# Chemical Information Review Document

# for

# Oral Exposure to Tetravalent and Pentavalent Vanadium Compounds

**Supporting Nomination for Toxicological Evaluation by the
National Toxicology Program**

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National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/

# Abstract

Vanadium (CAS No. 7440-62-2) is an element that exists in a number of oxidation states ranging from -1 to +5 and can be found in various locales around the world. Absorption of vanadium from the gastrointestinal tract is poor and most ingested vanadium is typically converted to vanadyl. Excretion of absorbed vanadium is primarily via urine while unabsorbed vanadium is mainly eliminated in feces. Studies indicate that toxicity is dependent on the valence of vanadium, increasing with increasing valence. Thus, pentavalent vanadium is more toxic than tetravalent vanadium. Acute toxicity studies indicate that administration of vanadium compounds is associated with locomotor impairments and effects on respiratory and cardiovascular systems. Short-term studies indicate that while pentavalent vanadium compounds produced effects on a variety of hematological markers, tetravalent compounds do not appear to have similar effects. Both valence states are associated with alterations in body weight, and food and fluid intake after short-term oral administration. Chronic studies with vanadyl sulfate indicated effects on body weight in animals while studies with sodium metavanadate showed effects on urinary markers. A few studies indicated that toxicological effects of vanadium compounds can be modified by the presence of other compounds. Tetravalent vanadium compounds were shown to have impacts on the structures within reproductive organs, survival rate of weanlings, sperm density and motility, fertility, and litter size. Pentavalent vanadium compounds were shown to impact maternal body weight. Conflicting outcomes on the impact of vanadium exposure (via drinking water) on tumor development were observed in two studies. Over 20 studies have shown that vanadium compounds exert chemopreventive effects against chemically-induced carcinogenesis. Genotoxicity studies indicate that vanadium compounds can increases the number of cells with hypoploidy, the number of aberrant cells, and the number of micronucleated polychromatic erythrocytes. Immunotoxicity in animals was observed after administration of pentavalent vanadium compounds. Studies in offspring of dams administered sodium metavanadate indicated neurotoxicological effects, suggesting placental transfer of the chemicals to the fetuses.

# Executive Summary

**Basis for Nomination**
Tetravalent and pentavalent forms of vanadium, species present in drinking water and dietary supplements, were nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological characterization including chronic toxicity and carcinogenicity studies and multigeneration reproductive toxicity studies via the oral route of administration. The nomination is based on known and anticipated exposure to humans due to the occurrence of vanadium as a drinking water contaminant and use as a dietary supplement, demonstrated carcinogenicity of the pentavalent form in experimental animals, research needs identified through the U.S. EPA's Drinking Water Contaminant Candidate List process and by other authoritative groups, and the overall lack of adequate toxicological data to assess the potential health risk of oral exposures.

Previous Evaluations by Authoritative Bodies
The Institute of Medicine has established a tolerable upper intake level (UL) of 1.8 mg/day of elemental vanadium for adults aged ≥19 years. A UL for infants (0-12 months), children (1-13 years), adolescents (14-18 years), pregnant women (14-50 years), and lactating women (14-50 years) could not be derived. The European Food Safety Authority reported that no UL could be established. The available subacute and subchronic oral rat toxicity studies of vanadium compounds were deemed incapable of deriving a no-observed-adverse-effects level (NOAEL). A NOAEL also could not be established for developmental toxicity in rats; however, in mice, NOAELs of ~2 and 4 mg vanadium/kg body weight (bw)/day were reported for maternal toxicity and developmental toxicity, respectively. Additionally, an adequate evaluation of the carcinogenic potential of vanadium by oral exposure could not be made. However, a risk of adverse effects was noted as possible from prolonged ingestion of supplements containing vanadium. Athletes and body builders were estimated to have a daily intake of up to 18 mg vanadium/person from supplements taken, which is equivalent to ~300 μg vanadium/kg bw, a dose similar to that reported to cause gastrointestinal effects in humans and kidney lesions in rats. The International Programme on Chemical Safety agreed with the European Food Safety Authority in that "the toxicokinetic and toxicological database on vanadium and vanadium pentoxide is limited, and attempts to utilize information from other inorganic vanadium compounds are not entirely satisfactory." The U.S. Environmental Protection Agency (EPA) reference dose (RfD) for chronic oral exposure for vanadium pentoxide (0.009 mg/kg/day; 0.62 mg/day for a 70-kg person) is also reported with low confidence. Vanadium pentoxide is scheduled to be on the EPA Integrated Risk Information System (IRIS) 2008 agenda.

**Nontoxicological Data**
Vanadium (also called vanadium, elemental; V) exists in a number of different oxidation states (-1, 0, +2, +3, +4, and +5) with vanadium pentoxide ($V_2O_5$) being the most common commercial form. Vanadium is found in the environment in various forms. In the United States, vanadium is regulated by NIOSH and EPA. Depending on the sample form, vanadium can be detected using a variety of analytical methods. For solid and liquid samples, analytical methods such as electrothermal absorption spectrophotometry (AAS), graphite furnace AAS, gas chromatography, inductively coupled plasma mass spectrometry, and instrumental neutron activation analysis. For air samples, inductively coupled plasma-atomic emission spectrometry and flameless AAS have been used. Vanadium is available from several U.S. and international suppliers. It is mined in several countries and usually obtained as a recovery product from other materials (e.g., industrial waste). Physical-chemical properties of vanadium depend upon the oxidation state and the other elements present in the compound. Vanadium is used in a variety of products including tungsten carbide tool bits and pigments. It also is used for its catalyst properties in the production of maleic anhydride and sulfuric acid and in the refining stage of steelmaking. Vanadium is used as a constituent of pills and dietary supplements. Vanadium has been reported to have a variety of beneficial effects including treatment for osteoporosis or osteopenia, cancer, and diabetes. The average

dietary intake of vanadium in adults has been estimated to range from 10-60 μg/day. Vanadium is currently on the U.S. EPA drinking water contaminant candidate list; research needs in this area include evaluation of neurotoxicity and toxicokinetics for inhalation and oral exposure, as well as further research to identify appropriate treatment technologies.

**Toxicological Data**
Toxicological data summarized here is generally restricted to studies of tetravalent and pentavalent compounds by the oral route of administration. No oral exposure studies of cytotoxicity, initiation/promotion, or antigenotoxicity were available for either the tetravalent or pentavalent forms of vanadium.

Human Data
Normal serum concentrations in unexposed human populations are < 1–2 μg vanadium/L. Human studies indicate that exogenously administered vanadium compounds are poorly absorbed from the gastrointestinal tract. Short-term and subchronic studies with both tetravalent and pentavalent vanadium compounds indicate that the most severe observed effects included upper abdominal pain, anorexia, nausea, and weight loss. All effects were reversed with the dose was reduced or the treatment ended. Evaluation of various biochemical and hematological levels (e.g., serum cholesterol levels, blood glucose) also were not significantly affected by vanadium compound administration.

Chemical Disposition, Metabolism, and Toxicokinetics
Absorption of vanadium from the gastrointestinal tract is poor. Most ingested vanadium is typically converted to vanadyl in the stomach of nonruminants. In plasma and body fluids, vanadium is converted to vanadyl as vanadyl-transferrin and vanadyl-ferriting complexes. Excretion of absorbed vanadium is primarily via urine while unabsorbed vanadium is mainly eliminated in feces. Absorbed vanadium (tetravalent and pentavalent forms) is distributed mainly to the bone, liver, kidney, and the spleen. Studies in pregnant mice fed vanadyl sulfate pentahydrate showed increased vanadium concentrations in the whole fetus and placenta indicating that the chemical could cross the placental-fetal barrier.

Acute Toxicity
Animals treated with tetravalent vanadium compounds exhibited decreased locomotor activity, paralysis of the rear legs, high tolerance for pain, diarrhea, irregular respiration, increased cardiac rhythm, and/or increased ataxia.

Acute toxicity in animals treated with pentavalent vanadium compounds included lethargy, lacrimation, diarrhea, and coma; histologically, necrosis of liver cells and cloudy swelling of renal tubules were observed. Animals receiving aqueous sodium metavanadate exhibited the same effects as animals administered tetravalent vanadium compounds.

Short-term and Subchronic Exposure
There is conflicting data on the impact of tetravalent vanadium compounds on body weight. A shorter-length study (4 weeks) indicates that tetravalent compounds decrease body weight, while longer-length studies (12 weeks) show no effect. Diarrhea developed in some treated rats; however, no other evaluated physiological parameters appeared altered by administration of tetravalent vanadium compounds.

Overall, studies indicated that short-term and subchronic exposure to pentavalent vanadium compounds decreases food intake, fluid intake and body weights. Most studies indicated that exposure to pentavalent vanadium compounds decreased levels of measured hematological markers (e.g., erythrocyte levels, hemoglobin levels). Histopathological studies reports indicate effects on spleen, kidneys, and lungs. Locomotor behavior appears to be altered at doses starting at 1.5 mg V/kg bw/day.

Chronic Exposure
Rats treated with vanadyl sulfate in drinking water for up to one year, exhibited decreases in the rate of weight gain, which became more significant with increasing dose. When mice were administered vanadyl sulfate for their lifetime, increases in body weight were observed in both sexes and animals had lower mortality and longer lifespans.

When groups of male rats received varying doses of sodium metavanadate in drinking-water for 180 or 210 days no effect on cardiovascular function or histopathological changes in the brain, liver, lungs, heart, or blood vessels were observed. Urinary potassium and calcium levels were altered and urinary kininase activities I and II were increased at the high dose.

Synergistic/Antagonistic Effects
Vanadium was reported to increase the weight-reducing effects of leptin in rats. Treatment of rats with vanadium and 1α,25-dihydroxyvitamin D3 offered protection against diethylnitrosamine-induced rat liver carcinogenesis. In other studies, other compounds (e.g., Tiron, zinc sulfate, ascorbic acid) were shown to reduce the toxicity observed after vanadium administration.

Reproductive and Teratological Effects
Administration of tetravalent vanadium compounds was shown to have impacts on the structures within reproductive organs (e.g., seminiferous tubules and epididymides). Higher dose studies described decreases in survival rate of weanlings, sperm density and motility, fertility, and litter size.

Overall, pentavalent vanadium compounds were shown to have no significant effects on the number of implantations, resorptions, or live/dead fetuses. Maternal body weight was shown to decrease during exposures. Delayed ossification also was observed.

Carcinogenicity
Two studies, both with significant limitations, presented conflicting outcomes on the impact of vanadium exposure (via drinking water) on tumor development. One study indicated that the incidence of spontaneous tumors did not increase while in a second study the number of tumors in female mice, but not in male mice, was increased.

Whole-body inhalation exposure to vanadium pentoxide caused increased incidence of lung neoplasms in an NTP bioassay. Vanadium pentoxide also induced micronucleated erythrocytes in mouse peripheral blood. Based on these studies, several organizations have classified vanadium pentoxide as a possible human carcinogen.

Anticarcinogenicity
Over 20 studies were identified relating to chemopreventive effects of vanadium compounds.

Genotoxicity
The bone marrow of male mice given vanadyl sulfate had statistically significant increases in cells with hypoploidy, in the number of aberrant cells, and in the number of micronucleated polychromatic erythrocytes (PCE). Induction of polyploidy was not observed. Comparatively, another study did not show an increase the number of PCEs and slightly increased micronucleated reticulocytes.

In bone marrow of mice administered a single dose of sodium orthovanadate or ammonium metavanadate in water, there were increased numbers of chromosome aberrations. Statistically significant increases were seen in cells with hypoploidy and hyperploidy, but none with polyploidy. In another study, the bone marrow of mice given vanadium pentoxide exhibited no increased induction of micronuclei. Comparatively, mice treated with a range of concentrations of sodium orthovanadate in drinking water

exhibited statistically significant increases of micronuclei in bone marrow and increase of comet tail length in splenocytes also at the highest tested concentration.

Immunotoxicity

ICR mice administered vanadium pentoxide exhibited an enlargement of the spleen with weakened spleen cellularity. Significant increases in leukocyte count in peripheral blood and a decrease in phagocytosis were also observed. Activation of T- and B-cells and a strong mitogenic response to concanavalin A suggested potential hypersensitivity. Wistar rats administered vanadium pentoxide also exhibited an enlarged spleen, as well as a significant increase in leukocyte count in peripheral blood and a decrease in phagocytosis. Significant increases in antibody-synthesizing lymphocytes in the spleens of BALB/c mice and Wistar rats were observed after administration of ammonium vanadate.

Other Data

Lactation-exposed offspring of dams treated with sodium metavanadate exhibited neurological delays including delays in eye opening and decreases in forelimb support and locomotor activity.

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## 1.0    Basis for Nomination

Tetravalent and pentavalent forms of vanadium, species present in drinking water and dietary supplements, were nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological characterization including chronic toxicity and carcinogenicity studies and multigeneration reproductive toxicity studies via the oral route of administration. The nomination is based on known and anticipated exposure to humans due to the occurrence of vanadium as a drinking water contaminant and use as a dietary supplement, demonstrated carcinogenicity of the pentavalent form in experimental animals, research needs identified through the U.S. EPA's Drinking Water Contaminant Candidate List process and by other authoritative groups, and the overall lack of adequate toxicological data to assess the potential health risk of oral exposures.

Based on an NTP two-year inhalation study of vanadium pentoxide (a pentavalent vanadium compound), the International Agency for Research on Cancer (IARC) concluded the chemical to be a possible human carcinogen (Group 2B). Vanadium remains on the U.S. EPA Drinking Water Contaminant Candidate List (CCL) as a priority contaminant with insufficient information to support a regulatory determination. Specific health effects research needs identified in the vanadium CCL listing include data on neurotoxicity and toxicokinetics studies by the oral and inhalation routes. The EPA Office of Water supports the nomination of vanadium for additional testing by the NTP and is especially interested in a 2-year cancer bioassay as well as a 2-generation reproductive/developmental toxicity study of a pentavalent vanadium compound (e.g. sodium metavanadate or ammonium metavanadate) via the drinking water route of exposure.

Previous Evaluations by Authoritative Groups
The Food and Nutrition Board, Institute of Medicine (2001), has established a tolerable upper intake level (UL) of 1.8 mg/day of elemental vanadium for adults aged ≥19 years, based on a lowest-observed-adverse-effects level (LOAEL) of 7.7 mg/kg/day and an uncertainty factor of 300. A UL for infants (0-12 months), children (1-13 years), adolescents (14-18 years), pregnant women (14-50 years), and lactating women (14-50 years) has not been derived due to the lack of toxicity data for these sensitive life stage groups. The Institute of Medicine has recommended the following research:

- Determination of the biochemical role of vanadium in both higher animals and humans and a reliable status indicator of vanadium for further work in humans.
- The efficacy and safety of the use of vanadium as a nutritional supplement.

