VANADIUM PENTOXIDE

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1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

The nomenclature of selected vanadium compounds is given in Table 1.
Chem. Abstr. Serv. Reg. No.: 1314-62-1
Deleted CAS Reg. No.: 12503-98-9; 56870-07-6; 87854-55-5; 87854-56-6; 166165-37-3; 172928-47-1; 184892-22-6; 200577-85-1; 203812-34-4; 251927-12-5; 410546-90-6
Chem. Abstr. Serv. Name: Vanadium oxide (V_2O_5)
IUPAC Systematic Name: Vanadium oxide
Synonyms: CI 77938; divanadium pentaoxide; pentaoxodivanadium; vanadic acid anhydride; vanadin (V) oxide (see also Table 1)

1.1.2 *Empirical formula and relative molecular mass*

V_2O_5 Relative molecular mass: 181.88

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Yellow to rust-brown orthorhombic crystals (O'Neil, 2001; Lide, 2003); yellow-orange powder or dark-gray flakes (Bauer *et al.*, 2003; National Institute for Occupational Safety and Health, 2005)
(*b*) *Boiling-point*: 1800 °C, decomposes (Lide, 2003)
(*c*) *Melting-point*: 670 °C (Lide, 2003); 690 °C (O'Neil, 2001)
(*d*) *Density*: 3.36 (O'Neil, 2001; Lide, 2003)
(*e*) *Solubility*: Slightly soluble in water (0.1–0.8 g/100 cm^3); soluble in concentrated acids and alkalis; insoluble in ethanol (Woolery, 1997; O'Neil, 2001)
(*f*) *Stability*: Reacts with chlorine or hydrochloric acid to form vanadium oxytrichloride; absorbs moisture from the air (ESPI, 1994).

Table 1. Nomenclature of selected vanadium compounds

Molecular formula	Name used in Monograph [Registry number]	Synonyms
NH_4VO_3	Ammonium metavanadate [7803-55-6]	Ammonium monovanadate Ammonium trioxovanadate Ammonium trioxovanadate(1-) Ammonium vanadate Ammonium vanadate(V) Ammonium vanadium oxide Ammonium vanadium trioxide Vanadate (VO_3^-), ammonium Vanadic acid, ammonium salt Vanadic acid (HVO_3), ammonium salt
Na_3VO_4	Sodium orthovanadate [13721-39-6]	Sodium pervanadate Sodium tetraoxovanadate(3-) Sodium vanadate Sodium vanadate(V) (Na_3VO_4) Sodium vanadium oxide (Na_3VO_4) (9CI) Trisodium orthovanadate Trisodium tetraoxovanadate Trisodium vanadate Vanadic acid (H_3VO_4), trisodium salt (8CI) Vanadic(II) acid, trisodium salt
VO^{2+}	Vanadyl [20644-97-7]	Oxovanadium(2+) Oxovanadium(IV) ion Vanadium monoxide(2+) Vanadium oxide (VO), ion(2+) Vanadium oxide (VO^{2+}) Vanadyl(II) Vanadyl ion(2+) (8CI, 9CI)
VO_3^-	Vanadate [13981-20-9]	Metavanadate Metavanadate(1-) Trioxovanadate(1-) Vanadate (VO_3^-) Vanadate, ion –
$NaVO_4$	Sodium peroxyvanadate [15593-26-7]	Hydrogen peroxide, vanadium complex Peroxyvanadic acid ($HVO_2(O_2)$), sodium salt
Unspecified	Sodium vanadium oxide [11105-06-9]	Peroxyvanadic acid, sodium salt Sodium peroxyvanadate Sodium vanadate Vanadic acid, sodium salt

Table 1 (contd)

Molecular formula	Name used in Monograph [Registry number]	Synonyms
$VO(SO_4)$	Vanadyl sulfate [27774-13-6]	Oxo(sulfato)vanadium Oxovanadium(IV) sulfate Vanadic sulfate Vanadium oxide sulfate Vanadium(IV) oxide sulfate Vanadium oxosulfate Vanadium, oxosulfato- (8CI) Vanadium, oxo(sulfato(2-)-O)- Vanadium, oxo(sulfato(2-)-κO)- (9CI) Vanadium oxysulfate Vanadium sulfate
Unknown	Ferrovanadium [12604-58-9]	Ferrovanadium alloy Ferrovanadium dust
V_2O_3	Vanadium trioxide [1314-34-7]	Divanadium trioxide Vanadic oxide Vanadium oxide (V_2O_3) (8CI, 9CI) Vanadium(3+) oxide Vanadium sesquioxide Vanadium trioxide
V_2O_5	Vanadium pentoxide [1314-62-1]	Divanadium pentoxide Pentaoxodivanadium Vanadia Vanadic anhydride Vanadium oxide Vanadium oxide (V_2O_5) (8CI, 9CI) Vanadium(V) oxide Vanadium pentoxide
VCl_3	Vanadium trichloride [7718-98-1]	Vanadium chloride (VCl_3) (8CI, 9CI) Vanadium(3+) chloride Vanadium(III) chloride Vanadium trichloride

From STN International (2003); National Library of Medicine (2003)

1.1.4 *Technical products and impurities*

Vanadium pentoxide is commercially available in the USA in purities between 95% and 99.6%, with typical granulations between 10 mesh [~ 1600 μm] and 325 mesh [~ 35 μm] × down (Reade Advanced Materials, 1997; Strategic Minerals Corp., 2003). Vanadium pentoxide is also commercially available as a flake with the following specifications: purity, 98–99%; silicon, < 0.15–0.25%; iron, < 0.20–0.40%; and phosphorus, < 0.03–0.05%; and as a powder with the following specifications: purity, 98%; silicon dioxide, < 0.5%; iron, 0.3%; and arsenic, < 0.02% (American Elements, 2003).

