than historical controls but not concurrent controls). Carcinogenicity has not been adequately assessed in laboratory animals following oral exposure. IARC classified vanadium pentoxide in group 2B (possibly carcinogenic to humans) based on inadequate evidence in humans and sufficient evidence in animals. The Department of Health and Human Services and EPA have not classified carcinogenicity of vanadium.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for vanadium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these types of levels (Barnes and Dourson 1988; EPA 1990), 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.

Inhalation MRLs

Acute-Duration Inhalation MRL

- An MRL of 0.0008 mg vanadium/m^3 has been derived for acute-duration inhalation exposure (14 days or less) to vanadium pentoxide dust.

Data on acute toxicity of vanadium in humans are limited to an experimental study in which a small number of subjects were exposed to vanadium pentoxide dust for 8 hours (Zenz and Berg 1967). A persistent cough lasting for 8 days developed in two subjects exposed to 0.6 mg vanadium/m^3; at 0.1 mg vanadium/m^3, a productive cough without any subjective complaints or impact on work or home activities were observed in five subjects. The available studies in laboratory animals focused on potential respiratory tract effects. Impaired lung function, characterized as airway obstructive changes (increased resistance and decreased airflow), was observed in monkeys exposed to 2.5 or 1.7 mg vanadium/m^3 as vanadium pentoxide for 6 hours (Knecht et al. 1985, 1992); the highest no-observed-adverse-effect level (NOAEL) for this effect was 0.34 mg vanadium/m^3. In female rats exposed to 0.56 mg vanadium/m^3 6 hours/day, 5 days/week for 13 days, minimal inflammation and histiocytic infiltration were observed (NTP 2002). Alveolar and bronchiolar epithelial hyperplasia and inflammation were observed in the lungs of mice similarly exposed to 1.1 mg vanadium/m^3 as vanadium pentoxide (NTP 2002). Although the Knecht et al. (1985, 1992) or NTP (2002) studies did not include examination of potential end points outside of the respiratory tract, longer-duration studies have identified the respiratory tract as the most sensitive target of toxicity (NTP 2002). The NTP (2002) rat study was selected as the basis of the acute-duration inhalation MRL.

In the NTP (2002) study, groups of male and female F344 rats received whole-body exposure to 0, 1, 2, or 4 mg vanadium pentoxide/m^3 (0, 0.56, 1.1, or 2.2 mg vanadium/m^3) as particulate aerosols 6 hours/day, 5 days/week. On days 6 and 13, 10 rats/group were killed and a histopathological examination of the lungs was conducted. Four rats per group were killed for examination of the onset and extent of lung

lesions after 1, 2, 5, 10, or 16 days of exposure. Hyperplasia of alveolar epithelium and bronchiole epithelium were observed in 100% of the female rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days. Significant increases in the incidence of histiocytic infiltrate and inflammation were observed in rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days and in rats exposed to 0.56 mg vanadium/m^3 for 13 days. A significant increase in fibrosis was observed in rats exposed to 2.2 mg vanadium/m^3 for 13 days. No histopathological alterations were observed in the four female rats killed after 1 day of exposure; by day 2, inflammation and histiocytic infiltrates (increased number of alveolar macrophages) were observed in the rats exposed to 2.2 mg vanadium/m^3. Hyperplasia of the alveolar and bronchiolar epidthelium was first observed on day 5 in rats exposed to 1.1 or 2.2 mg vanadium/m^3.

A benchmark dose (BMD) approach was considered for derivation of the acute-duration inhalation MRL; however, the fit was not considered adequate due to the limited amount of information from the study on the shape of the exposure-response curve for lung inflammation; more information regarding the BMD analysis is presented in Appendix A. A NOAEL/lowest-observed-adverse-effect level (LOAEL) approach was used to derive the MRL. The LOAEL of 0.56 mg vanadium/m^3 for lung inflammation was selected as the point of departure for the MRL. This LOAEL was converted to a human equivalent concentration ($LOAEL_{HEC}$) of 0.073 mg vanadium/m^3 (see Appendix A for more information on the calculation of the $LOAEL_{HEC}$) and divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for animal to human extrapolation using dosimetric adjustments, and 10 for human variability), resulting in an acute-duration inhalation MRL of 0.0008 mg vanadium/m^3.