The International Programme on Chemical Safety (IPCS, 2001) noted the following when discussing uncertainties in the evaluation of health effects for vanadium pentoxide and other inorganic vanadium compounds:

> Overall, the toxicokinetic and toxicological database on vanadium and vanadium pentoxide is limited, and attempts to utilize information from other inorganic vanadium compounds are not entirely satisfactory. Of particular concern is the limited understanding of the potential for dermal absorption and the potential longterm effects as a result of sequestration in body tissues such as bone. Furthermore, the significance of effects seen in developmental toxicity studies using vanadium pentoxide is not well understood. At present, studies are generally poorly reported or poorly conducted. Skeletal anomalies have been seen in a number of studies with pentavalent and
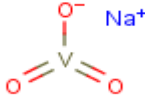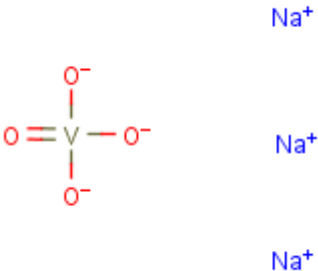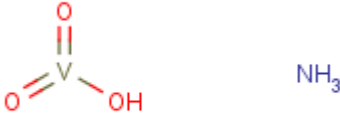
tetravalent vanadium compounds, although it is difficult to ascertain the role of the severe maternal toxicity that has also been evident. It is plausible that the skeletal anomalies in pups may be related to the disturbance of calcium balance (Younes & Strubel 1991) and interference with phosphate metabolism.

According to a more recent publication by the European Food Safety Authority (2004), the available subacute and subchronic oral rat toxicity studies with vanadium compounds do not allow the derivation of a no-observed-adverse-effects level (NOAEL). Additionally, no NOAEL for developmental toxicity has been established for rats; however, in mice, NOAELs of ~2 and 4 mg vanadium/kg body weight (bw)/day have been reported for maternal toxicity and developmental toxicity, respectively. No adequate evaluation of the carcinogenic potential of vanadium by oral exposure can be made. Furthermore, a UL cannot be made. (Note: This is in contrast to those established by the Institute of Medicine noted above.) However, the risk of adverse effects is possible from the prolonged ingestion of supplements containing vanadium. Athletes and body builders are estimated to intake a daily dose of up to 18 mg vanadium/person in supplements, which is equivalent to ~300 µg vanadium/kg bw, a dose similar to those reported to cause gastrointestinal effects in humans and kidney lesions in rats.

Furthermore, the reference dose (RfD) for chronic oral exposure for vanadium pentoxide (0.009 mg/kg/day; 0.62 mg/day for a 70-kg person), established by the U.S. Environmental Protection Agency (EPA) in 1986, is reported with low confidence. The RfD is based on a single unpublished study and coupled with the lack of other available data for the compound (U.S. EPA, 2002a [IRIS]), low confidence was assigned to the reference study and the database. Vanadium pentoxide is scheduled for review in the U.S. EPA's Integrated Risk Information System (IRIS) program beginning in 2008 (U.S. EPA, 2007 [72FR72715 12/21/07]).

## 2.0     Introduction

| Vanadium<br>[7440-62-2] | |
|---|---|
| V | |
| *Tetravalent Vanadium Compounds* | |
| Vanadyl Sulfate<br>[27774-13-6] | Vanadyl Oxydichloride<br>[10213-09-9] |
|  |  |

| *Pentavalent Vanadium Compounds* | |
|---|---|
| Vanadium Pentoxide<br>[1314-62-1] | Sodium Metavanadate<br>[13718-26-8] |
| | |
| Sodium Orthovanadate<br>[13721-39-6] | Ammonium metavanadate<br>[7803-55-6] |
| | |

## 2.1    Chemical Identification and Analysis

Vanadium (V; mol. wt. = 50.94) also is called vanadium, elemental (ChemIDplus, undated).  It exists in a number of different oxidation states (-1, 0, +2, +3, +4, and +5) with vanadium pentoxide ($V_2O_5$) being the most common commercial form (IPCS, 2001).

### 2.1.1    Tetravalent Vanadium Compounds

Vanadyl sulfate ($VOSO_4$; mol. wt. = 163.00) also called:

> Vabadub(IV) oxide sulfate
> Vanadic sulfate
> Vanadium oxide sulfate (VO(SO4))
> Vanadium, oxo(sulfato(2-)-O)-
> Vanadium, oxosulfato-
> Vanadium oxysulfate
> Vanadium sulfate
> Vanadyl(IV)-sulfate hydrate
> Vanadyl monosulfate

Source(s):  Chemfinder (2004); ChemIDplus (undated); Registry (1984)

Vanadyl oxydichloride ($VOCl_2$; mol. wt. = 137.85) also called:

> Dichlorooxovanadium
> Oxovanadium (IV) chloride
> Vanadium chloride oxide
> Vanadium dichloride oxide

> Vanadium, dichlorooxo-
> Vanadium oxychloride
> Vanadyl chloride
> Vanadyl dichloride

Source(s):  ChemIDplus (undated); Registry (1984)

### 2.1.2  Pentavalent Vanadium Compounds

Vanadium pentoxide ($V_2O_5$; mol. wt. = 181.90) also called:

> Divanadium pentaoxide
> Divanadium pentoxide
> Vanadic acid anhydride
> Vanadic anhydride
> Vanadin(V) oxide
> Vanadium oxide
> Vanadium pentaoxide
> Vanadium pentoxide

Source(s):  ChemIDplus (undated); IPCS (2001)

Sodium metavanadate ($NaVO_4$; mol. wt. = 121.93) also called:

> Monosodium trioxovanadate (1-)
> Sodium vandate (V) (NaVO3) (6CI, 7CI)
> Sodium trioxovanadate (1-)
> Sodium vanadate
> Sodium vanadate oxide (NaVO3)
> Sodium vanadate trioxide
> Vanadate (VO31-). sodium (9CI)
> Vanadic acid (HVO3), sodium salt (8CI)

Source(s):  Registry (1984)

Sodium orthovanadate ($Na_3O_4V$; mol. wt. = 183.91) also called:

> Sodium *o*-vanadate
> Sodium tetraoxovanadate (3-)
> Sodium vanadate (V) (Na3VO4)
> Vanadate (VO43-), trisodium, (t-4)-
> Vanadic acid (H3VO4), trisodium salt (8CI)

Source(s):  Chemfinder (2004); Registry (1984)

Ammonium metavanadate ($NH_4VO_3$; mol. wt. = 116.98) also called:

> Ammonium vandate (V) ((NH4 (VO3) (6CI, 7CI)
> Vanadate (VO31-), ammonium (9CI)
> Vanadic acid (HVO3), ammonium salt (8CI)
> Ammonium monovanadate
> Ammonium trioxovanadate
> Ammonium vanadate (VO31-)
> Ammonium vanadium oxide (NH4VO3)
> Ammonium vanadium trioxide

Source(s):  ChemIDplus (undated) Registry (1984)

## 2.2     Physical-Chemical Properties

| Property | Information | Reference(s) |
|---|---|---|
| *Vanadium [7440-62-2]* | | |
| Physical State | soft, silvery-grey metal | IPCS (2001) |
| Boiling Point (°C) | 3380 | IPCS (2001) |
| Melting Point (°C) | 1890 ± 10; 1917 | IPCS (2001) |
| Vapor Pressure (mm Hg)* | N/A | |
| Specific Gravity | not provided | |
| Water Solubility | insoluble | IPCS (2001) |
| Octanol-water partition coefficient (log $K_{OW}$)* | N/A | |
| **Tetravalent Vanadium Compounds** | | |
| *Vanadyl Sulfate [27774-13-6]* | | |
| Physical State | blue crystalline powder | Chemfinder (2004) |
| Boiling Point (°C) | not applicable | Fisher Scientific (2005) |
| Melting Point (°C) | decomposes | Fisher Scientific (2005) |
| Specific Gravity | 3.0 | Fisher Scientific (2005) |
| Water Solubility | very soluble in cold water, 20-25 °C | IPCS (2001) |
| *Vanadyl Oxydichloride [10213-09-9]* | | |
| Physical State | yellow to brown liquid | Chemicalland21 (undated) |
| Boiling Point (°C) | 126-127 | Chemicalland21 (undated) |
| Melting Point (°C) | -76.5 | Chemicalland21 (undated) |
| Specific Gravity | 1.83 | Chemicalland21 (undated) |
| Water Solubility | decomposes in cold water, 20-25 °C | IPCS (2001) |
| **Pentavalent Vanadium Compounds** | | |
| *Vanadium Pentoxide [1314-62-1]* | | |
| Physical State | yellow-red or green crystalline powder | IPCS (2001) |
| Boiling Point (°C) | 1750 | IPCS (2001) |
| Melting Point (°C) | 690 | IPCS (2001) |
| Specific Gravity | 3.4 g/cm$^3$ | Registry (1984) |
| Water Solubility | 8 g/L (cold water, 20-25 °C) | IPCS (2001) |
| *Sodium Metavanadate [13718-26-8]* | | |
| Physical State | colorless to yellow crystals | Chemfinder (2004) |
| Boiling Point (°C) | not provided | |
| Melting Point (°C) | 690 | Registry (1984) |
| Specific Gravity | 3.241 g/cm$^3$ @ 20 °C | Registry (1984) |
| Water Solubility | 211 g/L (cold water, 20-25 °C) | IPCS (2001) |
| | 388 g/L  (hot water, 75 °C) | |
| *Sodium Orthovanadate [13721-39-6]* | | |
| Physical State | Not provided | |
| Boiling Point (°C) | Not provided | |
| Melting Point (°C) | 850-856 | IPCS (2001) |
| Specific Gravity | Not provided | |
| Water Solubility | soluble in cold water, 20-25 °C | IPCS (2001) |
| *Ammonium Metavanadate [7803-55-6]* | | |
| Physical State | white or slightly yellow crystals | Chemfinder (2004) |
| Boiling Point (°C) | Not provided | |
| Melting Point (°C) | 200 (decomposes) | IPCS (2001) |
| Specific Gravity | 2.326 | Registry (1984) |
| Water Solubility | 58 g/L (cold water, 20-25 °C) | IPCS (2001) |

*Vapor pressures and octanol/water partition coefficients are not available for vanadium compounds (IPCS, 2001).

Analytical Methods for Measuring Vanadium Levels in Solid and Liquid Samples
A widely used technique for measuring vanadium in urine, which is pre-concentrated by chelation and solvent extracted, is electrothermal atomic absorption spectrophotometry (AAS; detection limits of 0.1 μg/L urine). This method is reported to have an analytical precision of 11% relative standard deviation at 1 μg/L and 4% at 10 μg/L (IPCS, 2001).

Vanadium in water can be determined by direct aspiration and analysis by graphite furnace AAS (detection limits at 200 and 4 μg/L, respectively, as reported by the U.S. EPA) (IPCS, 2001). Vanadium in bottled drinking water and in composite diets was quantified by inductively coupled plasma mass spectrometry (ICP-MS) (Al-Dayel et al., 2005; Melnyk et al., 2003; Suzuku et al., 2000).

Vanadium in sea mammal tissues have been measured by instrumental neutron activation analysis and by ICP-MS, both have a detection limit of 0.1 μg/g tissue (IPCS, 2001). Infant foods in Nigeria also have been analyzed by instrumental neutron activation using thermal and epithermal neutrons from a 30-kw research reactor (Jonah et al., 2003).

Vanadium (0-0.31 mg/kg) in canned fish samples was determined by direct mercury analyzer and inductively coupled plasma-optical emission spectrometer (ICP-OES) (Iken and Egiebor, 2005).

Analytical Methods for Measuring Vanadium Levels in Air Samples
The MDHS 91 *Metals and metalloids in workplace air by X-ray fluorescence spectrometry* method published by the Health and Safety Executive (1998; cited by IPCS, 2001) determines vanadium in workplace air; no data were reported on the performance of this method.

Generic methods for measuring metals and metalloids have been published by the U.S. National Institute of Occupational Safety and Health Administration (NIOSH, 1994; cited by IPCS, 2001) and the U.S. Occupational Safety and Health Administration (OSHA, 1991; cited by IPCS, 2001). Methods for the collection of air samples via a membrane filter mounted in a cassette-type filter holder, dissolving in acid on a hotplate and analyzing by inductively coupled plasma-atomic emission spectrometry are described. The lowest detection limit for a 500-liter sample was determined at ~0.005 mg/m$^3$ for both methods (IPCS, 2001).

Flameless AAS with a detection limit of 1 ng vanadium/mL air, relating to an absolute sensitivity of 0.1 ng vanadium, had a working range of 5-2000 μg/m$^3$ for a 500-liter air sample (NIOSH, 1994; IPCS, 2001).

## 2.3    Commercial Availability
Numerous companies in the United States (e.g. Acros Organics, Fisher Chemicals, International Laboratory Limited, Spectrum Chemicals, and Laboratory Products Inc.), Germany (e.g., ABCR GmBH, Fox Chemicals, Alfa Aeser), China (e.g., Leputech, Debayer Chemical Co., Ltd.), and India (e.g., Adarsh Petrochemical Agency, Loba Chemie Pvt. Ltd.) supply vanadium and its tetravalent and pentavalent forms (Chemexper.com, 2007). Strategic A minerals plant in Hot Springs Arkansas produces and supplies high-purity vanadium oxides and vanadates (Stratcor

Inc., 2007).  Gallade Chemical in California supplies sodium metavanadate in 2.5 kg containers and ammonium metavanadate in 125 g containers (Gallade Chemical, 2007).

## 3.0 Production Processes
Vanadium is mined in South Africa, Russia, and China.  Slag containing vanadium pentoxide, which is formed during iron ore smelting, is used for manufacturing vanadium metal.  A solvent extraction of uranium ores and a salt roasting process of boiler residues or residues from elemental phosphate plants also produce vanadium pentoxide (IPCS, 2001).  In the U.S. vanadium production is entirely from recovery of various industrial waste materials, such as vanadium-bearing fly ash, petroleum residues, pig iron slag, and spent catalysts (Magyar, 2007).

## 4.0 Production and Import Volumes
Between 1976 and 1990, worldwide production of vanadium was 27,000 tonnes/annum.  In 1990, the estimated production was 30,700 tonnes (15,400 from South Africa, 4100 from China, 8200 from the former USSR, 2100 from the United States, and <900 from Japan) (IPCS, 2001).