Vanadium pentoxide is commercially available in Germany as granules and powder with a minimum purity of 99.6% (GfE mbH, 2003), and in the Russian Federation as a powder with the following specifications: purity, 98.6–99.3%; iron, < 0.05–0.15%; silicon, < 0.05–0.10%; manganese, < 0.04–0.10%; chromium, < 0.02–0.07%; sulfur, < 0.005–0.010%; phosphorus, < 0.01%; chlorine, < 0.01–0.02%; alkali metals (sodium and potassium), < 0.1–0.3%; and arsenic, < 0.003–0.010% (AVISMA titanium-magnesium Works, 2001).

Vanadium pentoxide is also commercially available in South Africa as granular and R-grade powders with a minimum purity of 99.5% and grain sizes of > 45 μm and < 150 μm, respectively (Highveld Steel & Vanadium Corporation Ltd, 2003).

1.1.5 *Analysis*

Occupational exposure to vanadium pentoxide is determined by measuring total vanadium in the workplace air or by biological monitoring.

(*a*) *Monitoring workplace and ambient air*

Respirable fractions (< 0.8 μm) of airborne vanadium pentoxide are collected by drawing air in a stationary or personal sampler through a membrane filter made of polycarbonate, cellulose esters and/or teflon. The filter containing the collected air particulates can be analysed for vanadium using several methods. In destructive methods, the filter is digested in a mixture of concentrated mineral acids (hydrochloric acid, nitric acid, sulfuric acid, perchloric acid) and the vanadium concentration in the digest determined by GF–AAS (Gylseth *et al*., 1979; Kiviluoto *et al*., 1979) or ICP–AES (Kawai *et al*., 1989). Non-destructive determination of the vanadium content on a filter can be performed using INAA (Kucera *et al*., 1998).

Similar methods can be used for the measurement of vanadium in ambient air.

X-ray powder diffraction allows quantification of vanadium pentoxide, vanadium trioxide and ammonium metavanadate separately on the same sample of airborne dust (Carsey, 1985; National Institute for Occupational Safety and Health, 1994).

(*b*) *Biological monitoring*

(i) *Tissues suitable for biomonitoring of exposure*

Vanadium concentrations in urine, blood or serum have been suggested as suitable indicators of occupational exposure to vanadium pentoxide (Gylseth *et al*., 1979; Kiviluoto *et al*., 1979, 1981; Pyy *et al*., 1984; Kawai *et al*., 1989; Kucera *et al*., 1998). The concentration of vanadium in urine appears to be the best indicator of recent exposure, since it rises within a few hours after the onset of exposure and decreases within a few hours after cessation of exposure (Kucera *et al*., 1998). Table 2 presents data of vanadium concentrations in urine from workers exposed to vanadium.

Detailed information on the kinetics of vanadium in human blood after exposure is still lacking. Kucera *et al*. (1998) regarded vanadium concentrations in blood as the most suitable indicator of the long-term body burden (see Section 4.1.1). However, in a study of vanadium pentoxide exposure in rats, blood concentrations showed only marginal increases. This seems to indicate that there was limited absorption of vanadium (National Toxicology Program, 2002).

(ii) *Precautions during sampling and sample handling*

Biological samples are prone to contamination from metallic parts of collection devices, storage containers, some chemicals and reagents; as a result, contamination-free sampling, sample handling and storage of blood and urine samples prior to analysis are of crucial importance (Minoia *et al.*, 1992; Sabbioni *et al*., 1996). There is also a great risk of contamination during preconcentration, especially when nitric acid is used (Blotcky *et al*., 1989).

(iii) *Analytical methods*

Several reviews are available on analytical methods used for the determination of vanadium concentrations in biological materials (Seiler, 1995) and on the evaluation of normal vanadium concentrations in human blood, serum, plasma and urine (Versieck & Cornelis, 1980; Sabbioni *et al*., 1996; Kucera & Sabbioni, 1998). Determination of vanadium concentrations in blood and/or its components and in urine is a challenging analytical task because the concentrations in these body fluids are usually very low (below the µg/L level). A detection limit of < 10 ng/L is therefore required and only a few analytical techniques are capable of this task, namely GF–AAS, isotope dilution mass spectrometry (IDMS), ICP–MS and NAA. Furthermore, sufficient experience in applying well-elaborated analytical procedures is of crucial importance for accurate determination of vanadium concentrations in blood, serum and urine.

Direct determination of vanadium concentrations in urine or diluted serum by GF–AAS is not feasible because the method is not sufficiently sensitive and because the possibility of matrix interferences; however, GF–AAS with a preconcentration procedure has been applied successfully (Ishida *et al*., 1989; Tsukamoto *et al*., 1990).

