

Risk Assessment

Vanadium

General information

Chemistry

Vanadium occurs as two natural isotopes, ^{50}V and ^{51}V , the latter being the naturally occurring radioisotope. It forms oxidation states of -1, 0, +2, +3, +4 and +5. Within this risk assessment, the word vanadium refers to ionic vanadium, except when specific compounds are mentioned.

Natural occurrence

Metallic vanadium does not occur in the free form in nature but does occur in over 65 naturally occurring minerals. The predominant forms in biological materials are vanadate (+5 V, VO_3^-) and vanadyl (+4 V, VO^{+2}), respectively.

Occurrence in food, food supplements and medicines

Beverages, fats, oils, fresh fruits and vegetables contain the lowest levels of vanadium, whereas whole grains, seafood, meats and dairy products contain more (0.005 – 0.03 mg/kg). A few foods, including spinach, parsley, mushrooms and oysters, contain relatively high amounts of vanadium (> 0.10 mg/kg). Vanadium is present in a number of multi-vitamin/mineral dietary supplements at levels of approximately 0.025 mg per day. There are no licensed medicines containing vanadium.

Other sources of exposure

Exposure to vanadium by inhalation may occur occupationally. In the production of vanadium pentoxide, dust concentrations of the pentoxide can range from 0.1 to 30 mg/m³, and concentrations of 0.5–5 mg/m³ are not uncommon in the production of vanadium metal and vanadium catalysts.

Recommended amounts

Vanadium has not yet been proven to be an essential trace element for mammals.

Analysis of tissue levels and vanadium status

Vanadium can be measured in whole blood, serum and various tissues. Markers of vanadium status have not been established.

Overview of non-nutritional beneficial effects

It has been claimed that vanadium may be a possible treatment for diabetes mellitus (types I and II). Information on the internet suggests that the element is used by body builders, although the rationale for this and any possible effects are uncertain.

Function

No specific function has been identified for vanadium in higher animals. *In vitro* and animal studies suggest that vanadium may function as an oxidation-reduction catalyst, and may regulate the sodium, potassium-adenosine triphosphatase enzyme, however, this has not been proven.

Deficiency

In humans, the reported signs of deficiency are questionable, although it has been suggested that low intakes may be associated with cardiovascular disease.

Interactions

Although no specific data have been identified, it is possible that vanadium may interfere with the storage and metabolism of iron, because absorbed vanadium is bound to transferrin.

Absorption and bioavailability

Intestinal absorption of vanadium is low, less than 5%. The mechanism of absorption has not been defined.

Distribution

Absorbed vanadium is mainly transported in the plasma, associated with transferrin. Concentrations reported in human blood vary widely, with levels in whole blood and serum in the range of 0.01 – 0.4 mg/L. The concentrations in all tissues are low, but are higher in the liver, kidney and lung. Vanadium is also present in breast milk and saliva and passes through the blood brain barrier. Small amounts have been identified in the placenta. Based on animal studies, bones and teeth retain the highest concentrations of vanadium.

Excretion

Ingested vanadium is predominantly eliminated unabsorbed via the faeces. Absorbed vanadium is mainly excreted via the urine.

Toxicity

Human data

The toxicity of vanadium compounds increases as valency increases, V^{5+} being the most toxic. In humans, exposure by inhalation causes diverse toxic effects on the respiratory, digestive, and central nervous systems, the kidney and skin. There are very few reported cases of vanadium toxicity in humans, when it is taken by mouth.

Supplementation trials

Supplementation of human volunteers with vanadyl compounds at oral doses of 50-125 mg/day caused cramps, loosened stools and 'green tongue' in all patients, and fatigue and lethargy in a minority.

Animal data

Orally administered vanadium has low overt toxicity, but is reported to have adverse effects on reproduction and development in both males and females. There is some evidence of increased pre- and post-implantation foetal loss and significant accumulation of vanadium in the foetus. Skeletal anomalies and reduced ossification in the offspring, as well as an increased incidence of cleft palate have been reported.

Carcinogenicity and genotoxicity

Lifetime studies in animals indicate that vanadium is not carcinogenic. Positive results have been obtained in some *in vitro* mutagenicity tests.

Mechanism of toxicity

No data have been identified

Dose-response characterisation

No data have been identified

Vulnerable groups

No vulnerable groups have been identified in human studies. However, animal data suggest that high doses of vanadium may have adverse effects on reproduction in both males and females and on development of offspring.

Genetic variations

No genetic variation of effects with vanadium have been identified.

Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD).

Human data

Dimond et al., 1963

Oral supplements of ammonium vanadium tartrate (increasing doses in the range of 25, 50, 75 and 125 mg/day) were administered to at least 6 volunteers for a minimum of six weeks. The total daily dose was limited by cramps and diarrhoea in all six patients. Haematological studies and urinalysis revealed no abnormalities. Non-significant and temporary decreases in cholesterol levels were observed in two (of six) patients. Doses of 50 mg or more resulted in 'green tongue'. Two patients complained of fatigue and lethargy. Few subjects were involved and the dose was increased during the study. The authors suggested that the tolerated dose varied from 50 to 125 mg, although it was also noted that 'green tongue' developed at this dose range. No effects were observed at 25 mg ammonium vanadium tartrate per day in 4 subjects, which is equivalent to approximately 5 mg vanadium/day (0.08 mg vanadium/kg bw/day).

Somerville et al., 1992

125 mg/day of diammonium oxy-tartrato vanadate was administered for approximately five months, to patients with coronary heart disease. Half the subjects reported abdominal pains, anorexia and weight loss.