From 2001 to 2005, estimated vanadium production (in metric tons) was reported in Australia (100-3060); China (12,000-17,000); Kazakhstan (1000); Russia (5,800-15,100); and South Africa (18,184-27,172).  Japan reported production from petroleum residues and ash spent catalysts ranging from 499-560 metric tons.  The U.S. imported a total of 1,230,000 kg of vanadium-bearing ash, residues, and slags in 2004 and 10,500,00 kg in 2005.  Other imports in 2002-2006 included vanadium pentoxide anhydride (406-2370 metric tons) and other vanadium oxides and hydroxides ranging from 66 to 231 metric tons (Magyar, 2007).

## 5.0 Uses
The hard metals industry uses vanadium carbide in the production of tungsten carbide tool bits.  In the United Kingdom, vanadium is used in some ferrovanadium alloys during the refining stage of steelmaking.  Vanadium pentoxide is used as a catalyst for various gas-phase oxidation processes, in pigments, inks, and as a coloring agent that provides ultraviolet filtering properties in some glasses (IPCS, 2001).  Vanadium also is used in the production of ferrovanadium, vanadium pentoxide, vanadium metal, and vanadium-bearing chemicals or specialty alloys from processing materials such as petroleum residues, spent catalysts, utility ash, and vanadium-bearing pig iron slag.  It is used as an alloying agent for iron and steel and as catalyst for the production of maleic anhydride and sulfuric acid.  Small amounts of pure vanadium are also used in research (Magyar, 2007).  Vanadium is used as a constituent in several pills and other dietary supplements to enhance strength and prevent diabetes (NRC, 2005).  Pentavalent vanadium ions in drinking water purportedly improve sugar, nitrogen and lipid metabolism and thereby decrease blood glucose and lipid levels, avert obesity, increase insulin resistance, ease gout symptoms, increase motor functions, and/or hasten sweating and urination (Aoki and So, 2005 pat.).

Dietary/Therapeutic Applications
Vanadium has been reported to have a number of beneficial effects as a dietary supplement.  Although some dietary supplements recommend it for building muscle strength, vanadium compounds have not been shown to be effective for this purpose (Fawcett et al., 1996; cited by IPCS, 2001).  Use as a therapeutic agent, including applications for cancer treatment and treatment for osteoporosis or osteopenia also has been reported (Evangelou, 2002; Hulley et al.,

2002).  One recent opinion however stated that:  "...since many toxic metals also accumulate in the bones without strengthening them, this doesn't prove that vanadium is good for bones" (EBSCO, 2007).

The best documented application of vanadium is use as an insulin mimetic.  A large portion of the studies of V(IV) and V(V) in the literature pertain to the antidiabetic action and related activity of different vanadyl inorganic salts and complexes with organic ligands, of inorganic vanadates, and of vanadate compounds, usually with ester-like linkages to organic moieties (e.g., see publications listed by Willsky and Crans).  Antidiabetic arylalkylamine vanadium salts also have been tested in diabetic rats (García-Vicente et al., 2007).  Several reviews related to this application are available (e.g., human studies: Balasubramanyam and Mohan, 2001; and Gutierrez, 2002; comparison of bioavailability and lability: Sakurai et al., 2003; and chemistry and biochemistry of organic complexes: Sakurai et al., 2006; Srivastava and Mehdi, 2005; Yeh et al., 2003).  Although "preliminary studies involving humans have been conducted, with mostly promising results [6 citations]…no meaningful double-blind placebo-controlled studies on vanadium as a treatment for diabetes have yet been reported" (EBSCO, 2007 [based on data reviewed through 2003]).

Vanadyl compounds have been shown to completely or partially correct several conditions associated with induced diabetic states in rats, including hyperglycemia, polydipsia, polyphagia, and high cholesterol and triglyceride levels.  Results from a number of *in vitro* and *in vivo* toxicity studies on the insulin-mimetic and anticarcinogenic activity of various vanadium compounds were tabulated in a review by Scior et al. (2005).  The authors noted that both V(IV) and V(V) complexes with ligands having O and/or N donor atoms were less toxic than those with one or two S donor atoms.  The nonspecific inhibition of protein tyrosine phosphatase family enzymes (PTPs) by vanadium compounds may result in negative as well as positive effects on the action of insulin.  PTPs are signaling enzymes involved in many cell functions such as growth, mitogenesis, motility, cell-cell interactions, metabolism, gene transcription, and the immune response.  Vanadium mediated enzyme actions that may influence cell signaling include:
- Direct activation of tyrosine kinases
- Inhibition of glucose-6-phosphatase
- Inhibition of protein degradation
- Alteration of phosphoinositide metabolism
- Binding to ADP, GDP, and NADH

Intracellular vanadyl compounds were weaker inhibitors than vanadate.  The only effective insulin-mimetic V(V) organic compound was dipicolinato[di]oxovanadium(V) (Scior et al., 2005).

## 6.0     Environmental Occurrence and Persistence

Vanadium occurs in ~60 known vanadium-containing minerals as sulfide or oxidized forms, only four of which–vanadinite, roscoelite, patronite, and the uranium ore carnotite–are used as commercial sources of vanadium (Anke, 2004).  Erosion of rocks and soil release natural vanadium generally through oxidation of V(III) in mineral particles to more soluble V(V) species (ATSDR, 1992).  Vanadium pentoxide is found in fuel oils, solid residues, soot, boiler scale, and fly ash when fuel oils in boilers and furnaces are burned.  The vanadium content of the residues

ranged from <1 to 60%.  An estimated 90% of the ~64,000 tonnes of vanadium released into the atmosphere each year from both natural and anthropogenic sources comes from oil and coal combustion.  Natural and anthropogenic vanadium is released to the atmosphere primarily as simple or complexed vanadium oxides and some sulfates (IPCS, 2001).
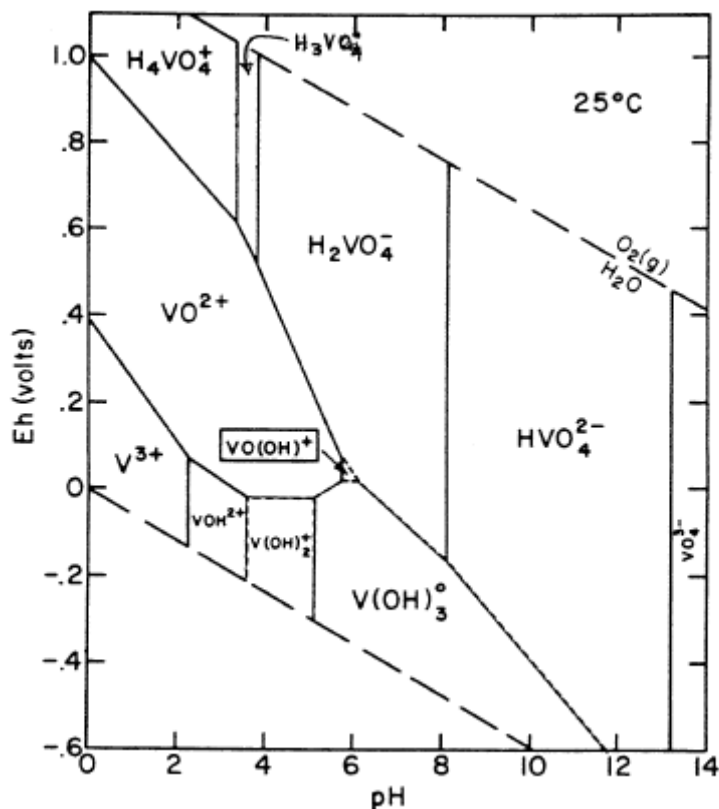
Worldwide atmospheric emission (~8.4 tonnes/annum; range: 1.5-49.2 tonnes) from natural sources (continental dust, volcanoes, sea salt spray, forest fires, and biogenic processes) also contributes to vanadate in the soil and water.  Surface fresh water contains <3 µg vanadium/L with levels of up to around 70 µg/L in areas with high geochemical sources.  Vanadium in water from the Colorado River basin ranged 0.2-49.2 µg/L; the highest levels were attributed to uranium-vanadium mining.  A broader survey reported 2.0-9.0 µg/L vanadium levels in Wyoming, Idaho, Utah, and Colorado.  Unfiltered water from the Yangtze River in China was reported to contain between 0.24 and 64.5 µg/L; filtered water ranged from 0.02-0.46 µg/L.  The highest levels in surface waters reported in two springs (14.8 and 16.4 µg/L) and five river samples (range 17.7-48.8 µg/L) were in the Mount Fuji area in Japan.  Seawater levels in the open ocean ranged 1-3 µg/L; highest level at 7.1 µg/L.  Sediment levels ranged 20-200 µg/g dry weight with coastal sediments showing higher concentrations.  Vanadium levels in the United States ranged from <7 to 500 mg/kg; median around 60 mg/kg and 90th percentile at 130 mg/kg.  Average worldwide soil levels were reported at ~100 mg/kg (IPCS, 2001).

Vanadium plant concentrations vary depending on the content of vanadium in the environment.  For example, crops grown on alluvial, riverside soils have ~60% of the vanadium content of crops grown on loess soils (Anke, 2004).

Environmental Speciation
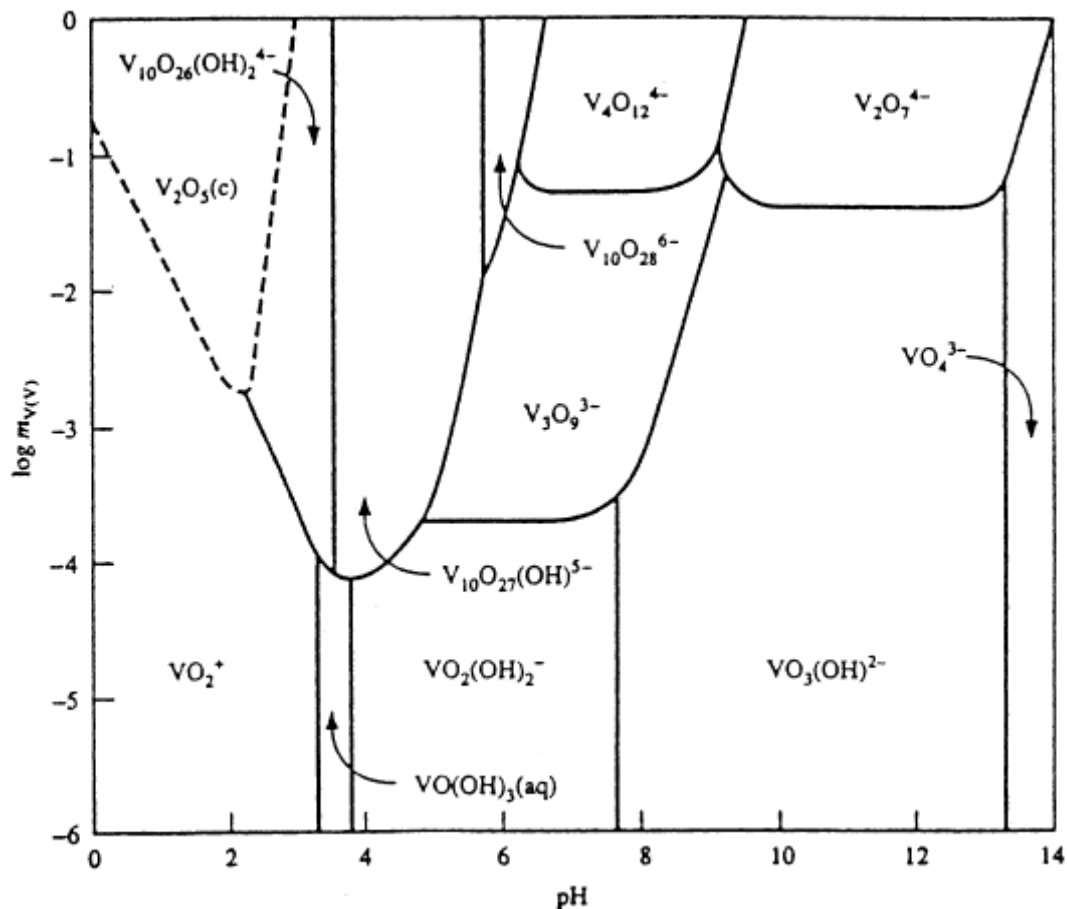Two comprehensive descriptions of vanadium speciation in aqueous media augment their descriptions with numerous speciation diagrams and equilibrium equations (Baes and Mesmer, 1976; Langmuir et al., 2003 draft).  **Figure 1** is a Pourbaix diagram showing the hydrolyzed and unhydrolyzed vanadium species in valences from V(II) through V(V) at different oxidation potential (Eh) and pH.

**Figure 1.** Eh-pH diagram for the system V-$O_2$-$H_2O$, for total dissolved vanadium <0.0001 mol/kg (11.5 mg/L as orthovanadate).  Source:  Langmuir et al. (2003 draft)

In **Figure 2** below, which depicts speciation of V(III)-V(V) at different vanadium concentrations and pH, the dashed lines represent $V_2O_5$ solubility in terms of V(V) concentration.  [Note: $VO_3(OH)^{2-}$ is also represented as $HVO_4^{2-}$ and $VO_2(OH)_2^-$ is also represented as $H_2VO_4^-$ by other authors.]  Except for toxicity studies and perhaps specific intracellular compartments having nonneutral pH, most aqueous V(V) solutions are dilute (<2 x $10^{-5}$ $m$) and only mononuclear (monomeric) species are expected:  $VO_2^+$, $VO(OH)_3$ (aq.), $VO_2(OH)_2^-$, $VO_3(OH)^{2-}$, and $VO_4^{3-}$, depending on pH.  At pH ~2 to ~6 and V(V) concentrations higher than 0.0001 $m$, decavanadates may be present.  These species are $V_{10}O_{26}(OH)_2^{4-}$, $V_{10}O_{27}(OH)^{5-}$, and $V_{10}O_{28}^{6-}$.  From pH 6 to 9, metavanadates, $(VO_3)_x^{x-}$, form slowly at 25 ˚C from depolymerization of decavanadates.  Species formed include trimer, $V_3O_9^{3-}$; tetramer, $V_4O_{12}^{4-}$, and hydrolyzed $VO_3^-$, $V_2O(OH)_2^-$ ($H_2VO_4^-$).  In the pyrovanadate region (pH 9 to 12) at higher V(V) concentrations, the predominant species is $V_2O_7^{4-}$ with $V_2O_6(OH)^{3-}$ and $OH^-$ in equilibrium with $VO_3(OH)^{2-}$ ($HVO_4^{2-}$).  The orthovanadate species, $VO_4^{3-}$, exists in aqueous solution above pH 13 (Baes and Mesmer, 1976).