Intermediate-Duration Inhalation MRL

The available data on the toxicity of vanadium following intermediate-duration inhalation exposure are limited to several rat and mouse studies (NTP 2002) involving exposure to vanadium pentoxide for 6 hours/day, 5 days/week. These studies demonstrate that the respiratory tract is the most sensitive target of toxicity. Signs of respiratory distress (rapid respiration, difficulty breathing) have been observed in rats exposed to 4.4 mg vanadium/m^3 as vanadium pentoxide for at least 4 weeks (NTP 2002). A 3-month exposure resulted in increased incidences of lung lesions in rats and mice and nasal lesions in rats. Lung effects included alveolar and bronchiolar epithelial hyperplasia, histiocytic infiltrates, inflammation, and fibrosis. A NOAEL of 0.56 mg vanadium/m^3 was identified in both species. At 1.1 mg vanadium/m^3, epithelial hyperplasia and inflammation (male rats and female mice only) were observed. In mice, the severity of the lesions was graded as minimal. In rats, the epithelial hyperplasia was graded as mild in males and minimal to mild in females and the inflammation was graded as mild. These data suggest that

at a given air concentration, rats are more sensitive than mice based on the severity of the lesions. In both species, the severity of the lesions increased with increasing concentrations. Significant alterations in pulmonary function suggestive of a restrictive disease were observed in rats exposed to 2.2 or 4.4 mg vanadium/m^3; lung function tests were not performed in mice. Nasal effects in rats included hyperplasia and squamous metaplasia of the respiratory epithelium and inflammation. The NOAEL and LOAEL for nasal effects were 2.2 and 4.5 mg vanadium/m^3 in males and 1.1 and 2.2 mg vanadium/m^3 in females. In addition to the respiratory tract effects, mild microcytic erythrocytosis was observed in rats exposed to ≥1.1 mg vanadium/m^3.

The lowest LOAEL identified in intermediate-duration studies is 1.1 mg vanadium/m^3 for lung epithelial hyperplasia and inflammation in rats exposed 6 hours/day, 5 days/week for 13 weeks (NTP 2002); the NOAEL for these effects is 0.56 mg vanadium/m^3. However, this NOAEL is the same as the LOAEL for lung inflammation in rats exposed for 13 days (NTP 2002). As summarized in Table 2-1, lung inflammation was observed in rats exposed to 0.56 mg vanadium/m^3 for 6 days (not significant), 13 days, and 2 years. Although the three studies were conducted for the National Toxicology Program (NTP), the 13-week study was conducted at a different laboratory using the same strain of rats and vanadium pentoxide dusts with similar particles sizes as the acute and chronic studies. An explanation for the inconsistent findings is not apparent from the available data. Because an intermediate-duration inhalation MRL based on the NOAEL identified in the 13-week study would be higher than the acute-duration inhalation MRL, the database is not considered adequate for derivation of an intermediate-duration inhalation MRL. However, it would be expected that the acute-duration inhalation MRL would be protective of intermediate-duration exposure to vanadium.

Chronic-Duration Inhalation MRL

- An MRL of 0.0001 mg vanadium/m^3 has been derived for chronic-duration inhalation exposure (1 year or longer) to vanadium pentoxide dust.