IDMS has good potential for the determination of low concentrations of vanadium. This technique has been applied for the determination of vanadium concentrations in human

Table 2. Vanadium concentrations in workplace air and urine from workers occupationally exposed to vanadium

Industrial process	No. of subjects	Vanadium in air mean ± SD or range of means in mg/m^3	Vanadium in urine mean ± SD (range) in µg/L[b]	Reference
Ferrovanadium production	16	NK[c]	152 (44–360) nmol/mmol creatinine	Gylseth *et al.* (1979)
Smelting, packing and filtering of vanadium pentoxide	8	0.19 ± 0.24	73 ± 50 nmol/mmol creatinine	Kiviluoto *et al.* (1981)
Vanadium pentoxide processing	2	NK	13.9	Pyy *et al.* (1984)
Boiler cleaning	4	2.3–18.6 (0.1–6.4)[a]	(2–10.5)	White *et al*. (1987)
Vanadium pentoxide staining	2	[< 0.04–0.13]	(< 7–124)	Kawai *et al*. (1989)
Boiler cleaning	21	NK	0.7 (0.1–2.1)	Arbouine & Smith (1991)
Vanadium alloy production	5	NK	3.6 (0.5–8.8)	Arbouine & Smith (1991)
Removal of ashes in oil-fired power station	11	NK	2.2–27.4	Pistelli *et al.* (1991)
Boiler cleaning	10 (– RPE)[d] 10 (+ RPE)	NK	92 (20–270) 38 ± 26	Todaro *et al*. (1991)
Boiler cleaning	30	0.04–88.7	(0.1–322)	Smith *et al*. (1992)
Maintenance in oil-fired boiler	NK	0.28	57.1 ± 15.4 µg/g creatinine	Barisione *et al.* (1993)
Vanadium pentoxide production	58	Up to 5	28.3 (3–762)	Kucera *et al*. (1994)
Waste incineration workers	43	NK	0.66 ± 0.53 (< 0.01–2)	Wrbitzky *et al*. (1995)

Table 2 (contd)

Industrial process	No. of subjects	Vanadium in air mean ± SD or range of means in mg/m^3	Vanadium in urine mean ± SD (range) in μg/L[b]	Reference
Boilermakers	20	0.02 (0.002–0.032)	1.53 ± 0.53 mg/g creatinine	Hauser *et al.* (1998)

Updated from WHO (2001)
[a] Time-weighted average (TWA)
[b] Unless stated otherwise
[c] NK, not known
[d] RPE, respiratory protective equipment

serum in only one study (Fassett & Kingston, 1985); however, the high mean value obtained (2.6 ± 0.3 mg/L) suggested the possibility of contamination (Sabbioni *et al*., 1996; Kucera & Sabbioni, 1998).

ICP–MS cannot be used for the determination of low concentrations of vanadium because of spectral and non-spectral interferences, unless high-resolution ICP–MS is used (Moens *et al.*, 1994; Moens & Dams, 1995).

The problems of various interferences encountered with the above methods are mostly avoided by using NAA (Byrne, 1993). However, interfering radionuclides such as ^{24}Na or ^{38}Cl must be removed, preferably by post-irradiation radiochemical separation, so-called radiochemical NAA (RNAA). Also, because of the short half-life of the analytical radionuclide ^{52}V ($T_{1/2}$, 3.75 min), sample decomposition by irradiation and vanadium separation must be completed within 6–12 min (Byrne & Kosta, 1978a; Sabbioni *et al.*, 1996). This technique has been mastered by only a few research groups (Byrne & Kosta, 1978b; Cornelis *et al*., 1980, 1981; Byrne & Versieck, 1990; Heydorn, 1990; Byrne & Kucera, 1991a,b; Kucera *et al*., 1992, 1994). If dry ashing is carried out prior to irradiation, the separation time can be shortened by a few minutes and a lower detection limit can be achieved (Byrne & Kucera, 1991a,b). Various procedures of pre-irradiation separation have been employed to circumvent the necessity for speedy operations with radioactive samples; however, high values were obtained, indicating that contamination and problems with blank samples could not be excluded (Heydorn, 1990). The only exception to date is an analysis performed by NAA in a clean Class 100 laboratory (Greenberg *et al*., 1990), which yielded a vanadium concentration in serum similar to that determined by RNAA.

(iv) *Reference values in occupationally non-exposed populations*

The values for blood and serum vanadium concentrations obtained by RNAA (Byrne & Kosta, 1978a; Cornelis *et al*., 1980, 1981; Byrne & Versieck, 1990; Heydorn, 1990; Byrne & Kucera, 1991a,b; Kucera *et al*., 1992, 1994), by NAA with pre-irradiation sepa-

ration (Greenberg *et al*., 1990), by GF–AAS with preconcentration (Ishida *et al*., 1989; Tsukamoto *et al*., 1990) and by high-resolution ICP–MS (Moens *et al*., 1994) suggest that the true normal vanadium concentration in blood and serum of occupationally non-exposed populations is in the range of 0.02–0.1 μg/L. The accuracy of the results obtained by RNAA was confirmed by concomitant analysis of a variety of biological reference materials and comparison of the values obtained with certified or literature values. For the Second Generation Biological Reference Material (freeze-dried human serum), vanadium concentrations of 0.67 ± 0.05 μg/kg (dry mass) and 0.66 ± 0.10 μg/kg (dry mass) obtained by RNAA in two separate studies (Byrne & Versieck, 1990; Byrne & Kucera, 1991a) were consistent with the mean of 0.83 ± 0.09 μg/kg (dry mass) obtained by high-resolution ICP–MS (Moens *et al*., 1994). These values correspond to serum concentrations of 0.060–0.075 μg/L, which are in the range of the normal vanadium concentrations in blood and/or serum suggested above. [The concentration in μg/kg dry mass can be converted into a concentration in μg/L by dividing by a factor of 11 (Versieck *et al.*, 1988).]