**Figure 2.** Predominance diagram for V(V)-OH⁻ species at varying aqueous V(V) concentrations and pH at 1 *m* (1 molal) solution ionic strength and 25 ˚C (Weckhuysen and Keller, 2003; Note: erroneously called a Pourbaix diagram [potential vs. pH] in publication).

Most aqueous V(V) solutions in the environment are dilute and only mononuclear species are expected (e.g., $VO_2^+$). In aerobic natural waters and soils, vanadium occurs most often as vanadates. Reduced forms of vanadium in natural waters and mineral systems are $VO_2^+$, the vanadyl ion, and uncharged $V(OH)_3$ (Langmuir et al., 2003 draft). Approximately 87% of the total vanadium present (both V(V) and V(IV)) are strongly bound by complexation or adsorption to mineral and biogenic compounds that are present (ATSDR, 1992).

Groundwater that is a source of drinking water in the Mount Etna region of Sicily, Italy had mean vanadium concentrations of 165 μg/L as compared to vanadium concentrations in bottled spring water from Switzerland which ranged from 4-290 μg/L. Although V(IV) was the predominated species (90-100%) in the groundwater, sodium hypochlorite disinfection increased the fraction of V(V) to nearly 20%. Different residence times and the distribution systems did not alter the original V(IV):V(V) ratio of the finished drinking waters (Veschetti et al., 2007).

The vanadium particulates in surface waters may adsorb to hydroxides or be associated with organic compounds, being eventually deposited on the sea bed. Redox potential, pH, the presence of particulates, and other factors govern the transport, partitioning, valence, and

hydrolysis in surface waters, soils, and sediments. The vanadates $H_2VO_4^-$ and $HVO_4^{2-}$ and particulate-adsorbed V(V) predominate in oxidizing conditions, and $VO^{2+}$ and $VO(OH)^+$ predominate under reducing conditions. [Uncomplexed $VO^{2+}$ is stable only at $\leq$ pH 2, being gradually oxidized at pH 5 to 6 and rapidly oxidized to V(V) in air at pH $\geq$9 (Hu and Coetzee, 2007).] Only about 0.001% of vanadium remains soluble in seawater. Seawater-soluble species are most likely $H_2V_4O_{13}^{4-}$, $HVO_4^{2-}$, and $VO_3^-$. Adsorption to seabed sediments is largely to manganese and iron hydrous oxides and organic matter. During sedimentation in soils, vanadium is largely associated with ferric hydroxides and solid bitumens. Vanadates are somewhat mobile in oxidizing conditions in neutral and alkaline soils while the less soluble V(III) and V(IV) species exist under reducing conditions and/or acidic soils. Humic acids will convert the mobile metavanadate ions to immobile vanadyl ions. The metavanadates may be held in anion-exchange positions in clays (ATSDR, 1992).

Analytical methods using various chromatographic and ion-exchange columns and chelating agents to determine both V(IV) and V(V) species in environmental and biological samples (not further speciated beyond the valence state) were reviewed recently (e.g., Hu and Coetzee, 2007).

## 7.0    Human Exposure
Only sources and pathways relevant to oral exposures are presented in this section. More complete human exposure information can be found in ATSDR (1992) and IPCS (2001).

Food: The average dietary intake of vanadium in the general population (adults) was estimated to be 11-30 µg/day by the IPCS (2001) and 10-60 µg/day by the NRC (2005). Vanadium in the vanadyl form is present in food at <1 ng/g. However, some foods such as black pepper, mushrooms, parsley, dill seed, shellfish and some prepared foods have high vanadium content (0.05-2 µg/g). Dairy products, meat, seafood, and whole grains can contain 5-30 ng/g. Vanadium measured in diets from five regions of the United States ranged from $30.9 \pm 1.5$ µg/kg dry weight in the southeast region to $50.5 \pm 1.5$ µg/kg dry weight in the western region (Harland and Harden-Williams, 1994). Tissue levels of vanadium in muscle, kidney, liver and milk from cattle farmed near a vanadium processing plant and slaughtered over a 5 year period were <0.05-11.51 mg/kg (wet-mass basis); potential daily vanadium intake from milk was >0.44 µg/kg/day for adults (Gummow et al., 2005). The recommended tolerable upper intake level (maximum daily nutrient intake that is likely to pose no risk of adverse effects) is 1.8 mg/day for males and females age 19 to >70 years (Trumbo et al., 2001).

Human infants (<1 year old) have been shown to have several-fold higher concentrations of vanadium in their kidneys, prostate glands, and ribs than older children and adults (Anke, 2004). The higher concentration is apparently not correlated to vanadium concentrations in infant formula or breast milk. Vanadium concentrations of 0.1-0.2 ng/g and 34 µg/L have been reported in human milk (Anke, 2004; WHO, 2000). Vanadium concentration of 9.1 µg/L has been reported in infant formula (Anke, 2004). Vanadium (no levels specified) was found to be one of several elements present in four infant foods marketed in Nigeria (Jonah et al., 2003).

Limited effort was expended searching for vanadium speciation in foods. The distributions of vanadium and other metals among cytosolic ligands of the mussel (*Mytilus edulis*) were reported recently (Ferrarello et al., 2000). Vanadyl porphyrins also were identified in mussel tissues

(Rivaro and Frache, 1997). Plants growing in soils contaminated with vanadium mining wastes in South Africa contained up to 24.3 μg V(V)/g while total vanadium was found at up to 350 μg/g (Mandiwana and Panichev, 2006; Panichev et al., 2006).

Drinking Water: Vanadium levels up to 100 μg/L in drinking water have been reported. The average content in drinking water in Cleveland, Ohio, was 5 μg/L with a maximum level of 100 μg/L. Wells near a vanadium slag processing plant in the Czech Republic had vanadium levels of 0.01-0.44 μg/L (the local municipal supply reported a concentration of 0.01 μg/L). The vanadium concentration in samples of drinking water from Kanagawa Prefecture in Japan was 22.6 μg/L (IPCS, 2001).

Vanadium intake from drinking water ranged from negligible to 140 μg/day with a mean of 8 μg/day and in some areas was the greatest contributor to daily vanadium intake. In the older literature, a median of <4.3 μg/L was reported for U.S. Public Water Supplies, a mean of 1-6 μg/L was reported for municipal water supplies, and a mean of 19 μg/L was reported for drinking water from nine New Mexico municipalities (Irwin et al., 1997).

The National Tap Water Quality Database, reporting on 927 U.S. communities that served vanadium-contaminated water, noted that most suppliers do not report testing for vanadium; between 1998 and 2003, only 1,610 of 39,751 water suppliers tested for vanadium. In California, 926 water suppliers, serving nearly 41 million customers, distributed vanadium-contaminated water. Average vanadium concentrations for the nine most highly vanadium-contaminated California systems serving 15,357 customers ranged from 50.6-90 μg/L. In New Mexico, drinking water from one system serving 56,000 customers contained 83 μg V/L (EWG, 2007).

Dietary supplements: Vanadium is present in many dietary supplements, including multicomponent vitamin and mineral supplement formulations and products marketed for weight control, bodybuilding, and diabetes control. The National Library of Medicine's Dietary Supplements Label Database (http://dietarysupplements.nlm.nih.gov/dietary/) lists >50 multicomponent products containing vanadium from dozens of manufacturers or distributors. Most of these products contain low concentrations (1-10 μg) of vanadium, often as a vanadium amino acid chelate (undefined), while products with higher concentration usually contain vanadyl sulfate (up to 12.5 mg/tablet or capsule). Stand-alone vanadyl sulfate dietary supplements products containing up to 20 mg/tablet or capsule are widely available on the internet and in retail outlets.

## 8.0   Regulatory Status

The OSHA permissible exposure limit of vanadium fume is 0.1 mg $V_2O_5/m^3$, and the NIOSH recommended exposure limit is 0.05 mg $V/m^3$ (15-minute) (NIOSH, 2007). Vanadium was listed in the first U.S. EPA Drinking Water Contaminant Candidate List (CCL) in 1998. Since then, the EPA has found that there is insufficient information to support a regulatory determination for vanadium; research is needed on the neurotoxicity and toxicokinetics of vanadium exposure by inhalation and oral routes and to identify appropriate treatment technologies (U.S. EPA, 2002b [40CFR141, 67FR38222 6/3/02]). As of 2005, vanadium was still listed in the second CCL (i.e., final CCL2) (U.S. EPA, 2005 [40CFR141, 70FR9071

2/24/05]).  The U.S. EPA provides an oral RfD for vanadium pentoxide of 9 μg/kg/day (U.S. EPA, 2002a [IRIS]).

A Preliminary Remediation Goal of 260 μg/L for tap water was set by the U.S. EPA; the Virginia Department of Environmental Quality set an alternate level for groundwater of 110 μg/L, and Arizona has a drinking water guideline of 7 μg/L (Irwin et al., 1997).  The California Department of Public Health (CDPH) briefly required monitoring of vanadium in community drinking water systems (four quarterly samples for surface waters and two for groundwater at least 5-7 months apart).  Monitoring was to be completed by December 31, 2003 (CDPH, 2001). Vanadium was detected in 5,483 samples taken 2000 through 2004, reflecting its natural occurrence.  Only 146 samples from 16 counties were above the 0.05 mg/L notification level (NL) for vanadium (2.7% frequency).  In most of these 16 counties, the frequency of occurrence greater than the NL was ≤7.7%, with frequencies of 20% and 25% for counties with 10 and four sources, respectively (CDPH, 2005).  The NLs are health-based advisory levels for chemicals lacking U.S. EPA-promulgated maximum contaminant levels.  The response level (concentration at which CDPH will recommend removal of the drinking water source from service) for vanadium is 10 times the NL.  Several kinds of public notice are recommended when water is served above the response level, including monthly sampling and analysis so long as the contaminant exceeds its response level.  After the level drops below the response level, the CDPH recommends quarterly sampling for 12 months thereafter (CDPH, 2007a).  The vanadium detection limit for purposes of reporting (DLR) was 3 μg/L.  Only one of the unregulated chemicals monitored had a DLR of 0.005 μg/L, which was considered the minimum for data with nondetects to provide meaningful information for standard setting.  The all-facility monitoring regulations were repealed effective October 18, 2007 (CDPH, 2007b).

Vanadium pentoxide (orthorhombic crystalline form) is listed as a carcinogen by the Office of Environmental Health Hazard Assessment of the California EPA for the purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code section 25249.5 et seq., Proposition 65) effective February 11, 2005 (OEHHA, 2005).

## 9.0    Toxicological Data
## 9.1    General Toxicology
In general, vanadium toxicity is fairly low via ingestion, moderate via inhalation, and high via injection (EVM, 2002; NRC, 2005).  Toxicity increases with increasing valence; thus, vanadate ($V^{+5}$) is more toxic than vanadyl ($V^{+4}$) (EVM, 2002; IPCS, 2001; NRC, 2005).  When rats were exposed via inhalation, vanadium was found to accumulate in the lungs.  Intratracheal studies in animals showed that vanadium (as tetravalent or pentavalent compounds) was significantly absorbed from the lungs, while oral studies showed vanadium compounds to be poorly absorbed from the gastrointestinal tract (~3% of the administered dose) (IPCS, 2001).

The following sections summarize toxicological data related to oral exposures to vanadium and its tetravalent and pentavalent forms.  Data from studies where vanadium or vanadium compounds were administered by other routes are presented only where particularly relevant.  A more thorough discussion of the toxicology of vanadium compounds can be found in ATSDR (1992), IARC (2006), and IPCS (2001).

### 9.1.1 Human Data

When volunteers were given ammonium vanadyl tartrate (50-125 mg) daily (exposure period not provided), poor absorption from the gastrointestinal (GI) tract was observed; <1% of the dose was eliminated in the urine within the 24 hours after administration (Dimond et al., 1963; cited by IPCS, 2001). In a study using diammonium oxytatrateovanadate (100 mg V) [see section below for further study details presented by IPCS], 0.1-1.0% of the administered dose was absorbed from the GI tract and 60% excreted in urine within 24 hours (Curran et al., 1959; cited by EVM, 2002). Analytical methods indicate that normal serum concentrations of vanadium in unexposed human populations were <1–2 μg/L. Approximately 90% of the vanadium transported in the plasma was bond by transferrin. The mean serum concentration of vanadium in patients with kidney failure and on dialysis was high (24±11 μg /L), likely from the transfer of vanadium from the purified water used for the dialysate into the blood. No deleterious effects were reported for these concentrations (Barceloux, 1999).

Short-term and subchronic toxicity studies have been conducted with both tetravalent and pentavalent vanadium compounds. When 12 volunteers were given diammonium vanadotartrate (75 mg/day for two weeks and then 125 mg/day for the next 5.5 months), five reported experiencing upper abdominal pain, anorexia, nausea, and weight loss; these were reversible when treatment was reduced or ended. Serum cholesterol levels remained unchanged (Somerville and Davies, 1962; cited by IPCS, 2001). When six volunteers were given ammonium vanadyl tartrate (50-125 mg/day) for 45-90 days, no toxicity was reported; measurements on hematological or biochemical measurements were conducted (Dimond et al., 1963; cited by IPCS, 2001). Weight-training athletes (11 males, 4 females) administered vanadyl sulfate (0.5 mg/kg body weight [bw]/day for 12 weeks) also exhibited no toxic signs; measurements included body weight, blood pressure, and standard hematological and blood biochemistry measurements (Fawcett et al., 1996, 1997; cited by IPCS, 2001). When seven volunteers (5 male, 2 female) were given vanadyl sulfate (100 mg initial dose followed by 50 mg doses twice daily for 6 days), no effect was found in fasting plasma glucose and insulin concentrations (Jentjens and Jeukendrup, 2002).

Five male volunteers receiving an oral administration of diammonium oxytartratovandate (100 or 125 mg/day [~1.7 mg/kg bw/day, assuming a bw of 70 kg]) for six weeks exhibited no toxic signs or symptoms. Analysis included blood counts, urine, blood urea nitrogen, blood glucose, serum cholesterol esters, serum alkaline phosphatase, serum transaminase, and serum bilirubin (Curran et al., 1959; cited by IPCS, 2001).

### 9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

Neither the state of oxidation nor of complexation is predictive of vanadium tissue uptake or the effect on other trace metal concentrations in the tissue. Accumulation of vanadium (unspeciated) in bone, liver and kidney of rats that received vanadyl sulfate, vanadyl bis(acetylacetonate) (BMOV), or ammonium metavanadate in drinking water (100 or 250 mM for 12 weeks) was greatest for BMOV and ammonium metavanadate than for vanadyl sulfate. The difference in uptake is likely due to the more rapid excretion of vanadyl sulfate. (None of the vanadium treatments significantly affected V, Fe, Cu, or Zn concentrations in muscle tissue.) Both of the vanadyl compounds significantly decreased $Zn^{2+}$ concentrations in kidney tissue but

metavanadate did not, which suggests that V(IV) compounds may remain unchanged long enough to compete with 2+-cations before intracellular incorporation (Thompson et al., 2002).