Two-year rat and mouse studies conducted by NTP (2002) examined the chronic toxicity of inhaled vanadium pentoxide 6 hours/day, 5 days/week for 2 years. At the lowest concentration tested in rats (0.28 mg vanadium/m^3), lung (increases in the incidence of alveolar and bronchiolar epithelial hyperplasia), larynx (degeneration and hyperplasia of the epiglottis epithelium), and nasal (goblet cell hyperplasia in respiratory epithelium) effects were observed. Similar lung and larynx effects were observed in mice at the lowest concentration tested (0.56 mg vanadium/m^3). The nasal effects observed in mice exposed to 0.56 mg vanadium/m^3 included goblet cell hyperplasia in the respiratory epithelium

Table 2-1. Lung Effects Observed in Rats Exposed to Vanadium Pentoxide 6 Hours/day, 5 Days/week for 6 or 13 Days, 13 Weeks, or 2 Years

	mg vanadium/m^3						
Air concentration	0	0.28	0.56	1.1	2.2	4.5	9.0
			6-Day study				
Alveolar hyperplasia	0/10		0/10	10/10[a] (1.1)[b]	8/10[a] (1.4)		
Bronchiole hyperplasia	1/10 (1.0)		0/10	10/10[a] (1.7)	10/10[a] (1.8)		
Histiocytic infiltrate	2/10 (1.0)		6/10 (1.3)	10/10[a] (1.4)	10/10[a] (1.8)		
Inflammation	0/10		3/10 (1.0)	10/10[a] (1.5)	10/10[a] (2.5)		
			13-Day study				
Alveolar hyperplasia	0/10		3/10 (1.0)	10/10[a] (1.0)	10/10[a] (2.0)		
Bronchiole hyperplasia	0/10		0/10	10/10[a] (1.0)	10/10[a] (1.8)		
Histiocytic infiltrate	0/10		10/10[a] (1.3)	10/10[a] (1.9)	10/10[a] (2.2)		
Inflammation[c]	0/10		8/10[a] (1.3)	10/10[a] (1.7)	10/10[a] (2.0)		
Fibrosis	0/10		0/10	0/10	6/10[a] (1.5)		
			13-Week study (males)				
Epithelial hyperplasia[d]	0/10		0/10	10/10[a] (2.0)	10/10[a] (3.0)	10/10[a] (3.6)	10/10[a] (3.3)
Inflammation[d]	0/10		0/10	9/10[a] (1.0)	10/10[a] (1.0)	10/10 (1.6)	10/10[a] (2.1)
Fibrosis	0/10		0/10	2/10 (1.0)	10/10[a] (1.9)	10/10[a] (3.2)	10/10 (3.1)
			13 Week study (females)				
Epithelial hyperplasia	0/10		0/10	10/10[a] (1.3)	10/10[a] (2.9)	10/10[a] (3.5)	10/10[a] (3.2)
Inflammation	0/10		0/10	0/10	10/10[a] (1.0)	10/10[a] (1.9)	10/10[a] (1.2)
Fibrosis	0/10		0/10	0/10	10/10[a] (1.0)	10/10[a] (2.9)	10/10[a] (3.2)

Table 2-1. Lung Effects Observed in Rats Exposed to Vanadium Pentoxide 6 Hours/day, 5 Days/week for 6 or 13 Days, 13 Weeks, or 2 Years

	mg vanadium/m^3						
Air concentration	0	0.28	0.56	1.1	2.2	4.5	9.0
	2-Year study (males)						
Alveolar hyperplasia	7/50 (2.3)	24/49[a] (2.0)	34/48[a] (2.0)	49/50[a] (3.3)			
Bronchiole hyperplasia	3/50 (2.3)	17/49[a] (2.2)	31/48[a] (1.8)	49/50[a] (3.3)			
Inflammation	5/50 (1.6)	8/49 (1.8)	24/48[a] (1.3)	42/50[a] (2.4)			
Fibrosis	7/50 (1.4)	7/49 (2.0)	16/48[a] (1.6)	38/50[a] (2.1)			
Histiocyte infiltration	22/50 (1.3)	40/49[a] (2.0)	45/48[a] (2.3)	50/50[a] (3.3)			
	2-Year study (females)						
Alveolar hyperplasia	4/49 (1.0)	8/49 (1.8)	21/50[a] (1.2)	50/50[a] (3.1)			
Bronchiole hyperplasia	6/49 (1.5)	5/49 (1.6)	14/50[a] (1.3)	48/50[a] (3.0)			
Inflammation	10/49 (1.5)	10/49 (1.1)	14/50 (1.2)	40/50[a] (1.7)			
Fibrosis	19/49 (1.4)	7/49[a] (1.3)	12/50 (1.6)	32/50[a] (1.4)			
Histiocyte infiltration	26/49 (1.4)	35/49[a] (1.3)	44/50[a] (2.0)	50/50[a] (1.9)			