Cohen et al., 1995.

Vanadyl sulphate, administered at 100 mg/day for three weeks to six patients with non-insulin dependant diabetes mellitus (NIDDM) in a single-blind placebo controlled trial, resulted in mild gastrointestinal effects: nausea, mild diarrhoea and abdominal cramps. This is equivalent to approximately 0.52 mg/kg bw/day as vanadium.

Goldfine et al., 1995

125 mg sodium metavanadate/day was administered to ten diabetic patients (5 insulin dependant and 5 with NIDDM) for two weeks. Mild gastrointestinal intolerance and diarrhoea were reported in both groups, including vomiting in one patient, which limited the total daily dose to 75 mg in this patient. No biochemical evidence of toxicity was detected by screening, which included electrolytes, blood urea nitrogen, creatinine, liver function studies, thyroid functions, urine analysis and a complete blood count. The daily dose of 125 mg/day was equivalent to approximately 0.83 mg/kg bw/day as vanadium)

Boden et al., 1996

Vanadyl sulphate was administered at 100 mg/day (equivalent to approximately 0.52 mg/kg bw/day as vanadium) to eight NIDDM patients for a total of four weeks. Two of the eight patients reported no adverse effects. Adverse gastrointestinal effects were reported in the other six patients, including nausea, diarrhoea, abdominal cramps and flatulence. In one patient, diarrhoea and abdominal cramps lasted for eleven days. In the others all symptoms disappeared during the first week of treatment.

Halberstam et al., 1996

Transient gastrointestinal effects were reported in seven diabetic patients given 100 mg/day vanadyl sulphate (equivalent to approximately 0.52 mg/kg bw/day as vanadium) for three weeks. These included nausea, mild diarrhoea and abdominal cramps, which subsided after one week of treatment. Additionally, some patients noted discolouration of the stool; however, stool examinations were negative for occult blood.

Animal data

Domingo et al., 1986

Sodium metavanadate was administered to adult male rats by oral gavage (0, 5, 10 and 20 mg/kg bw/day, equivalent to approximately 0, 2, 4 and 8 mg vanadium/kg bw/day) for sixty days, before mating with females that received the same vanadate doses for the 14 days prior to mating. Treatment of the females was continued during the periods of gestation and lactation. No significant effects on fertility, reproduction and parturition were observed; the number of dead foetuses and resorptions was increased in the highest dose group, but this was not significant. The development of the offspring (body weight, body length and tail length) was significantly decreased from birth and during the lactation period, at all dose levels, which were equivalent to approximately 2 to 8 mg/kg bw/day as vanadium.

Paternain et al., 1990

Vanadyl (V⁴⁺) sulphate pentahydrate (0, 37.5, 75 and 150 mg/kg bw/day) was administered by oral gavage to pregnant mice on days 6 to 15 of gestation. Maternal toxicity, embryotoxicity and foetotoxicity (including teratogenicity) were reported at 75 and 150 mg/kg bw/day, which is equivalent to approximately 7.5 mg/kg bw/day as vanadium.

Llobet et al., 1993

Sodium metavanadate was given in drinking water to male mice for 64 days before mating with untreated females. The concentrations of sodium metavanadate used were 0, 0.1, 0.2, 0.3 and 0.4 mg/mL, giving doses of 0, 20, 40, 60 and 80 mg/kg bw/day. A significant decrease in the pregnancy rate was seen at 60 and 80 mg/kg bw/day. Decreased body and epididymis weights were observed in the 80 mg/kg bw/day group, but testicular weights were not altered at any of the doses administered. The sperm count was significantly diminished at 60 and 80 mg/kg bw/day, but sperm motility was unaffected and histopathological examination revealed that the testes were normal. The development of subsequent offspring was not assessed. No effects were observed with sodium metavanadate at 40 mg/kg bw/day, which is equivalent to approximately 16 mg/kg bw/day as vanadium.

Exposure assessment

Total exposure/intake:

Food	Mean: 0.013 mg/day (1980 UK TDS) 97.5 percentile: No data available
Supplements	up to 0.025 mg/day (Annex 4)
Drinking Water	0.01 mg/day (estimated from 0.005 mg/L, WHO 1988)
Estimated maximum daily intake*	$0.013 + 0.025 + 0.01 = 0.05$ mg/day

No potential high intake groups were identified.

* Note that no data on high level intakes are available, so this is an underestimate.

Risk assessment

Few data are available. Vanadium compounds have been reported to cause gastrointestinal effects in supplementation studies in human volunteers.

In rodents, orally administered vanadium has low overt toxicity, but is reported to have adverse effects at high doses on reproduction and development in both males and females. It is unclear whether these effects could also occur in humans.

EVM OPINION

It has not been proven that vanadium is an essential element in humans, although vanadium-dependent enzymes occur in lower organisms. There are insufficient data from human or animal studies to establish a safe upper level for vanadium.

Supplementation of human volunteers with vanadium compounds at doses of 50-125 mg/day has been reported to cause cramps, loosened stools and 'green tongue' in all patients and fatigue and lethargy in a minority of participants. Few human data are available and interpretation is limited by the small number of participants and the relatively short duration of studies.

Data from animal studies suggest that vanadium has adverse effects on both male and female reproduction and on the development on the subsequent offspring. There are insufficient data to establish whether or not this effect could occur in humans.

The available studies are inadequate to support the safe use of vanadium in supplements. It should be noted that vanadium supplements aimed at body builders are available (particularly via the internet) at doses between 7.5 and 10 mg/day. Supplements containing these levels of vanadium may not be safe.

References

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