In oral studies in rats, absorption of vanadium from the GI tract was reported as ~3% of the administered dose (IPCS, 2001). Values as low as ≤1% and >10% have been reported (NRC, 2005). For instance, 40% of an administered dose of sodium metavanadate (5 or 25 ppm) in the diet of rats was retained, while 59% was excreted in the feces (Bodgen et al., 1982; cited by EVM, 2002). Most ingested vanadium is typically converted to vanadyl in the stomach of nonruminants. Interestingly, studies indicate that unmetabolized vanadate, was absorbed in the GI tract three to five times more efficiently than vanadyl (NRC, 2005). In plasma and body fluids, vanadium is converted to vanadyl as vanadyl-transferrin and vanadyl-ferriting complexes (EVM, 2002). Excretion of absorbed vanadium is primarily via urine. It is a fast process, with 40-60% of an administered dose removed in one to three days; a half-time of 12 days was reported in rats given vanadyl sulfate in drinking water. Unabsorbed vanadium was mainly eliminated in feces (EVM, 2002; IPCS, 2001).

Absorbed vanadium (tetravalent and pentavalent forms) is distributed mainly to the bone (10-25% of the administered dose after 3 days), followed by the liver (~5%), kidney (~4%), and the spleen (~0.1%); small amounts also have been detected in the testes (~0.2%) (IPCS, 2001]). In general, vanadium levels in tissues increase with increasing dose (NRC, 2005). In pregnant mice fed vanadyl sulfate pentahydrate (37.5, 75, and 150 mg/kg bw) daily on gestation days 6-15, the increases in concentrations were seen in the liver (1.59 mg/kg wet weight [ww] at the high dose vs. 0.48 mg/kg ww at the low dose), kidney (1.91 vs. 0.49 mg/kg ww), spleen (2.37 vs. 0.70 mg/kg ww), whole fetus, and placenta (Paternain et al., 1990; cited by EVM, 2002, and NRC, 2005). [Noted: The study showed that tetravalent could cross the placental-fetal barrier (IPCS, 2001).] In rats, administration of sodium vanadate (1.71, 3.42, and 6.84 mg/kg bw) daily for eight weeks also showed the linear relationship in several organs, including bone (2.85 mg/kg ww at the high dose vs. 0.54 mg/kg ww at the low dose), liver (0.39 vs. 0.08 mg/kg ww), kidney (1.38 vs. 0.41 mg/kg ww), muscle (0.20 vs. 0.04 mg/kg ww), and spleen (2.53 vs. 0.92 mg/kg ww) (Sanchez et al., 1998; cited by NRC, 2005). [See Tables 30-2 and 30-2 in NRC (2005) for additional studies.] Studies by Delbono and colleagues (2003) in pigs given feed with varying concentrations of vanadium oxide (doses not provided) led to increased levels of vanadium in the liver, spleen, and kidneys compared to control animals.

Experimental results from *in vitro* studies published in 1996 suggested that intracellular reduction of V(V) to V(IV) may not be rapid and that V(IV) may be re-oxidized spontaneously inside the cell at pH 7.4 and 37 °C. For example, vanadyl added to rat adipocytes or to a cell-free system was 45- to 100-fold more potent than vanadate in activating cytosolic protein-tyrosine kinase (CytPTK) after a 20-minute incubation. The study also showed that reduced glutathione was a poor reducing agent for V(V) [contrary to accepted "dogma"] and that organically complexed BMOV was a better insulin mimic in stimulating lipogenesis in rat adipocytes than vanadyl sulfate because of greater resistance to intracellular oxidation and hydrolysis (Li et al., 1996 [co-authors included D.C. Crans]).

Earlier *in vitro* experiments indicated that interconversion between oxidation states of vanadium was rapid relative to the residence time of vanadium in the blood stream. Results from

incubating a 50% human erythrocyte suspension with 1.3 mM sodium metavanadate at 37 °C, showed ~70% of the vanadate that had entered the cells after one-hour had been reduced to vanadyl complexes, primarily with hemoglobin. The total intracellular vanadium concentration, as determined by EPR, was 1.14 mM and the vanadyl concentration was 0.8 mM (Cantley and Aisen, 1979). Other studies reported that vanadate was rapidly acquired by adipocytes and yeast cells and reduced to V(IV) (Chasteen et al., 1986). Vanadate added to fresh serum was quantitatively reduced to vanadyl by the reducing substances present in the serum. Albumin and transferrin complexes that were formed were subject to air oxidation. Half-lives for the reduction and oxidation reactions at pH 7.5 were in the range 5-30 minutes, suggesting that vanadium in the bloodstream is present in both oxidation states (Chasteen et al., 1986).

***In Vivo* Speciation:** Although the comment that vanadium valence "interconversion *in vivo* is common" was made in a recent review without attribution (Thompson et al., 2002) and redox cycling is occasionally mentioned in the vanadium biological literature, evidence for the extent of interconversion is less readily found. Evangelou (2002) summarized (with appropriate attributions) the Fenton-like and other reactions proposed to accompany redox cycling of V(IV) and V(V) with formation of superoxide anion radical, hydroxyl free radicals, and possibly peroxovanadyl and vanadyl hydroperoxide. Other researchers have proposed variations on the reactions accompanying vanadium redox cycling (e.g., Byczkowski et al., 1988; Ramasarma, 2003). The Fenton-like reaction is especially favored in cancer cells due to their constant production of hydrogen peroxide and low pH. [Hydrogen peroxide and superoxide anion are generated in mitochondria as a consequence of aerobic respiration and are reduced by glutathione (Fernández-Checa et al., 1998).] A proposed mechanism for the lung toxicity of vanadium pentoxide given to rats intratracheally involved one-electron redox cycling of V(V) in the presence of NAD(P)H with reoxidation of V(IV) initiating lipid peroxidation under aerobic conditions (Zychlinski et al., 1991; cited by NTP, 2002; Toya et al., 2001 [who proposed an alternative mechanism involving generation of reactive oxygen species accompanying acute inflammatory lung injury]).

The following discussion of vanadium speciation *in vivo* is not a comprehensive review but rather presents an overview of *in vivo* speciation. An expert review on many vanadium speciation and biological topics is available from Crans (2005). Studies of vanadium speciation usually include one or more of the following determinations:
- Valence changes - most frequently summarized as extracellular V(V) and intracellular V(IV) (e.g., Nechay et al., 1986). V(III) species also were reported in acidic blood cells of *Ascidians* (sea squirts) (Michibata et al., 2002).
- Complexes of V(V) (Gorzsás, 2005 diss.; Gorzsás et al., 2006; Shrivastava et al., 2007)
- Complexes of V(IV) (Setyawati et al., 1998)
- Complexes with ligands in blood and various tissues (no valence identifications or molecular formulas) (De Cremer et al., 2002)
- Protein complexes in human and bovine blood (Wang et al., 1999)
- Lability (metabolism) of xenobiotic ligand complexes such as V(V) with maltol or picolinic acid (e.g., Gorzsás, 2005 diss.; Gorzsás et al., 2006)
- Rates of formation and dissociation (oligomers, complexes, redox reaction products) (e.g., Yokel et al., 2006).
- Oligomerization (See below)

**Speciation in Blood:** A model of the distribution of V(V) (1 μM V) in human blood was constructed based on studies of various serum constituents at physiological concentrations [Note: Source, purity, preparation, and identity of the metavanadate salt were not given; formation of V(IV) species was neglected.] Transferrin (37 μM) was predicted to be the major carrier of V(V) according to findings from other studies. It was also noted that V(IV) bound more strongly to transferrin than V(V) (Gorzsás, 2005 diss.; Gorzsás et al., 2006). The intracellular neutral pH and binding of vanadyl to chemicals such as ATP, ADP, AMP, inorganic phosphate, creatine phosphate, glutamic acid, aspartic acid, human serum albumin, glutathione, ascorbic acid, and citric acid protect it from reoxidation to vanadates (Nechay et al., 1986). Experiments in dogs indicated the interconversion of vanadate and vanadyl in the blood. Erythrocyte uptake of $^{48}$V labeled vanadate or vanadyl injected i.v. was initially greater for vanadate, but the rates equalized after five hours. Thirty hours after injection of either species, 77% of the plasma vanadium was bound to transferrin (Harris et al., 1984).

**Speciation in Tissues:** Complexes with both oxidized and reduced glutathione lead to reduction of vanadate to vanadyl. Inside the cell, vanadate is reduced to $VO^{2+}$ [V(IV)], the predominant intracellular species. The major V(V) complexes in serum and packed cells from rats injected with V(V) were transferrin and hemoglobin, respectively. Residual blood was stated to be inside the tissues, and ferritin, transferrin, and/or hemoglobin complexes were found in all tissues studied (kidney, spleen, liver and lung). Readily exchangeable vanadium species and an unidentified complex that was unique to the lung were also found. Total vanadium, but not speciation, was given for bone, heart, stomach, bladder, small intestine, and skin and hair (De Cremer et al., 2002). Reduced bioenergetic functions of liver mitochondria in rats dosed intratracheally with vanadium pentoxide was also reported. Accumulation of significant amounts of vanadate in the intermembrane space of liver mitochondria was proposed as an explanation for the observed effect (Zychlinski and Buczkowski, 1990).

Coordination of vanadyl with amino acids is dependent upon pH and concentration of the vanadium ion and occurs through the carboxylate oxygen (or with sulfur, if present) and nitrogen atoms. Vanadyl interacts in acid media with phosphate groups of nucleotides. At high pH, it interacts through deprotonated D-ribose hydroxyl groups. Most carbohydrates complex vanadyl (usually through the carboxyl group) and reduce vanadates. The best detoxification agent for vanadate poisoning may be L-ascorbic acid, which will both reduce and complex the vanadium species (Baran, 2003).

**Oligomers:** Some of the toxic activities ascribed to vanadate monomer may be due to certain oligomers (e.g., Crans and Schelble, 1990; Crans and Simone, 1991). Decavanadate for example was the most toxic oligomer tested, usually in fish species (e.g., Borges et al., 2003). *In vivo*, protein binding may prevent depolymerization of decavanadate to vanadate and reduction to vanadyl (Aureliano and Gândara, 2005). Inside the cell, vanadate reduction to vanadyl, the predominant intracellular species, is due to the cytosolic pH of 7.0-7.3. However, some subcellular environments (e.g., the lacunae of osteoclasts) are acidic. The luminal pH of different organelles also vary and are tightly controlled for optimal function of their resident enzymes [e.g., endosomes (pH 5-6), lysosomes (pH 4.5-5.5), phagolysosomes (~pH 5), secretory organelles (pH ≥5.5), and the Golgi apparatus (pH 6.17-6.5)]. Intracellular concentrations of

decavanadate, or vanadium species other than vanadyl, may therefore be formed and the toxicity of this oligomer is often overlooked in studies of vanadium (Aureliano and Gândara, 2005).

Oligomers were not expected to be found under normal physiological conditions. The toxicity of decavanadate has been compared to other vanadium species mainly in fish studies. One study reported differences in oxidative stress, lipid peroxidation, and intracellular accumulation of vanadate in toadfish given decavanadate or metavanadate i.v. [in hepatic tissue ~10% of the decavanadate was observed in the mitochondria and 10% in the cytosol; in cardiac tissue 20% was in the mitochondria and 20% in the cytosol] (Gândara et al., 2005). In isolated rat hepatocyte mitochondria, decavanadate was a much stronger depolarizer of mitochondrial membranes and inhibitor of mitochondrial oxygen consumption than metavanadate (Soares et al., 2007).

Depending on the total vanadium concentration, the ionic strength, and pH of an aqueous medium, mono- and oligovanadates are formed (Gorzsás, 2005 diss.). At physiological pH and concentrations <0.001 M, the monomeric species $H_2VO_4^-$ predominates. Complexation with ligands donating F, Cl, O, and N atoms prevents formation of polymeric solids from vanadyl ions at physiological pH (Scior et al., 2005).

*Other resources on this topic*:
- Speciation of V(IV) and V(V) in serum (Chasteen et al., 1986)
- "The emerging redox profile of vanadium" (Ramasarma, 2003)

### 9.1.3   Acute Exposure
Oral acute toxicity values for vanadium are presented in **Table 1**.

Tetravalent Vanadium Compounds
Mice and rats receiving vanadyl sulfate pentahydrate showed decreased locomotor activity, paralysis of the rear legs, high tolerance for pain, diarrhea, irregular respiration, increased cardiac rhythm, and/or increased ataxia; most disappeared by 48 hours post-treatment (Llobet and Domingo, 1984; cited by IPCS, 2001).

Pentavalent Vanadium Compounds
In mice, rats, and rabbits, orally exposed to vanadium pentoxide signs of acute toxicity included lethargy, lacrimation, and diarrhea; histologically, necrosis of liver cells and cloudy swelling of renal tubules were observed (Yao et al., 1986b; cited by IPCS, 2001). Coma was also reported in rats (ChemIDplus, undated). Mice and rats receiving aqueous sodium metavanadate exhibited the same effects as animals administered vanadyl sulfate pentahydrate [see above], but the toxic signs were more severe (Llobet and Domingo, 1984; cited by IPCS, 2001).