Vanadium concentrations in urine of occupationally non-exposed populations determined by RNAA (Kucera *et al*., 1994) and by GF–AAS with preconcentration (Buchet *et al*., 1982; Buratti *et al*., 1985; Ishida *et al*., 1989; Minoia *et al*., 1990) have been shown consistently to have mean values ranging from 0.2 to 0.8 μg/L.

1.2 Production and use

1.2.1 *Production*

Although vanadium is widely dispersed and relatively abundant in the earth's crust, deposits of ore-grade minable vanadium are rare (see Section 1.3.1). The bulk of vanadium production is derived as a by-product or coproduct in processing iron, titanium, phosphorus and uranium ores. Vanadium is most commonly recovered from these ores in the form of pentoxide, but sometimes as sodium and ammonium vanadates.

Only about a dozen vanadium compounds are commercially significant; of these, vanadium pentoxide is dominant (Woolery, 1997; Nriagu, 1998; O'Neil, 2001; Atomix, 2003).

Vanadium was discovered twice. In 1801, Andres Manuel del Rio named it erythronium, but then decided he had merely found an impure form of chromium. Independently, Nils Gabriel Sefstrom found vanadium in 1830, and named it after the Scandinavian goddess of beauty and youth — the metal's compounds provide beautiful colours in solution. Henry Enfield Roscoe first isolated the metal in 1867, from vanadium dichloride. It was not until 1925 that relatively pure vanadium was obtained — by reducing vanadium pentoxide with calcium metal (Atomix, 2003).

According to the US Geological Survey (2002), nearly all the world's supply of vanadium comes from primary sources. Seven countries (China, Hungary, Japan, Kazakhstan, the Russian Federation, South Africa and the USA) recover vanadium from ores, concentrates, slag or petroleum residues. In five of the seven countries, the mining and processing

of magnetite-bearing ores was reported to be an important source of vanadium production. Japan and the USA are believed to be the only countries to recover significant quantities of vanadium from petroleum residues. World demand for vanadium fluctuates in response to changes in steel production. It is anticipated to increase due to the demands for stronger and lighter steels and new applications, such as the vanadium battery (Magyar, 2002).

Raw materials processed into vanadium compounds include the titanomagnetite ores and their concentrates, which are sometimes processed directly, vanadium slags derived from ores, oil combustion residues, residues from the hydrometallization process and spent catalysts (secondary raw materials) (Hilliard, 1994; Bauer *et al*., 2003). Primary industrial compounds produced directly from these raw materials are principally 98% (by weight) fused pentoxide, air-dried (technical-grade) pentoxide and technical-grade ammonium metavanadate (Woolery, 1997).

The titanomagnetite ore in lump form, containing approximately 1.5–1.7% vanadium pentoxide, is first reduced by coal at approximately 1000 °C in directly-heated rotary kilns. A further reduction is then performed in an electric furnace to obtain a pig iron which contains approximately 1.4% vanadium pentoxide. The molten pig iron is oxidized in a shaking ladle, causing the vanadium to be transferred to the slag in the form of a water-soluble trivalent iron spinel. A typical vanadium slag has the following approximate composition: 14% vanadium (equivalent to 25% vanadium pentoxide), 9% metallic iron, 32% total iron, 7% silica, 3.5% manganese, 3.5% titanium, 2.5% magnesium, 2.0% aluminium and 1.5% calcium. This is the world's principal raw material for vanadium production (Hilliard, 1994; Bauer *et al*., 2003).

The main process used today to produce vanadium pentoxide from vanadium slags is alkaline roasting. The same process, with minor differences, can also be used for processing titanomagnetite ores and vanadium-containing residues. The slag is first ground to $< 100\ \mu m$, and the iron granules are removed. Alkali metal salts are added, and the material is roasted with oxidation at 700–850 °C in multiple-hearth furnaces or rotary kilns to form water-soluble pentavalent sodium orthovanadate. The roasted product is leached with water, and ammonium polyvanadate or sparingly-soluble ammonium metavanadate are precipitated in crystalline form from the alkaline sodium orthovanadate solution by adding sulfuric or hydrochloric acid and ammonium salts at elevated temperature. These compounds are converted to high-purity, alkali-free vanadium pentoxide by roasting. The usual commercial 'flake' form of vanadium pentoxide is obtained from the solidified melt (Hilliard, 1994; Bauer *et al*., 2003).

Hydrometallurgical methods or a combination of pyrometallurgical and hydrometallurgical processes are used to produce vanadium oxides and salts from other raw materials. In the combined processes, thermal treatment is followed by alkaline or, more rarely, acid processing (Hilliard, 1994; Bauer *et al*., 2003).