[a]$p \leq 0.05$
[b]Average severity grade of lesions in affected animals: 1=minimal; 2=mild, 3=moderate; 4=marked
[c]Basis of acute-duration inhalation MRL
[d]Considered as the basis for the intermediate-duration inhalation MRL

Source: NTP 2002

and nasal olfactory epithelial atrophy and hyaline degeneration. In addition to these effects, a significant increase in alveolar/bronchiolar carcinoma incidence was also observed in mice exposed to ≥0.56 mg vanadium/m^3. In male rats, an increased combined incidence of alveolar/bronchiolar adenoma or carcinoma was also observed; however, the incidence was not significantly higher than concurrent controls, but was higher than historical controls. Because the rat study identified a lower LOAEL for lung, larynx, and nasal effects, it was selected as the basis of a chronic-duration inhalation MRL.

In the NTP (2002) study, groups of 50 male and 50 female F344 rats were exposed to 0, 0.5, 1, or 2 mg vanadium pentoxide/m^3 (0, 0.28, 0.56, and 1.1 mg vanadium/m^3) 6 hours/day, 5 days/week for 104 weeks. No significant alterations in survival or body weight gain were observed in the vanadium-exposed rats. Alveolar histiocytic infiltrates were observed in males and females exposed to ≥0.28 mg vanadium/m^3. Significant increases in the incidence of hyperplasia of the alveolar and bronchiolar epithelium were observed in males exposed to ≥0.28 mg vanadium/m^3 and females exposed to ≥0.56 mg vanadium/m^3. Squamous metaplasia was observed in alveolar epithelium of males and females exposed to 1.1 mg vanadium/m^3 and in the bronchiolar epithelium of males exposed to 1.1 mg vanadium/m^3. Chronic inflammation was observed in males exposed to 0.56 or 1.1 mg vanadium/m^3 and females exposed to 1.1 mg vanadium/m^3 and interstitial fibrosis was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.28 or 1.1 mg vanadium/m^3. An increased incidence of brownish pigment in alveolar macrophages was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.56 or 1.1 mg vanadium/m^3; this effect was considered to be of little biological relevance. Chronic inflammation, degeneration and hyperplasia of the epiglottis were observed in the larynx of males and females exposed to ≥0.28 mg vanadium/m^3; squamous metaplasia of the epiglottis respiratory epithelium was also observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3. Goblet cell hyperplasia of the nasal respiratory epithelium was observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3.

BMD analyses of the incidence data for alveolar and bronchiolar epithelial hyperplasia, chronic inflammation of the larynx, degeneration of epiglottis respiratory epithelium, and hyperplasia of nasal respiratory epithelial goblet cells in male rats were used to determine the point of departure for the MRL. As described in greater detail in Appendix A, the $BMCL_{10}$ values for these effects were 0.09, 0.10, 0.07, 0.04, and 0.16 mg vanadium/m^3, respectively.

These $BMCL_{10}$ values were converted to a human equivalent concentrations (as described in detail in Appendix A); the $BMCL_{HEC}$ values were 0.008, 0.017, 0.005, 0.003, and 0.012 mg vanadium/m^3 for

alveolar epithelial hyperplasia, bronchiolar epithelial hyperplasia, chronic inflammation of the larynx, degeneration of epiglottis respiratory epithelium, and hyperplasia of nasal respiratory epithelial goblet cells, respectively. The $BMCL_{HEC}$ of 0.003 mg vanadium/m^3 for degeneration of epiglottis respiratory epithelium was selected as the point of departure. This value was divided by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability), resulting in a chronic-duration inhalation MRL of 0.0001 mg vanadium/m^3.