**Table 1. Oral Acute Toxicity Values for Vanadium**

| Compound | Species (sex and strain) | LD$_{50}$ | Reference(s) |
|---|---|---|---|
| V$^{+4}$ | mice (sex and strain n.p.) | 90.3 mg/kg bw (14 days) | (2) |
| V$^{+4}$ | rats (sex and strain n.p.) | 94.2 mg/kg bw (14 days) | (2) |
| V$^{+5}$ | mice (sex and strain n.p.) | 40 mg/kg bw (14 days) | (2) |
| V$^{+5}$ | rats (sex and strain n.p.) | 31.2 mg/kg bw (14 days) | (2) |
| NaVO$_3$ | mice (M, strain n.p.) | 74.6 mg/kg bw (14 days) | (2) |
| NaVO$_3$ | rats (M, strain n.p.) | 98 mg/kg bw (14 days) | (2) |
| VOSO$_4$·5H$_2$O | mice (sex and strain n.p.) | 467.2 mg/kg bw (14 days) | (2) |
| VOSO$_4$·5H$_2$O | rats (M, strain n.p.) | 448 mg/kg bw (14 days) | (2) |
| V$_2$O$_5$ [CASRN n.p.] | mice, albino (sex n.p.) | 23 mg/kg | (3) (4) |
| V$_2$O$_5$ [CASRN n.p.] | mice (sex and strain n.p.) | 64-117 mg/kg bw | (5) |
| V$_2$O$_5$ [CASRN n.p.] | rats (sex and strain n.p.) | 10 mg/kg bw | (3) |
| V$_2$O$_5$ [CASRN n.p.] | rats (sex and strain n.p.) | 86-137 mg/kg bw | (5) |
| V$_2$O$_5$ [CASRN n.p.] | rabbits (sex and strain n.p.) | 64 mg/kg bw | (5) |
| V$_2$O$_5$ [1314-62-1] | mouse (sex and strain n.p.) | 5 mg/kg | (1) |
| V$_2$O$_5$ [1314-62-1] | rat (sex and strain n.p.) | 10 mg/kg | (1) |
| NH$_4$VO$_3$ | mouse (sex and strain n.p.) | 25 mg/kg | (1) |
| NH$_4$VO$_3$ | rat (sex and strain n.p.) | 58.1 mg/kg | (1) |
| NH$_4$VO$_3$ | rat (sex and strain n.p.) | 18-160 mg/kg bw | (3) |

Abbreviations: bw = body weight; LD$_{50}$ = lethal dose for 50% of test animals; M = male(s); n.p. = not provided; NaVO$_3$ = sodium metavanadate; NH$_4$VO$_3$ = ammonium metavanadate; VOSO$_4$·5H$_2$O = vanadyl sulfate pentahydrate; V$_2$O$_5$ = vanadium pentoxide; V$^{+4}$ = vanadyl; V$^{+5}$ = vanadate
References: (1) ChemIDplus (undated); (2) Llobet and Domingo (1984; cited by IPCS, 2001, and NRC, 2005); (3) MAK (1992; cited by IPCS, 2001); (4) Roshchin et al. (1965; cited by EVM, 2002); (5) Yao et al. (1986b; cited by IPCS, 2001)

### 9.1.4 Short-term and Subchronic Exposure
Details of the following studies are presented in **Table 2**.

Tetravalent Vanadium Compounds
There is differing data on the impact of tetravalent vanadium compounds on body weight. While a shorter-length study (4 weeks) indicates that V(IV) compounds decrease body weight, longer-length studies (12 weeks) show no effect on body weight. Other than the development of diarrhea in some treated rats, no other evaluated physiological parameters appeared altered by administration of tetravalent vanadium compounds (Dai et al., 1995 [cited by IPCS, 2001, and NRC, 2005]; Majithiya et al., 2005).

**Table 2. Short-term and Subchronic Exposure to Vanadium (Oral Studies)**

| Species, Strain, and Age, Number, and Sex of Animals | Chemical Form | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| *Tetravalent Vanadium Compounds* | | | | |
| Rats, strain n.p., age n.p., 8M | $VOSO_4$ | oral; 7.64 mg V/kg bw/day in drinking water for 12 wk | No significant change in daily fluid intake or body weight was observed between treated and control rats. There was also no significant change in any hematological parameters—hematocrit, hemoglobin concentration, erythrocyte count, leukocyte count, platelet count, reticulocyte count, and erythrocyte osmotic fragility.<br><br>Noted: NRC states that there was a "significant decrease in daily fluid intake." | Dai et al. (1995; cited by IPCS, 2001, and NRC, 2005) |
| Rats, strain n.p., age n.p., 8M | bis(maltolato)oxo-vanadium | oral; 9.17 mg V/kg bw/day in drinking water for 12 wk | No significant change in daily fluid intake or body weight was observed between treated and control rats. There was also no significant change in any hematological parameters—hematocrit, hemoglobin concentration, erythrocyte count, leukocyte count, platelet count, reticulocyte count, and erythrocyte osmotic fragility.<br><br>Noted: NRC states that there was a "significant decrease in daily fluid intake." | Dai et al. (1995; cited by IPCS, 2001, and NRC, 2005) |
| Rats, Wistar, age n.p., 40M | $VOSO_4$ (16 animals) and bis[curcumino]oxovanadium (BCOV; 32 animals) | oral; 0.2 or 0.5 mmol/kg/day for 4 weeks for $VOSO_4$, 0.05, 0.1, or 0.2 mmol/kg/day for 4 wk for BCOV | Significant decrease in body weight was observed between vanadyl sulfate treated and control rats after 4 weeks of treatment. There was no change in body weights observed in BCOV treated animals, as compared to control. In the vanadyl sulfate-treated groups, diarrhea was observed, whereas no diarrhea was observed in BCOV treated animals. There was no significant effect on blood pressure or vascular reactivity to norepinephrine. | Majithiya et al. (2005) |
| *Pentavalent Vanadium Compounds* | | | | |
| Rats, strain, age, number and sex n.p. | $NaVO_3$ | oral; 1.5 mM in drinking water for 7 days | Decrease in body weight, food intake, and fluid intake observed. Activity of galactosyltranferase was decreased compared to control animals. Electron microscopy indicated ultrastructural changes (poorer state of mitochondrial membranes), greater number of vesicular structures, and less frequently seen Golgi structures. | Dabros et al. (2006) |

## Table 2.  Short-term and Subchronic Exposure to Vanadium (Oral Studies) (Continued)

| Species, Strain, and Age, Number, and Sex of Animals | Chemical Form | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| Rats, strain and age n.p., 10M | NaVO$_3$ | oral; 5, 10, and 50 mg/L (ppm) [2.09, 4.18, and 20.89 mg/kg V; 0.3, 0.6, 3 mg/kg bw/day, assuming 350-g bw and 20 mL/day water consumption] in drinking water for 3 mo | At the low and mid doses, no toxic effects were observed.<br><br>At the high dose, increases in plasma concentration of urea and uric acid were observed.<br><br>At all doses, no effects on weight gain, water consumption, urine volume, urinary protein levels, relative organ weights, or plasma creatinine concentrations were seen. Histologically, hypertrophy and hyperplasia in the white pulp of spleen, corticomedullary microhemorrhagic foci in kidneys, and mononuclear cell infiltration in lungs were reported. | Domingo et al. (1985; cited by IPCS, 2001, and NRC, 2005) |
| Rat, Wistar, 6-mo-old, 8F | NaVO$_3$ | oral; 3 mM in 0.09 M NaCl solution for 7 days | Decrease in body weight, food intake, and fluid intake observed.  Liver weight also was decreased.  Free blood sugar levels were not altered. | Kordowiak et al. (2005) |
| Rats, Sprague-Dawley, age n.p., 12M | NaVO$_3$ | gavage; 4, 8, and 16 mg/kg bw/day in water for 8 wk | At all doses, some changes in activity and learning were observed, such as decreased avoidance.  At the high dose, a decrease in body weight was also reported (20% lower vs. controls).  At the mid and high dose groups, a statistically significant decrease in total distance traveled in an open field activity was observed for the first 5 minutes of wk 3 post-treatment.<br><br>Note:  IPCS concludes that "it is impossible to draw any firm conclusions from this study."  [See document for reasons.] | Sanchez et al. (1998; cited by IPCS, 2001, and NRC, 2005) |
| Rat, Wistar, age n.p., number n.p., M | NaVO$_3$ | oral; 0.1 mg V/mL in drinking water for 6 wk | Statistically significant decrease in food and fluid intake, but no change in body weight observed.  Hematological studies demonstrated a statistically significant decrease in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration.  Slight decrease in the total antioxidant status of treated animals also was observed. | Scibior (2005) |
| Rat, Wistar, 2-mo-old, number n.p., M | NaVO$_3$ | oral; 0.1 mg V/mL in drinking water for 12 wk | Statistically significant decrease in fluid intake and body intake, as compared to control animals.  No change in food intake observed.  Statistically significant increase in malondialdehyde production was observed in spontaneous lipid peroxidation, as compared to control animals. | Scibior et al. (2006a) |

## Table 2.  Short-term and Subchronic Exposure to Vanadium (Oral Studies) (Continued)

| Species, Strain, and Age, Number, and Sex of Animals | Chemical Form | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| Rat, Wistar, 2-mo-old, number n.p., M | $NaVO_3$ | oral; 0.125 mg V/mL in drinking water for 6 wk | No changes in physical appearance or motor behavior were observed.  Decreases in food intake, fluid intake, and body weight observed, when compared to control animals.  Statistically significant decreases in red blood cell counts, hemoglobin concentration, mean corpuscular volume and mean corpuscular hemoglobin, and malondialdehyde concentrations observed.  A statistically significant decrease in the plasma L-ascorbic acid concentration was found. | Scibior et al. (2006b) |
| Rat, Wistar, 2-mo-old, number n.p., M | $NaVO_3$ | oral; 0.1 mg V/mL in drinking water for 12 wk | A significant increase in liver and kidney relative weight was noted.  Vanadium administration was associated with significantly decreased glutahione (GSH) content in the liver and kidneys and increased oxidized glutathione (GSSG) concentration in the liver. GSH/GSSG ratio in liver and kidney were decreased. | Scibior and Zaporowska (2007) |
| Rats, strain, age, number, and sex n.p. | $Na_3VO_4$ | oral; 2.76 mg/kg bw/day in drinking water for 77 days | No toxic effects were observed. | Roman et al. (1981; cited by NRC, 2005) |
| Rats, strain, age, number, and sex n.p. | $V_2O_5$ | oral; 0.509, 1.018, 5.09, 7.635, or 10.18 mg/kg bw/day in water and NaOH solution for 3 days | At the three lower doses, increases in phosphatase activity and in DNA content in wet bone were observed.  At 7.635 mg/kg, increases in calcium concentration in serum and in alkaline phosphatase activity were observed.  At the high dose, increases in calcium and phosphorus concentration in serum and in alkaline phosphatase activity and death were reported. | Yamagushi et al. (1989; cited by NRC, 2005) |
| Rats, strain n.p., age n.p., 8M | $NH_4VO_3$ | oral; 9.68 mg V/kg bw/day in drinking water for 12 wk | No significant change in daily fluid intake or body weight was observed between treated and control rats.  There was also no significant change in any hematological parameters —hematocrit, hemoglobin concentration, erythrocyte count, leukocyte count, platelet count, reticulocyte count, and erythrocyte osmotic fragility.  Noted:  NRC states that there was a "significant decrease in daily fluid intake." | Dai et al. (1995; cited by IPCS, 2001, and NRC, 2005) |
| Rats, strain n.p., 2-mo-old, 11M | $NH_4VO_3$ | oral; 19.7 mg/kg bw in drinking water for 4 wk | Decreases in average weight gain, fluid and feed intake, and erythrocyte and hemoglobin levels were observed. | Zaporowska and Wasilewski (1991; cited by NRC, 2005) |

**Table 2. Short-term and Subchronic Exposure to Vanadium (Oral Studies) (Continued)**

| Species, Strain, and Age, Number, and Sex of Animals | Chemical Form | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| Rats, strain n.p., 2-mo-old, 13M, 14F | $NH_4VO_3$ | oral; 19.7 or 25.8 mg/kg bw in drinking water for 4 wk in M and F, respectively | Decreases in average weight gain, fluid intake, erythrocyte levels, and hemoglobin levels were observed. Additionally, diarrhea, polychromatophilic erythroblasts, and death were reported. | Zaporowska and Wasilewski (1992; cited by NRC, 2005) |
| Rats, strain n.p., age n.p., 15-16, M and F | $NH_4VO_3$ | oral; 1.5 or 5-6 mg V/kg bw/day in drinking water for 4 wk | Compared to controls, body weight increase was lower. There was a slight but statistically significant decrease in erythrocyte number at all doses, in hemoglobin concentration at the high dose only, and in hematocrit in M only. Changes in external appearance, locomotor behavior, leukocyte numbers, or biochemical parameters were not observed. | Zaporowska et al. (1993; cited by IPCS, 2001) |

Abbreviations: bw = body weight; F = female(s); M = male(s); mo = month(s); n.p. = not provided; V = vanadium; wk = week(s)

Pentavalent Vanadium Compounds
Overall, studies indicated that short-term and subchronic exposure to pentavalent vanadium compounds decreases food intake, fluid intake and body weights. Most studies indicated that exposure to pentavalent vanadium compounds decreased levels of a variety of hematological markers measured (e.g., erythrocyte levels, hemoglobin levels). Histopathological studies reports indicate effects on spleen, kidneys, and lungs. Locomotor behavior appears to be altered at doses starting at 1.5 mg V/kg bw/day (administered in drinking water for 4 weeks) (Dabros et al., 2006; Dai et al., 1995 [cited by IPCS, 2001, and NRC, 2005]; Domingo et al., 1985 [cited by IPCS, 2001, and NRC, 2005]; Kordowiak et al., 2005; Roman et al., 1981 [cited by NRC, 2005]; Sanchez et al., 1998 [[cited by IPCS, 2001, and NRC, 2005]; Scibior, 2005; Scibior et al., 2006a,b; Scibior and Zaporowska, 2007; Yamagushi et al., 1989 [cited by NRC, 2005]; Zaporowska and Wasilewski, 1991, 1992 [both cited by NRC, 2005]; Zaporowska et al., 1993 [cited by IPCS, 2001]).

### 9.1.5  Chronic Exposure
Tetravalent Vanadium Compounds
When rats were given vanadyl sulfate (10.6, 16.9, or 28.1 mg/kg bw) in drinking water daily for up to one year, a decrease in the rate of weight gain was observed, which became more significant with increasing dose (Dai et al., 1994a; cited by NRC, 2005). This was part of a study investigating diabetes; 8-23 male Wistar rats were used and received ~34, 54, and 90 mg vanadyl sulfate/kg bw daily. At the low and mid doses, ~10% reduction was seen in body weight gain; at the high dose, ~33% reduction was reported (Dai and McNeill, 1994; Dai et al., 1994a,b [all cited by IPCS, 2001]).

### 9.1.6  Synergistic/Antagonistic Effects
In male rats, vanadium was reported to increase the weight-reducing effects of leptin (Wilsey et al., 2006). Treatment of rats with vanadium (in the form of ammonium vanadate) and $1\alpha,25$-dihydroxyvitamin $D_3$ offered protection against diethylnitrosamine (DEN)-induced rat liver carcinogenesis. Supplementation of both chemicals 4 weeks before DEN injection offered significant protection against generation of single-strand breaks when compared with control animals (Basak et al., 2000).