Uranium production from carnotite and other vanadium-bearing ores also yields significant amounts of vanadium pentoxide (Atomix, 2003).

Total world production of vanadium pentoxide in 1996 was approximately 131 million pounds [59 500 tonnes] (Woolery, 1997). Based on vanadium pentoxide produc-

tion capacity in 1994 from all sources, it has been estimated that the world's production of vanadium was split as follows: South Africa, 43%; USA, 17%; the Russian Federation, 15%; China, 13%; Venezuela, 4%; Chile, 4%; and others, 4% (Perron, 1994). In 2001, vanadium production capacity was estimated as follows: South Africa, 44%; the Russian Federation, 21%; Australia, 10%; USA, 8%; China, 8%; New Zealand, 4%; Kazakhstan, 2%; Japan, 1%; and others, 4% (Perron, 2001).

Available information indicates that vanadium pentoxide is produced by 12 companies in China, seven companies in the USA, six companies in India, five companies in Japan, four companies in the Russian Federation, two companies each in Germany and Taiwan, China, and one company each in Austria, Brazil, France, Kazakhstan, South Africa and Spain (Chemical Information Services, 2003).

1.2.2 *Use*

The major use of vanadium pentoxide is in the production of metal alloys. Iron–vanadium and aluminium–vanadium master alloys (e.g. for automotive steels, jet engines and airframes) are produced preferably from vanadium pentoxide fused flakes because of the low loss on ignition, low sulfur and dust contents, and high density of the molten oxide compared with powder.

Vanadium pentoxide is also used as an oxidation catalyst in heterogeneous and homogeneous catalytic processes for the production of sulfuric acid from sulfur dioxide, phthalic anhydride from naphthalene or *ortho*-xylene, maleic anhydride from benzene or *n*-butane/butene, adipic acid from cyclohexanol/cyclohexanone, acrylic acid from propane and acetaldehyde from alcohol. Minor amounts are used in the production of oxalic acid from cellulose and of anthraquinone from anthracene. Vanadium pentoxide has not found any significant uses in microelectronics but does have some applications in cathodes in primary and secondary (rechargeable) lithium batteries and in red phosphors for high-pressure mercury lamps and television screens. Vanadium pentoxide is used in the industries of enamelling, electrics and electronics, metallurgy, glass, catalysts, petrochemistry, and paint and ceramics. It is also used as a corrosion inhibitor in industrial processes for the production of hydrogen from hydrocarbons, as a coating for welding electrodes, as ultraviolet absorbent in glass, as depolariser, for glazes, for yellow and blue pigments, as a photographic developer, and in colloidal solution for anti-static layers on photographic material. It is also used as starting material for the production of carbides, nitrides, carbonitrides, silicides, halides, vanadates and vanadium salts (Woolery, 1997; O'Neil, 2001; ACGIH Worldwide®, 2003; Bauer *et al*., 2003).

1.3 Occurrence and exposure

1.3.1 *Natural occurrence*

Vanadium is widely but sparsely distributed in the earth's crust at an average concentration of 150 mg/kg and is found in about 80 different mineral ores, mainly in phosphate rock and iron ores. The concentration of vanadium measured in soil appears to be closely related to that of the parent rock from which it is formed and a range of 3–300 mg/kg has been recorded, with shales and clays exhibiting the highest concentrations (200 mg/kg and 300 mg/kg, respectively) (Byerrum *et al*., 1974; Waters, 1977; WHO, 1988; Nriagu, 1998).

Vanadium is also found in fossil fuels (oil, coal, shale). It is present in almost all coals, in concentrations ranging from extremely low to 10 g/kg. It is found in crude oil and residual fuel oil, but not in distillate fuel oils. Venezuelan crude oils are thought to have the highest vanadium content, reaching 1400 mg/kg. Flue-gas deposits from oil-fired furnaces have been found to contain up to 50% vanadium pentoxide. In crude oil, residual fuel oil and asphaltenes, the most common form of vanadium is the +4 oxidation state (Byerrum *et al*., 1974; Lagerkvist *et al.*, 1986; WHO, 1988; Nriagu, 1998).

1.3.2 *Occupational exposure*

Exposure to vanadium pentoxide in the workplace occurs primarily during the processing and refining of vanadium-rich ores and slags, during production of vanadium and vanadium-containing products, during combustion of fossil fuels (especially oil), during the handling of catalysts in the chemical industry, and during the cleaning of oil-fuelled boilers and furnaces (Plunkett, 1987). Data on vanadium concentrations in workplace air and the urine of workers exposed to vanadium in various industries are summarized in Table 2.

The processing of metals containing vanadium includes chemical treatment and high-temperature operations. However, only moderate concentrations of vanadium have been recorded in air in the breathing zone of workers engaged in these operations: 0.006–0.08 mg/m^3 during the addition of vanadium to furnaces, 0.004–0.02 mg/m^3 during tapping, 0.008–0.015 mg/m^3 during oxyacetylene cutting and 0.002–0.006 mg/m^3 during arc-welding (WHO, 1988).