Oral MRLs

Acute-Duration Oral MRL

Gastrointestinal effects (diarrhea, cramps, nausea, and vomiting) have been observed in noninsulin-dependent diabetic patients administered vanadyl sulfate or sodium metavanadate capsules as a supplement to their diabetes treatment (Afkhami-Ardekani et al. 2008; Boden et al. 1996; Cohen et al. 1995; Cusi et al. 2001; Goldfine et al. 1995, 2000) and in patients with ischemic heart disease administered diammonium vanado-tartrate for lowering serum cholesterol levels (Somerville and Davies 1962); the results of these studies are summarized in Table 2-2. Gastrointestinal effects were observed in subjects ingesting capsules containing 14–42 mg vanadium and no effects were observed at 7.8–10 mg vanadium. In most studies, the effects subsided within the first couple of weeks of exposure. Information on the dose-response relationship comes from a study by Goldfine et al. (2000), which used three dose levels of 7.8, 16, or 31 mg vanadium administered as capsules 3 times/day. No gastrointestinal effects were observed at the lowest dose and mild effects were reported in some subjects exposed to the mid dose level. At the highest dose, all subjects reported cramping, abdominal discomfort, and/or diarrhea, which required the use of over-the-counter medication. A small number of studies in laboratory animals have examined the acute toxicity of vanadium following oral exposure. Significant increases in reticulocyte levels in peripheral blood and polychromatophilic erythroblasts in the bone marrow were observed in rats exposed to 27.72 mg vanadium/kg/day as ammonium metavanadate in drinking water for 2 weeks (Zaporowska and Wasilewski 1989). The remaining nonlethality studies reported developmental effects in the offspring of rats and mice administered 7.5–8.4 mg vanadium/kg/day via gavage during gestation (Paternain et al. 1987, 1990; Sanchez et al. 1991). The observed developmental effects included decreases in fetal growth, increases in resorptions, and gross, visceral, and skeletal malformations and anomalies.

Although the human studies have a number of limitations, particularly the small number of subjects (typically <10 subjects per study) and no control group, they provide consistent evidence that bolus

Table 2-2. Summary of Human Studies Reporting Gastrointestinal Effects Following Oral Exposure to Vanadium

Daily dose, compound	Frequency of administration	Exposure duration	Gastrointestinal effects	Reference
52 mg vanadium/day, sodium metavanadate	21 mg 2 times/day 10 mg 1 time/day	14 days	4/10 subjects reported mild diarrhea, effects "rapidly dissipated"; no effects at 10 mg/day	Goldfine et al. 1995
28 mg vanadium/day, vanadyl sulfate	14 mg 2 times/day	3 weeks	Five of six subjects reported effects (nausea in three subjects, diarrhea in four subjects, and abdominal cramping in three subjects); all effects only reported during first week	Cohen et al. 1995
32 mg vanadium/day, vanadyl sulfate	16 mg 2 times/day	4 weeks	Six of eight subjects reported symptoms including diarrhea and abdominal cramps during first week	Boden et al. 1996
23.4 mg vanadium/day, vanadyl sulfate	7.8 mg 3 times/day	6 weeks	No effects; three subjects tested	Goldfine et al. 2000
48 mg vanadium/day, vanadyl sulfate	16 mg 3 times/day	6 weeks	Gastrointestinal complaints reported in "several subjects"; five subjects tested	Goldfine et al. 2000
93 mg vanadium/day, vanadyl sulfate	31 mg 3 times/day	6 weeks	Eight of eight subjects reported cramping, abdominal discomfort, and/or diarrhea	Goldfine et al. 2000
16–48 mg vanadium/day, vanadyl sulfate	8 mg 2 times/day, increased to 16 mg 3 times/day by week 2	6 weeks	4/11 subjects reported effects (diarrhea in 4 subjects and abdominal cramps in 2 subjects); effects only reported during first 2 weeks in 3/4 affected subjects	Cusi et al. 2001
42 mg vanadium/day, sodium metavanadate	Not reported	6 weeks	17/20 subjects reported nausea during first 3 weeks; 8/20 subjects reported vomiting	Afkhami-Ardekani et al. 2008
10–20 mg vanadium/day, ammonium vanadyl tartrate	5 mg 2–4 times/day	45–68 days	Diarrhea and cramps noted at higher doses (no additional information provided); six subjects tested	Dimond et al. 1963
Diammonium vanado tartrate	25 mg diammonium vando tartrate 3 times/day for 2 weeks and 42 mg diammonium vando tartrate 3 times/day for 5.5 months	6 months	5/12 subjects reported effects (abdominal pain, nausea)	Somerville and Davies 1962