In other studies, other chemicals have reduced the toxicity of vanadium. For instance, vanadium-loaded rats (16 mg/kg bw orthovanadate daily for six weeks) were observed to avoid stimuli an open-field tests; injections of Tiron (sodium 4,5-dihydroxybenzmine-1,3-disulfonate) returned the animals to normal behavior (Sanchez et al., 1999; cited by NRC, 2005). In weanling rats, injections of zinc sulfate with vanadium protected against toxic effects on bone metabolism (Yamaguchi et al., 1989; cited by NRC, 2005). Several studies in hens showed that several compounds could reduce the toxicity of vanadium; for example, ascorbic acid in the diet inhibited decreases in interior egg quality resulting from dietary vanadium (NRC, 2005).

### 9.1.7  Cytotoxicity
No data were available.

### 9.2  Reproductive and Teratological Effects
Details of the following studies are presented in **Table 3**.

## Table 3. Reproductive Toxicity and Teratology of Vanadium (Oral Studies)

| Species, Strain, and Age, Number, and Sex of Animals | Chemical Form | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| *Tetravalent Vanadium Compounds* | | | | |
| Mice, Swiss, age n.p., 16-22 F/group | $VOSO_4 \cdot 5H_2O$ | gavage (water); 37.5, 75, and 170 mg/kg bw/day [7.55, 15.10, and 30.19 mg V/kg bw/day] on gestation days 6-15 | At the high dose, a dose-related decreased in body weight gain was observed (62% of controls). Significant reductions in final bw (81, 83, and 80% of controls, respectively, for the low, mid, and high doses), corrected bw (88, 84, and 83%), fetal bw (87, 87, and 79%), and fetal body length (97, 85, and 82%) were also seen.<br><br>At all doses, micrognathia was seen. At the two higher doses, an increased incidence of cleft palate and hydrocephaly were reported. Delayed ossification was seen in all dose groups and in controls. [Noted: These occurred with significant maternal toxicity.]<br><br>No changes in the mean numbers of total implants per dam, live/dead fetuses per dam, or late resorptions per dam were reported. However, there was an increase in the number of early resorptions per litter.<br><br>Decreased maternal absolute liver and kidney weights at 75 and 150 mg/kg bw/day also were observed. | Paternain et al., (1990; cited by EVM, 2002, IPCS, 2001, and NRC, 2005) |
| Rat, strain and age n.p., 10M | $VOSO_4$ | oral; 32 mg/kg/day and 50 mEq/L NaCl (vehicle) in drinking water for 1 month | Significant decrease in blood testosterone level and sperm count, 51% and 80%, respectively when compared to control group.<br><br>Sperm motility, shape, and testes and epididymides histology were not different from control group. | Dehghani et al. (2002) |

## Table 3. Reproductive Toxicity and Teratology of Vanadium (Oral Studies) (Continued)

| Species, Strain, and Age, Number, and Sex of Animals | Chemical Form | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| Rats, Wistar, "adult," 7M | $VOSO_4$ | oral; 100 mg/kg bw in distilled water for 60 days; sacrificed on day 61<br><br>mating with pro-estrus females done during last 5 days of treatment | A non-significant decline in body weight was observed. Relative weights of testes and accessory sex organs were slightly decreased (mg/100 g bw vs. controls [see paper for means ± SEM):<br><br>    testes: 1174 vs. 1435<br>    epididymides: 505 vs. 580<br>    seminal vesicle: 492 vs. 561<br>    ventral prostate: 246 vs. 302<br><br>Reductions were also seen in cauda epididymal sperm density (35 vs. 47 million/$mm^3$ controls) and motility (42 vs. 74%); fertility (50 vs. 100%); and litter size (5 vs. 8).<br><br>*Histological/histopathological examination of testes*: significant reduction in diameters of seminiferous tubules (232 vs. 270 μm) and Leydig cells nuclei (5.40 vs. 6.68 μm); exfoliation and degeneration of spermatogenic cell; decline in post meiotic germ cells and spermatozoa in lumen of seminiferous tubules.<br><br>*Biochemical examination* (mg/g): significant increase in cholesterol levels in testes (7.19 vs. 5.66); significant reductions in protein contents of testes (150 vs. 179) and cauda epididymis (172 vs. 206); significant reductions in sialic acid contents of testes (3.82 vs. 4.46) and cauda epididymis (4.22 vs. 5.11); significant reduction in fructose contents of seminal vesicle (4.39 vs. 5.28); no marked change in glycogen contents of testes and epididymis. | Jain et al. (2007) |
| Rats, strain, age, number, and sex n.p. | $VOSO_4$ | oral; 300 mg/L in 5 g/L NaCl in water given via drinking water the last 3 days of pregnancy and first 25 days of resulting pup's life | A delay in body growth, decrease in survival rate at weaning, and significant decrease in rearing posture numbers were observed. | Pogglioli et al. (2001; cited by NRC, 2005) |

**Table 3.  Reproductive Toxicity and Teratology of Vanadium (Oral Studies) (Continued)**

| Species, Strain, and Age, Number, and Sex of Animals | Chemical Form | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| *Pentavalent Vanadium Compounds* | | | | |
| Mice, Swiss, age n.p., 24M and 2F/M (for mating) | $NaVO_3$ | oral; 0, 20, 40, 60, and 80 mg/kg bw/day [8.36, 16.71, 25.07, and 33.42 mg V/kg bw/day] in drinking water for 64 days prior to mating<br><br>mating:  8 of 24M mated with 2F (untreated) for 4 days; F sacrificed 10 days after mating | NOAEL = 40 mg/kg bw/day; LOAEL = 60 mg/kg bw/day<br><br>At 60 and 80 mg/kg, decreased pregnancy rate and decreased spermatozoal count were observed.  At 80 mg/kg, decreases in body weight (13%), absolute epididymis weight (88% compared to controls), and spermatid count (30%) were also observed.<br><br>No significant changes were observed between groups in the numbers of implantations, early/late resorptions, dead/live fetuses, testes weights, sperm motility, or sperm abnormalities. Histopathological changes were also not seen.<br><br>Noted:  IPCS concludes that "Overall, the results do not provide convincing evidence that oral exposure to sodium metavanadate produced specific fertility effects in this study." | Llobet et al. (1993; cited by EVM, 2002, IPCS, 2001, and NRC, 2005) |
| Mice, strain n.p., age n.p., 18-20F/group | $Na_3VO_4$ | oral gavage; 7.5, 15, 30, and 60 mg/kg bw [2.1, 4.2, 8.3, and 16.6 mg V/kg bw] in deionized water on pregnancy days 6-15; sacrificed on pregnancy day 18 | At 30 and 60 mg/kg, deaths were seen in 4/18 and 17.19 mice, respectively.  At 15 mg/kg, a significant reduction in body weight gain (~20%) was observed but was not found at the end of the study. At 30 mg/kg, delayed ossification was regarded as a secondary effect of maternal toxicity.<br><br>There were no changes in final body weight, gravid uterine weight, corrected bw, number of total implants per dam, number of live fetuses per dam, sex ratio, average fetal bw, number of stunted fetuses, or incidences of skeletal/visceral abnormalities.<br><br>Noted:  IPCS states "Overall, sodium orthovanadate did not produce developmental toxicity in this thorough investigation." | Sanchez et al. (1991; cited by IPCS, 2001) |
| Rats, Sprague-Dawley, age, number, and sex n.p. | metavanadate ($V^{+5}$), compound n.p. | oral (p.o.); 0, 5, 10, and 20 mg/kg bw/day for 60 days prior to mating for males and during gestation and lactation for females | LOAEL = 5 mg/kg bw/day<br><br>In offspring, decreases in body weight, body length, and tail length were observed. | Domingo et al., (1986; cited by EVM, 2002) |

## Table 3.  Reproductive Toxicity and Teratology of Vanadium (Oral Studies) (Continued)

| Species, Strain, and Age, Number, and Sex of Animals | Chemical Form | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| Rats, Sprague-Dawley, age n.p., 20F | $NaVO_3$ | p.o./intragastric; 5, 10, and 20 mg/kg bw/day [2.1, 4.2, and 8.4 mg V/kg bw/day] in drinking water on gestation days 6-14; fetuses obtained on day 20 | NOAEL = 20 mg/kg bw/day<br><br>No embryolethal or teratogenic effects were observed.<br><br>At the low, mid, and high doses, numbers of litters were 14, 12, and 8, respectively (14 for controls).  The number of abnormal fetuses was increased.  At the high dose only, hydrocephaly occurred in 2 of 98 fetuses.<br><br>No statistically significant changes in the numbers per litter of corpora lutea, implantations, resorptions, or live fetuses were seen between groups.  There were also no significant differences for fetal bw or body length, as well as no visceral or skeletal abnormalities.<br><br>Noted:  IPCS states that "Overall, there is no clear evidence of direct developmental toxicity following exposure to sodium metavanadate." | Paternain et al. (1987; cited by EVM, 2002, and IPCS, 2001) |
| Rats, Sprague-Dawley, age n.p., 7F | $Na_3VO_4$ | oral; 0.25 and 0.50 mg/mL [~60 and 120 mg/kg/day] in drinking water given on gestation days 10-20 | A significant decrease in the number of fetuses per pregnancy (as well as in water consumption) was observed.  The amount found in blood was ~322 ppb vanadium. | Ganguli et al. (1994; cited by EVM, 2002 and NRC, 2005) |
| Rats, strain n.p., age n.p.,  30M and 60F | $NH_4VO_3$ | oral; 87.1 mg/kg in drinking water for 70 and 61 days in M and F, respectively | Both sexes showed reduced reproductive performance.  Males had greater reduced fertility than females. | Morgan and El-Tawil (2003; cited by NRC, 2005) |
| Rats, Wistar, age n.p., 18-21F/group | $V_2O_5$ | oral gavage; 1, 3, 9, and 18 mg/kg bw/day in vegetable oil on gestation days 6-15; sacrificed on gestation day 20 | At 9 and 18 mg/kg, statistically significantly decreased maternal body weight gains (75 and 40%, respectively) were observed.  At the highest dose, statistically significant decreases in fetal bw, body length, and tail length (87, 92, and 94%, respectively) were seen.<br><br>Delayed occipital ossification was also reported for high-dose animals, while non-ossification or delayed ossification of the sternum was reported for all treated animals.  At 9 and 18 mg/kg, skeletal abnormalities were also statistically significantly increased.  [Noted: All findings were not reported on a per litter basis.]<br><br>There were no increases in the numbers of resorptions or dead fetuses (not given on a per litter basis) and no visceral abnormalities.<br><br>Noted:  IPCS states that "no decision can be made regarding the reliability of the reported findings. | Yang et al., (1986a; cited by IPCS, 2001) |

Abbreviations:  bw = body weight; F = female(s); LOAEL = lowest-observed-adverse-effects level; M = male(s); NOAEL = no-observed-adverse-effects level; n.p. = not provided.

Tetravalent Vanadium Compounds
Impacts on the structures within reproductive organs (e.g., seminiferous tubules, epididymides) were noted. Higher dose studies described decreases in survival rate of weanlings, sperm density and motility, fertility, and litter size (Dehghani et al., 2002; Jain et al., 2007; Paternain et al., 1990 [cited by EVM, 2002, IPCS, 2001, and NRC, 2005]; Pogglioli et al, 2001 [cited by NRC, 2005]).

Pentavalent Vanadium Compounds
Overall, pentavalent vanadium compounds were shown to have no significant effects on the number of implantations, resorptions, or live/dead fetuses. Maternal body weight was shown to decrease during exposures. Delayed ossification also was observed (Domingo et al., 1986; Ganguli et al., 1994; Llobet et al., 1993; Morgan and El-Tawil, 2003; Paternain et al., 1987; Sanchez et al., 1991; Yang et al., 1986a [all cited by EVM, 2002, IPCS, 2001, and/or NRC, 2005]).

### 9.3    Carcinogenicity
In mice, administration of vanadyl sulfate (5 µg/mL) in drinking water during their lifespan did not increase the incidence of spontaneous tumors (Kanisawa and Schroeder, 1967; cited by EVM, 2002). Comparatively, studies by Schroeder and Mitchener (1975) indicated that administration of vanadyl sulfate (5 ppm V) to male and female mice in drinking water during their lifespans increased the number of tumors in female mice, but not in male mice.

Whole-body inhalation exposure to vanadium pentoxide increased the incidence of lung neoplasms in male and female mice and, to a lesser degree, in female rats in the NTP bioassay; neoplasms were not found in other organs. Vanadium pentoxide was not mutagenic in *Salmonella typhimurium* with or without metabolic activation, but did induce micronucleated erythrocytes in mouse peripheral blood (NTP, 2002; Ress et al., 2003). It was categorized as a carcinogen by the Commission of European Communities (Health and Safety Executive, U.K., 2004) and the German Senate Commission of the Deutsche Forschungsgemeinschaft (DFG, 2005; cited by Duffus, 2007); the IARC categorized it a possible human carcinogen (Group 2B) noting that vanadium pentoxide was clastogenic and aneugenic in cultured mammalian cells and inhibited DNA synthesis and repair enzymes (IARC, 2006).

### 9.4    Initiation/Promotion Studies
No data were available.

### 9.5    Anticarcinogenicity
Over 20 studies were identified relating to chemopreventive effects and mechanisms/modes of action of vanadium compounds. Overall the studies indicate that vanadium compounds exert chemopreventive effects against chemically-induced carcinogenesis. Studies indicate that administration of vanadium compounds to animal models of carcinogenesis is associated with decreased development of aberrant crypt foci, elevated superoxide dismutase activity, repair of hyperplastic lesions, reduction in incidence and size of tumors, increased delay in tumor appearance, regulation of cell-cycle modulator proteins (e.g., p53, BC12), protection against generation of single-stranded DNA breaks, and reduction of chromosomal aberrations (Bishayee et al, 2000; Kanna et al., 2003a,b, 2004, 2005; Ray et al., 2004, 2005a,b, 2007). A schematic

presentation of the anticarcinogenic modes of action of vanadium compounds in animal models also is reviewed (Evangelou, 2002).

### 9.6 Genotoxicity

Tetravalent Vanadium Compounds

The bone marrow of male mice given a single intragastric dose of vanadyl sulfate (100 mg/kg/bw [31 mg V/kg bw] had statistically significant increases in cells with hypoploidy at 24 and 36 hours; in cells with hyperploidy at 24 hours; in the number of aberrant cells at 24 and 36 hours (4.3 and 2.7%, respectively, versus 0.6% in controls); and in the number of micronucleated polychromatic erythrocytes (PCEs) at various intervals between 6 and 48 hours. A notable induction of polyploidy was not observed (Ciranni et al., 1995; cited by IPCS, 2001).

Compared to the above study, administration of vanadyl sulfate (2-1000 mg/L in drinking water for 5 weeks) to male mice did not increase the number of PCEs and slightly increased micronucleated reticulocytes, though the effect was not dose dependent (Villani et al. 2007).