In the main work areas of vanadium pentoxide production facilities where vanadium slag is processed, Roshchin (1968) recorded vanadium concentrations in dust of 20–55 mg/m^3 (reported to be mainly vanadium trioxide) and < 0.17 mg/m^3 vanadium pentoxide (cited by WHO, 1988). In another study in a vanadium pentoxide production plant, Kucera *et al*. (1998) recorded the highest concentration of total air particulates of 271 mg/m^3 at a pelletizer, with a corresponding vanadium concentration of 0.5 mg/m^3; the highest concentrations of vanadium were detected in air at a vibratory conveyer and reached 4.9 mg/m^3. Similarly high concentrations of vanadium (4.7 mg/m^3) were reported in air in the breathing zone of workers in the steel industry (Kiviluoto *et al*., 1979).

Breaking, loading and unloading, crushing and grinding, and magnetic separation of vanadium slag (about 120 g/kg vanadium pentoxide) causes formation of thick dust, with vanadium concentrations of 30–120 mg/m^3. About 70–72 % of the particles were reported to have a diameter of < 2 μm and 86–96% a diameter of < 5 μm. When the slag is roasted, free vanadium pentoxide is discharged and concentrations of vanadium in the vicinity of the furnace have been found to range from 0.04 to 1.56 mg/m^3. During leaching and precipitation, vanadium concentrations in the air can exceed 0.5 mg/m^3. Smelting and granulation of technical-grade vanadium pentoxide are accompanied by the formation of a vanadium-containing aerosol. During the loading of smelting furnaces, vanadium pentoxide concentrations in the surrounding air have been found to range from 0.15 to 0.80 mg/m^3; during smelting and granulation, from 0.7 to 11.7 mg/m^3; during the crushing, unloading and packaging of pure vanadium pentoxide, dusts are formed in the facilities and concentrations of 2.2–49 mg/m^3 vanadium pentoxide in air have been recorded (Roshchin, 1968; cited by WHO, 1988).

In the production of ferrovanadium alloys, a continuous discharge of vanadium pentoxide occurs during the smelting process. Vanadium pentoxide concentrations in air were reported to be 0.1–2.6 mg/m^3 in the work area of smelters and helpers, 2–124.6 mg/m^3 during charging of vanadium pentoxide in furnace, 0.07–9.43 mg/m^3 in the crane driver's cabin during smelting, 0.97–12.6 mg/m^3 during cutting up of ferrovanadium and 7.5–30 mg/m^3 during furnace maintenance (Roshchin, 1968; cited by WHO, 1988).

When ductile vanadium is produced by the aluminothermic process (based on the reduction of pure vanadium pentoxide with aluminium), a condensation aerosol of vanadium pentoxide is released, with 98% of the particles having a diameter of < 5 μm and 82% a diameter of < 2 μm. Vanadium pentoxide concentrations recorded in the surrounding air were 19–25.1 mg/m^3 during the preparation of the charge mixture, 64–240 mg/m^3 during placing of the burden inside the smelting chambers and 0.2–0.6 mg/m^3 in smelting operator's workplace (Roshchin, 1968; cited by WHO, 1988).

Usutani *et al*. (1979) measured vanadium pentoxide concentrations in air in a vanadium refinery. The highest concentrations (> 1 mg/m^3) were detected in samples collected during removal of vanadium pentoxide flakes from the slag (cited by WHO, 1988).

In facilities producing aluminium from bauxite, concentrations of vanadium pentoxide up to 2.3 mg/m^3 have been recorded in workplace air during tapping, packing and loading (Roshchin, 1968; cited by WHO, 1988).

Workers may be exposed to vanadium pentoxide in air during the handling of catalysts in chemical manufacturing plants. Exposure depends on the type of operations being carried out. During the removal and replacement of the catalyst, exposure to 0.01–0.67 mg/m^3 have been reported. Sieving of the catalyst can lead to higher exposures, and concentrations between 0.01 and 1.9 mg/m^3 (total inhalable vanadium) have been observed. Air-fed respiratory protective equipment is normally worn during catalyst removal and replacement and sieving (WHO, 2001).

Concentrations of vanadium pentoxide in the air during vanadium catalyst production have been reported as 1–7 mg/m^3 during grinding and unloading of vanadium pentoxide,

3.2–7.5 mg/m^3 during loading into the bin and 0.1–1 mg/m^3 during sifting and packing granules of contact substance (Roshchin, 1968; cited by WHO, 1988).

Hery *et al*. (1992) assessed exposures to chemical pollutants during the handling (loading and unloading of reactors, sieving of catalysts) of inorganic catalysts, including vanadium pentoxide. Concentrations of vanadium pentoxide in air were reported to be 0.08–0.9 mg/m^3 during unloading, 1.1–230 mg/m^3 during screening and 600–1200 mg/m^3 during loading.

Hery *et al*. (1994) assessed exposures during the manufacture and reprocessing of inorganic catalysts, including vanadium pentoxide. In one of four 1-h air samples taken in a reprocessing plant during the oven-cleaning operation, a vanadium pentoxide concentration of 2.2 mg/m^3 was measured.

Fuel oil combustion results in the formation of vanadium-containing dust, and large amounts of dust result from operations connected with removal of ash encrustations when cleaning boilers and the blades of gas turbines. Dust concentrations in the air inside the boilers have been reported to range from 20 to 400 mg/m^3, the most common range being 50–100 mg/m^3, with the dust containing 5–17% vanadium pentoxide (Roshchin, 1968; cited by WHO, 1988).