administration of vanadium results in gastrointestinal irritation. However, there is no evidence to support extrapolating the bolus amount to a daily dose expressed per unit of body weight. Goldfine et al. (2000) identified a NOAEL of 7.8 mg vanadium administered 3 times/day as vanadyl sulfate capsules in three subjects. Dividing the daily dose of 23.4 mg vanadium by the average body weight of 109 kg would result in a dose of 0.2 mg vanadium/kg/dose. The lowest LOAEL value is 14 mg vanadium taken twice a day (Cohen et al. 1995); this corresponds to a daily dose of 28 mg vanadium/day or 0.35 mg vanadium/kg/day (average body weight was 80.6 kg). This dose is 20 times lower than the lowest LOAEL of 7.5 mg vanadium/kg/day for developmental effects identified in animal studies (Paternain et al. 1990). However, it is very likely that the observed effects are due to local irritation rather than a systemic effect; thus, the amount of vanadium in the gastrointestinal tract is more important than the mg/kg/day dose. Deriving an MRL based the NOAEL of 0.2 mg/kg and an uncertainty factor of 10 for human variability would result in an MRL that is likely to be overly conservative. Thus, the available human data were not considered suitable for derivation of an acute-duration oral MRL.

As noted previously, Paternain et al. (1990) identified the lowest adverse effect level in animals. In this study, significant increases in early resorptions, decreases in fetal body weight and length, and increases in the incidence of soft tissue anomalies/malformations (hematomas in facial area, neck, and dorsal area, cleft palate), and skeletal defects (delayed ossification of supraoccipital bone, carpus, tarsus, and sternebrae) were observed in the offspring of Swiss mice administered via gavage 7.5 mg vanadium/kg/day as vanadyl sulfate on gestation days 6–15. This dose was also associated with significant decreases in maternal body weight gain (during gestation days 6–15, the dams gained 46% less weight than controls); no significant alterations in food intake were observed. Because 7.5 mg vanadium/kg/day is a serious LOAEL in the dams (ATSDR defines serious effects as those that evoke failure in a biological system and can lead to morbidity or mortality), this study is not suitable for derivation of an acute-duration oral MRL. It is ATSDR's policy to not use a LOAEL for serious health effects as the basis of an MRL.

Intermediate-Duration Oral MRL

- An MRL of 0.01 mg vanadium/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to vanadium.

Two human studies have examined the oral toxicity of vanadium. No significant alterations in hematological parameters, liver function (as measured by serum enzymes), cholesterol and triglyceride levels, kidney function (as measured by blood urea nitrogen), body weight, or blood pressure were