Pentavalent Vanadium Compounds

The bone marrow of male mice administered a single intragastric dose of sodium orthovanadate (75 mg/kg bw [21 mg V/kg bw]) or ammonium metavanadate (50 mg/kg bw [42 mg V/kg bw]; Note: Our calculations indicate that 21 mg V/kg bw administered.) in water showed increased numbers of chromosome aberrations after 36 hours with both compounds; these were not statistically significant. Statistically significant increases were seen in cells with hypoploidy and hyperploidy, but none with polyploidy. Ratios of PCE/normochromatic erythrocyte were 50% lower compared to controls, but the percentage of micronucleated PCEs was statistically significant increased (about twofold) with both vanadium compounds compared to controls (Ciranni et al., 1995; cited by IPCS, 2001).

In another study, the bone marrow of mice given vanadium pentoxide (1, 3, 6, or 11 mg/kg bw [0.6, 1.7, 3.4, or 6.2 mg V/kg bw]) in 3% starch suspension for six weeks exhibited no increased induction of micronuclei (IPCS, 2001).

Comparatively, male mice treated for 5 weeks with a range of concentrations of sodium orthovanadate in drinking water (0.75-1500 mg/L) exhibited statistically significant increases of micronuclei in bone marrow at the highest concentrations (750 and 1500 mg/L). A significant increase of comet tail length in splenocytes also was observed at the highest tested concentration. Additionally, no effect was observed on sperm chromatin structure (Leopardi et al., 2005).

### 9.7 Cogenotoxicity

No data were available.

### 9.8 Antigenotoxicity

No data were available.

### 9.9 Immunotoxicity

Tetravalent Vanadium Compounds

No data were available.

Pentavalent Vanadium Compounds
Male and female ICR mice administered vanadium pentoxide (6 mg/kg bw [3.4 mg/kg bw]) for 5 days per week for 6 weeks exhibited an enlargement of the spleen with weakened spleen cellularity.  A significant increase in leukocyte count in peripheral blood and a decrease in phagocytosis were also observed.  Activation of T- and B-cells and a strong mitogenic response to concanavalin A suggested potential hypersensitivity (Mravcova et al., 1993; cited by IPCS, 2001).

In male Wistar rats administered vanadium pentoxide (1 or 100 mg V/L) in drinking water for 6 months, as in mice, an enlarged spleen was observed (at the high dose only), as well as a significant increase in leukocyte count in peripheral blood and a decrease in phagocytosis (Mravcova et al., 1993; cited by IPCS, 2001).

Significant increases in antibody-synthesizing lymphocytes in the spleens of BALB/c mice and Wistar rats were observed after administration of ammonium vanadate (0.5 ppm) in drinking water for 40 and 200 days. Increases also were observed in levels of serum agglutinins and hemolysins (Alexandrova et al., 2002).

**9.10    Other Data**
Lactation-exposed offspring of dams treated with sodium metavanadate (i.p.; 3 mg/kg bw [1.25 mg V/kg bw/day] in distilled water on postnatal days 10-21) exhibited a significant delay in eye opening and decreases in forelimb support, locomotor activity, and myelin staining in corpus callosum and cerebellum when compared to controls (Soazo and Barcia, 2007).

**10.0    Structure-Activity Relationships**
Not applicable.

**11.0    Online Databases and Secondary References**
**11.1    Online Databases**
National Library of Medicine Databases (TOXNET)
ChemIDplus
EMIC and EMICBACK
HSDB
IRIS

STN International Files
| | |
|---|---|
| AGRICOLA | IPA |
| BIOSIS | MEDLINE |
| BIOTECHNO | NIOSHTIC |
| CABA | NTIS |
| CANCERLIT | Registry |
| EMBASE | RTECS |
| ESBIOBASE | TOXCENTER |

TOXCENTER includes toxicology data from the following files:

| | |
|---|---|
| Aneuploidy | ANEUPL[*] |
| BIOSIS Previews® (1969-present) | BIOSIS[*] |
| CAplus (1907-present) | CAplus |
| International Labour Office | CIS[*] |
| Toxicology Research Projects | CRISP[*] |
| Development and Reproductive Toxicology | DART®[*] |
| Environmental Mutagen Information Center File | EMIC[*] |
| Epidemiology Information System | EPIDEM[*] |
| Environmental Teratology Information Center File | ETIC[*] |
| Federal Research in Progress | FEDRIP[*] |
| Health Aspects of Pesticides Abstract Bulletin | HAPAB |
| Hazardous Materials Technical Center | HMTC[*] |
| International Pharmaceutical Abstracts (1970-present) | IPA[*] |
| MEDLINE (1951-present) | MEDLINE |
| Pesticides Abstracts | PESTAB[*] |
| Poisonous Plants Bibliography | PPBIB[*] |
| Swedish National Chemicals Inspectorate | RISKLINE |
| Toxic Substances Control Act Test Submissions | TSCATS[*] |

[*]These are also in TOXLINE.  Missing are TOXBIB, NIOSHTIC®, NTIS.

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

In-House Databases
Current Contents on Diskette®
The Merck Index, 2006, on CD-ROM

## 11.2   Secondary References
None used.

## 12.0   References

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**Appendix A:  Units and Abbreviations**
ºC = degrees Celsius
µg/L = microgram(s) per liter
µg/m$^3$ = microgram(s) per cubic meter
µg/mL = microgram(s) per milliliter
µM = micromolar
AAS = atomic absorption spectrophotometry
bw = body weight
CCL = contaminant candidate list
CDPH = California Department of Public Health
EPA = Environmental Protection Agency
F = female(s)
g = gram(s)
g/mL = gram(s) per milliliter
GI = gastrointestinal
h = hour(s)
IARC = International Agency for Research on Cancer
ICP-OES = inductively coupled plasma-optical emission spectrometer
IPCS = International Programme on Chemical Safety
i.g. = intragastric
kg = kilogram(s)
L = liter(s)
lb = pound(s)
LD$_{50}$ = lethal dose for 50% of test animals
LOAEL = lowest-observed-adverse-effects level
M = male(s)
mg/kg = milligram(s) per kilogram
mg/m$^3$ = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)
mol. wt. = molecular weight
NIOSH = National Institute for Occupational Safety and Health
NL = notification level
NOAEL = no-observed-adverse-effects level
n.p. = not provided
NTP = National Toxicology Program
OSHA = Occupational Safety and Health Administration
PEL = permissible exposure limit
ppb = parts per billion

ppm = parts per million
V = vanadium
wk = week(s)
yr = year(s)

## Appendix B:  Description of Search Strategy and Results

### Vanadium Oral Toxicity Search Strategy on STN International
### with a Tally of STN Results by Topic and Publication Dates

Files MEDLINE, AGRICOLA, CABA, EMBASE, IPA, BIOSIS, TOXCENTER, FSTA, FROSTI, ESBIOBASE, and BIOTECHNO were searched simultaneously on August 15, 2007. Preliminary searches of PubMed and reading of reviews found on the Internet (via PubMed Central, Google, and Google Scholar) helped shape the strategy.  Reviews were sought for all time periods.  The remaining answers were divided into pre- (1,309) and post-2007 sets (2,310 without duplicate removal).  The original pre-2000 answer set had been reduced further by removing records with terms for several poultry species and other livestock and by requiring terms related to humans, laboratory animals, or toxicity.  The CAS Registry Numbers were selected from vanadium compounds listed in the original TSCA inventory.  The history of the August 15 online session is reproduced below:

```
L1        67750   S VANAD? OR ORTHOVANAD? OR METAVANAD? OR TRICHLOROXOVANADIUM OR
                    TRICHLOROOXOVANADIUM OR OXOVANADIUM OR DICHLOROVANADIUM OR
                    OR DIVANADIUM [Tetrachlorovanadium was used but misspelled.]
L2         6834   S 11115-67-6 OR 7803-55-6 OR 13718-26-8 OR 11105-06-9 OR 1314-62-1
                    OR 1314-34-7 OR 7727-18-6 OR 10213-09-9 OR 27774-13-6 OR 12439-96-2
                    OR 14708-82-8 OR 13769-43-2
L3         2647   S 13721-39-6 OR 13476-99-8 OR 10580-52-6 OR 7718-98-1 OR 7632-51-1
                    OR 12036-21-4 OR 12057-86-2 OR 12035-98-2 OR 12036-21-4 OR 1315-03-3
                    OR 13701-70-7 OR 16229-43-9 OR 12165-48-9 OR 69235-01-4
L4         7708   S L2 OR L3
L5        68139   S L1 OR L4
                    SAVE L5 X470NAMES/A
L6         7358   S L5 AND (INGEST? OR DRINKING(W)WATER OR FEED? OR FED OR FOOD
                    OR DIET? OR SUPPLEMENT? OR INTRAGASTRIC?) [Retrieved 2000-2007 "oral"
records in
                    a second session.]
L7         2500   S L6 AND (2000-2007)/PY
L8         4858   S L6 NOT L7
                    SET DUPORDER FILE
L9         4169   DUP REM L6 (3189 DUPLICATES REMOVED)
            712   ANSWERS '1-712' FROM FILE MEDLINE
            105   ANSWERS '713-817' FROM FILE AGRICOLA
            347   ANSWERS '818-1164' FROM FILE CABA
            560   ANSWERS '1165-1604' FROM FILE EMBASE
             13   ANSWERS '1605-1617' FROM FILE IPA
           1149   ANSWERS '1618-2766' FROM FILE BIOSIS
           1200   ANSWERS '2767-3966' FROM FILE TOXCENTER
             43   ANSWERS '3967-4009' FROM FILE FSTA
            135   ANSWERS '4010-4144' FROM FILE FROSTI
             20   ANSWERS '4145-4164' FROM FILE ESBIOBASE
              5   ANSWERS '4165-4169' FROM FILE BIOTECHNO
L10         262   S L9 AND (REVIEW? OR REVIEW/DT)
L11         262   DUP REM L10 (0 DUPLICATES REMOVED)
             66   ANSWERS '1-66' FROM FILE MEDLINE
              8   ANSWERS '67-74' FROM FILE AGRICOLA
             30   ANSWERS '75-94' FROM FILE CABA
             89   ANSWERS '95-183' FROM FILE EMBASE
             13   ANSWERS '184-194' FROM FILE BIOSIS
             38   ANSWERS '195-232' FROM FILE TOXCENTER
             29   ANSWERS '233-261' FROM FILE FROSTI
              1   ANSWER '262' FROM FILE BIOTECHNO
L12         262   SORT L11 1-262 TI
                    SAVE L12 X470REVU/A
L13        2393   S L7 NOT L12
L14        4703   S L8 NOT L12
L15        2329   S L13 NOT (CHICK? OR HEN OR HENS OR POULTRY OR DUCK? OR GEESE)
L16        1309   DUP REM L15 (1020 DUPLICATES REMOVED)
            189   ANSWERS '1-189' FROM FILE MEDLINE
             20   ANSWERS '190-209' FROM FILE AGRICOLA
            122   ANSWERS '210-331' FROM FILE CABA
```

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                      162 ANSWERS '332-493' FROM FILE EMBASE
                        8 ANSWERS '494-501' FROM FILE IPA
                      238 ANSWERS '502-739' FROM FILE BIOSIS
                      500 ANSWERS '740-1239' FROM FILE TOXCENTER
                       13 ANSWERS '1240-1252' FROM FILE FSTA
                       40 ANSWERS '1253-1292' FROM FILE FROSTI
                       13 ANSWERS '1293-1305' FROM FILE ESBIOBASE
                        4 ANSWERS '1306-1309' FROM FILE BIOTECHNO
   L17        1309 SORT L16 1-1309 TI
   L18        4314 S L14 NOT (CHICK? OR HEN OR HENS OR POULTRY OR DUCK? OR GEESE)
                   SAVE L17 X470RECENT/A
   L19        1283 S L18 AND (RATS OR MICE OR GUINEA(W)PIG? OR HAMSTER? OR DOGS
                   OR CATS OR RABBITS)
   L20         662 S L18 AND (HUMAN OR INFANT? OR NEONAT? OR EPIDEMIOL? OR FETAL
                   OR FOETAL OR FETUS? OR FOETUS? OR OFFSPRING OR EMBRYO?)
   L21        1443 S L18 AND (CHRONIC? OR SUBCHRONIC? OR TOXIC? OR INTOXICA?)
   L22          68 S L18 AND (GENOTOXIC? OR NEUROTOXIC? OR HEPATOTOXIC?)
   L23        2396 S L19-L22
   L24        2310 S L23 NOT (CATTLE OR HEIFER? OR CALVES OR LIVESTOCK OR GOAT? OR
                   SHEEP OR LAMB?)
   L25        2310 SORT L24 1-2310 TI [Forgot to remove duplicates.]
                   SAVE L25 X470OLD/A
```

## Vanadium Compounds:  Recent Literature Availability on Reviews, ADME, and Oral Studies Based on STN International Results

Literature on testing vanadium organic complexes for diabetes control was largely excluded from these groups unless adverse effects were noted.  Studies in which exposure and nontoxicological topics are covered were not included.

| Subject Code and Description | Published 2000-2004 | Published 2005-2007 | Total Published 2000-2007 |
|---|---|---|---|
| 05 Authoritative reviews or 11 Other reviews | 7 | 0 | 7 |
| 18 Human studies | 7 | 3 | 10 |
| 03 Animal studies of acute duration | 2 | 4 | 6 |
| 06a Repeated-dose animal studies of 1-week to 13-week duration (toxic and/or beneficial effects) | 14 | 17 | 31 |
| 06b Repeated-dose animal studies of > 13-week duration.  (Have two studies on increased weight loss induced by vanadyl complexed by acetylacetone or maltol anions.) | 0 | 0 | 0 |
| 07c Anticarcinogenicity studies (Includes studies in which the vanadium compound retards the preneoplasia induced by a carcinogen. See also 09c.) | 12 | 5 | 17 |
| 08 Effects on the immune system | 2 | 1 | 3 |
| 09a Genotoxicity | 1 | 3 | 4 |
| 09c Antigenotoxicity | 1 | 11 | 12 |
| 10 Reproductive/developmental effects | 2 | 0 | 2 |
| 12 ADME (Mostly distribution after oral dosing) | 12 | 6 | 18 |
| 14 Miscellaneous physiological effects | 3 | 0 | 3 |
| **Totals** | **63** | **50** | **113** |

Additionally, records for specific vanadium compounds were also retrieved from RTECS (via the Environmental Chemistry Information System [fee-based subscription service] or via the web-based NIOSH Pocket Guide) and from the NLM databases HSDB, CCRIS, DART, EMIC, Genetox, and PubChem.