Occupational exposure to vanadium occurs during the cleaning of oil-fired boilers and furnaces in oil-fired heating and power plants and ships, although workers probably spend less than 20% of their time cleaning oil-fired boilers. Vanadium concentrations in air (total inhalable fraction) as high as 20 mg/m^3 were recorded when these tasks were performed, but typically were lower than 0.1 mg/m^3. The lowest results were obtained where wet cleaning methods were used. Respiratory protective equipment was usually worn during boiler cleaning operations (WHO, 2001).

Williams (1952) published air sampling data on boiler-cleaning operations in the British power industry. A vanadium concentration of 40.2 mg/m^3 was recorded in air in the superheater chamber, while the concentration was 58.6 mg/m^3 in the combustion chamber; 93.6% of the dust particles had a diameter of 0.15–1 μm (cited by WHO, 1988).

Kuzelova *et al*. (1977) reported dust concentrations during boiler-cleaning operations of about 136–36 000 mg/m^3 in the workplace air, in which vanadium concentrations ranged from 1.7 to 18.4 mg/m^3 (cited by WHO, 1988).

Barisione *et al*. (1993) assessed the acute exposure to vanadium pentoxide in maintenance personnel working inside an oil-fired boiler at an electric power station in Italy. The vanadium pentoxide concentration in the air in the work room was 0.28 mg/m^3, which exceeded exposure standards. The concentration of vanadium in the urine of the arc welders did not correlate with vanadium pentoxide concentration in the air (see Table 2).

In 26 boilermakers overhauling an oil-powered boiler in the USA, Hauser *et al*. (1995a) investigated exposure to air particulates with an aerodynamic diameter of ≤ 10 μm (PM_{10}) and respirable vanadium-containing dust for up to 15 work days. The peak PM_{10} concentration (1- to 10-h TWA) ranged from 1.48 to 7.30 mg/m^3; the peak vanadium concentration ranged from 2.2 to 32.2 μg/m^3, with a mean (SD) of 20.2 (11.4) μg/m^3. In a later study, the

authors determined vanadium concentrations in the urine of a subgroup of workers (Hauser *et al.*, 1998; see Table 2).

In another study of boilermakers overhauling an oil-fired boiler in the USA, lower exposures to PM_{10} particulates and to respirable vanadium-containing dust were reported (median, 0.6 mg/m^3 and 12.7 μg/m^3, respectively) (Woodin *et al.*, 1999).

The National Institute of Occupational Safety and Health in the USA conducted surveys on exposure to vanadium pentoxide in the industry. The National Occupational Hazard Survey, conducted in 1972–74, estimated that 2562 workers in 333 plants were potentially exposed to vanadium pentoxide in 1970. The largest number of workers exposed worked in the stone, clay and glass products industries, and the second largest group was involved with electric, gas and sanitary services (National Institute for Occupational Safety and Health, 1976). The National Occupational Exposure Survey, conducted in 1980–83, reported that approximately 5319 workers in 151 plants were potentially exposed to vanadium in 1980. Among them, 84% were exposed specifically to vanadium pentoxide. The largest number of workers were exposed in the chemical and allied products industry (National Institute for Occupational Safety and Health, 1984).

Workers in the manufacture of vanadium-containing pigments for the ceramics industry may be exposed to vanadium compounds. Exposure is controlled by the use of local exhaust ventilation, and data indicate that vanadium concentrations in air are normally below 0.2 mg/m^3 (total inhalable fraction) (WHO, 2001).

Other reports of occupational exposures to vanadium have been reviewed (Zenz, 1994).

1.3.3 *Environmental exposure*

(*a*) *Air*

(i) *Natural sources*

Natural sources of atmospheric vanadium include continental dust, marine aerosols (sea salt sprays) and volcanic emissions. The quantities entering the atmosphere from each of these sources are uncertain; however, continental dust is believed to account for the largest portion of naturally-emitted atmospheric vanadium; contributions from volcanic emissions are believed to be small (Zoller *et al.*, 1973; Byerrum *et al.*, 1974). Atmospheric emissions of vanadium from natural sources had been estimated at 70 000 to 80 000 tonnes per year. However, more recent estimates report much lower values (1.6–54.2 tonnes per year) and suggest that fluxes from natural sources were overestimated by earlier workers (Mamane & Pirrone, 1998; Nriagu & Pirrone, 1998).

Concentrations of vanadium in the atmosphere in unpopulated areas such as Antarctica have been found to range from 0.0006 to 0.0024 ng/m^3 (Zoller *et al.*, 1974). Measurements taken over the eastern Pacific Ocean averaged 0.17 ng/m^3 (range of means, ≤ 0.02–0.8 ng/m^3) (Hoffman *et al.*, 1969). Measurements over rural north-western Canada and Puerto Rico were one order of magnitude higher (0.2–1.9 ng/m^3) (Martens *et al.*, 1973; Zoller *et al.*, 1973).

(ii) *Anthropogenic sources*

Estimates of global anthropogenic emissions of vanadium into the atmosphere over the last decade range from 70 000 tonnes to 210 000 tonnes per year (Hope, 1994; Mamane & Pirrone, 1998; Nriagu & Pirrone, 1998).