observed in subjects administered via capsule 0.12 or 0.19 mg vanadium as ammonium vanadyl tartrate or vanadyl sulfate for 6–12 weeks (Dimond et al. 1963; Fawcett et al. 1997). Several studies have reported gastrointestinal effects in noninsulin-dependent diabetics that persisted for >2 weeks (Afkhami-Ardekani et al. 2008; Goldfine et al. 2000). The effects were observed at 31.3 mg vanadium (administered 3 times/day) and no effects were observed at 7.8 mg vanadium (Goldfine et al. 2000). Studies in laboratory animals have identified several sensitive effects including alterations in erythrocyte and reticulocyte levels, increased blood pressure, neurobehavioral alterations, and developmental toxicity. The lowest LOAEL identified in an intermediate-duration study was 0.12 mg vanadium/kg/day for increases in blood pressure observed in rats exposed to sodium metavanadate in drinking water for 210 days (Boscolo et al. 1994); several other studies by these investigators have reported similar effects at higher doses (Carmagnani et al. 1991, 1992). However, other studies have not found significant alterations in blood pressure at higher doses (Bursztyn and Mekler 1993; Sušić and Kentera 1986, 1988). Significant decreases in erythrocyte levels have been observed in rats exposed to 1.18 mg vanadium/kg/day as ammonium metavanadate in drinking water for 4 weeks (Zaporowska et al. 1993); at higher concentrations, decreases in hemoglobin and increases in reticulocyte levels have been observed (Ścibior 2005; Ścibior et al. 2006; Zaporowska and Wasilewski 1990, 1991, 1992a, 1992b; Zaporowska et al. 1993). However, other intermediate-duration studies have not found significant alterations at doses as high as 9.7 mg vanadium/kg/day (Dai et al. 1995; Mountain et al. 1953). At 1.72 mg vanadium/kg/day, impaired performance on neurobehavioral tests (open field and active avoidance tests) was observed in rats exposed to administered sodium metavanadate for 8 weeks (Sanchez et al. 1998). No other studies have examined the neurotoxic potential of vanadium. As with acute-duration exposure, the developing organism is a sensitive target of vanadium toxicity. Decreases in pup body weight and length were observed in the offspring of rats administered 2.1 mg vanadium/kg/day as sodium metavanadate for 14 days prior to mating and throughout gestation and lactation (Domingo et al. 1986). At higher doses (6, 10, or 12 mg vanadium/kg/day), decreases in pup survival, and increases in the occurrence of gross, visceral, or skeletal malformations and anomalies were observed (Elfant and Keen 1987; Morgan and El-Tawil 2003; Poggioli et al. 2001).

The animal database suggests that the most sensitive targets of vanadium toxicity are blood pressure, erythroctyes, nervous system, and the developing organism with LOAEL values of 0.12, 1.18, 1.72, and 2.1 mg vanadium/kg/day, respectively. Two approaches for derivation of an intermediate-duration oral MRL were considered. In the first approach, the NOAEL of 0.12 mg vanadium/kg/day identified in the Fawcett et al. (1997) study was used as the point of departure for the MRL. The Fawcett et al. (1997) study was selected over the Dimond et al. (1963) study, which identified a slightly higher NOAEL

(0.19 mg vanadium/kg/day) because more subjects (six subjects in Dimond study compared to 15–16 subjects in Fawcett study) were examined and the results of the study are described in greater detail. In the Fawcett et al. (1997) study, groups of men and women enrolled in a weight training program for at least 1 year were administered capsules containing 0 (11 men and 4 women) or 0.12 mg vanadium/kg/day as vanadyl sulfate trihydrate (12 men and 4 women) for 12 weeks. Fasting blood samples were collected at 0 and 12 weeks and analyzed for hematological (erythrocyte count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, platelet count, and total and differential leukocyte count) and serum chemistry (cholesterol, high density lipoprotein, triglycerides, albumin, total protein, total and direct bilirubin, alkaline phosphatase, alanine amino-transferase) parameters. Body weight and blood pressure were measured at weeks 4, 8, and 12. No significant alterations in blood pressure, body weight, or hematological or clinical chemistry parameters were found. Using the NOAEL of 0.12 mg vanadium/kg/day and an uncertainty factor of 10 for human variability, the MRL would be 0.01 mg vanadium/kg/day. As discussed previously, the studies of diabetics reporting gastrointestinal effects were not considered a suitable basis for an MRL because the effects are likely due to bolus administration of a large amount of vanadium.

Several animal studies were also considered as the basis of an MRL. Although an increase in blood pressure was observed at the lowest adverse effect level (0.12 mg vanadium/kg/day; Boscolo et al. 1994), this end point was not selected as the basis for an intermediate-duration oral MRL. This effect has not been consistently observed among rat studies and no alterations in blood pressure were observed in a study of healthy adults exposed to 0.12 mg vanadium/kg/day for 12 weeks (Fawcett et al. 1997). The next highest LOAEL of 1.18 mg vanadium/kg/day for a decrease in erythrocyte levels in rats (Zaporowski et al. 1993) was considered as the principal study for the MRL. In the Zaporowski et al. (1993) study, groups of 2-month-old male and female Wistar rats (15–16/sex/group) were exposed to ammonium metavanadate in drinking water for 4 weeks at doses of 0, 1.18, and 4.93 mg vanadium/kg/day (males) or 1.50 and 6.65 mg vanadium/kg/day (females). No alterations in behavior or motor activity were observed. A significant decrease in water consumption (14% less than controls) was observed in males exposed to 4.93 mg vanadium/kg/day. No significant alterations in body weight gain were observed. As summarized in Table 2-3, alterations in erythrocyte, hemoglobin, hematocrit, and reticulocyte levels were observed. This study identified a minimal LOAEL of 1.18 mg vanadium/kg/day for decreases in erythrocyte and hematocrit levels in male rats. The alteration in erythrocyte levels was considered minimally adverse because the magnitude of the change was small (approximately 11%). Dividing this minimal LOAEL by an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) results in an MRL of 0.004 mg vanadium/kg/day.

Table 2-3. Hematological Effects in Rats Exposed to Ammonium Metavanadate for 4 Weeks

	Dose (mg vanadium/kg/day)		
Males	0	1.18	4.93
Erythrocytes ($x10^{12}/dm^3$)	8.32	7.38[a]	7.47[b]
Hemoglobin (mmol/L)	9.37	8.94	8.65[a]
Hematocrit (L)	0.48	0.47[b]	0.47[a]
Reticulocytes (%)	2.55	2.64	3.82[b]
Females	0	1.50	6.65
Erythrocytes ($x10^{12}/dm^3$)	8.24	7.38[c]	7.12[c]
Hemoglobin (mmol/L)	9.41	8.76	8.72[a]
Hematocrit (L)	0.48	0.47	0.47
Reticulocytes (%)	2.55	2.91	3.64[b]

[a]Significantly different from control group ($p<0.01$)
[b]Significantly different from control group ($p<0.05$)
[c]Significantly different from control group ($p<0.001$)

Source: Zaporowska et al. 1993

Although an MRL based on the Zaporwska et al. (1993) rat study would be approximately 3 times lower than an MRL based on the Fawcett et al. (1997) human study, the Fawcett et al. (1997) study was selected as the basis of the intermediate-duration oral MRL because greater confidence was given to an MRL based on a reliable human study. Thus, the intermediate-duration oral MRL is 0.01 mg vanadium/kg/day.

Chronic-Duration Oral MRL

No studies examining the chronic toxicity of vanadium in humans were identified. Although several laboratory animal studies have examined chronic toxicity, most tested low doses and did not find effects. No adverse effects were observed in rats and mice exposed to 0.7 or 4.1 mg vanadium/kg/day, respectively, as vanadyl sulfate in drinking water for 2–2.5 years (Schroeder et al. 1970; Schroeder and Balassa 1967). In rats exposed to 28 mg vanadium/kg/day as vanadyl sulfate in drinking water, a 20% decrease in body weight gain was observed; no alterations in lungs, heart, liver, or kidneys histopathology, hematological parameters, or blood pressure were observed at 19 mg vanadium/kg/day (Dai and McNeill 1994; Dai et al. 1994a, 1994b). Because the most sensitive target of vanadium toxicity following chronic-duration oral exposure have not been identified, the animal studies that mostly identified free-standing NOAEL values were not considered suitable for derivation of an MRL.