The major point sources are metallurgical works (30 kg vanadium/tonne vanadium produced), and coal and residual oil burning (0.2–2 kg vanadium/1000 tonnes and 30–300 kg/10^6 L burnt, respectively) (Zoller *et al*., 1973; Lagerkvist *et al*., 1986). Crude oils have an average vanadium content of 50 mg/kg (see above). [*Residual fuel oils* (heavy fuel oils) are petroleum refining residues remaining after distillation or cracking, and blends of these residues with distillates. They are used primarily in industrial burners and boilers as sources of heat and power (IARC, 1989). During refining and distillation, the vanadium remains in the residual oil because of its low volatility, and as a result becomes more concentrated than in the original crude.] During combustion, most of the vanadium in residual oils is released into the atmosphere in the form of vanadium pentoxide as part of fly ash particulates. Vanadium concentrations in coal fly ash range from 0.1 to 1 mg/g, and in residual oil from 10 to 50 mg/g (Mamane & Pirrone, 1998).

Vanadium was found in 87% of all air samples taken in the vicinity of large metallurgical plants at concentrations in the range of 0.98–1.49 μg/m^3, and in 11% of the samples exceeded 2 μg/m^3 (Pazhynich, 1967). At a steel plant in the USA in 1967, concentrations of vanadium in ambient air ranged from 40 to 107 ng/m^3 and averaged 72 ng/m^3 (WHO, 1988). Concentrations as high as 1000 ng/m^3 vanadium pentoxide were found in air by Pazhynich (1967) in the former Soviet Union at a site 1500 m from areas of extensive metallurgical activity unconnected with vanadium production. In the same country, near a plant producing technical vanadium pentoxide, 24-h mean concentrations of vanadium pentoxide of 4–12, 1–6, and 1–4 μg/m^3 in air were recorded at distances of 500, 1000 and 2000 m from the source, respectively (WHO, 1988).

According to the US Toxic Release Inventory (TRI, 1987–2001), the amount of vanadium released into the atmosphere from manufacturing and processing facilities in the USA fluctuated between 5–9 tonnes between 1987 and 1997 and had dramatically increased to over 100 tonnes by 2001. However, this estimate is believed to be limited because the largest anthropogenic releases of vanadium to the atmosphere are attributed to the combustion of residual fuel oils and coal, which are probably not included.

Vanadium-containing particulates emitted from anthropogenic sources into the atmosphere are simple or complex oxides (Byerrum *et al*., 1974) or may be associated with sulfates (Mamane & Pirrone, 1998). Generally, lower oxides formed during combustion of coal and residual fuel oils, such as vanadium trioxide, undergo further oxidation to the pentoxide form before leaving the stacks (Environmental Protection Agency, 1985).

Concentrations of vanadium measured in ambient air vary widely between rural and urban locations; in general, these are higher in urban than in rural areas. Earlier reports suggested concentrations of 1–40 ng/m^3 (van Zinderen Bakker & Jaworski, 1980) or 0.2–75 ng/m^3 (Environmental Protection Agency, 1977) in air in rural sites, although the annual average was below 1 ng/m^3. This was attributed to the local burning of fuel oils with

a high vanadium content. Recent data from rural areas show concentrations ranging from 0.3 to about 5 ng/m^3, with annual averages frequently below 1 ng/m^3, which can be regarded as the natural background concentration in rural areas (Mamane & Pirrone, 1998).

Annual average concentrations of vanadium in air in large cities may often be in the range of 50–200 ng/m^3, although concentrations exceeding 200–300 ng/m^3 have been recorded, and the maximum 24-h average may exceed 2000 ng/m^3 (WHO, 1988). In the USA, cities can be divided into two groups based on the concentrations of vanadium present in their ambient air. The first group consists of cities widely distributed throughout the USA and characterized by vanadium concentrations in ambient air that range from 3 to 22 ng/m^3, with an average of 11 ng/m^3. Cities in the second group, primarily located in the north-eastern USA, have mean concentrations of vanadium that range from 150 to 1400 ng/m^3, with an average of about 600 ng/m^3. The difference is attributed to the use of large quantities of residual fuel oil in cities in the second group for the generation of heat and electricity, particularly during winter months (Zoller *et al*., 1973; WHO, 2000). Vanadium concentrations in ambient urban air vary extensively with the season. However, there are indications that vanadium concentrations in urban locations in 1998 were lower than those reported in the 1960s and 1970s (Mamane & Pirrone, 1998).

Hence, the general population may be exposed to airborne vanadium through inhalation, particularly in areas where use of residual fuel oils for energy production is high (Zoller *et al*., 1973). For instance, assuming vanadium concentrations in air of approximately 50 ng/m^3, Byrne and Kosta (1978b) estimated a daily intake of 1 µg vanadium by inhalation.

(*b*) *Water*

Vanadium dissolved in water is present almost exclusively in the pentavalent form. Its concentration ranges from approximately 0.1 to 220 µg/L in fresh water and from 0.3 to 29 µg/L in seawater. The highest concentrations in fresh waters were recorded in the vicinity of metallurgical plants or downstream of large cities (WHO, 1988; Bauer *et al*., 2003). Anthropogenic sources account for only a small percentage of the dissolved vanadium reaching the oceans (Hope, 1994).

(*c*) *Food*

Vanadium intake from food has been reasonably well established, based on the analysis of dietary items (Myron *et al.*, 1977; Byrne & Kosta, 1978b; Minoia *et al*., 1994) and total diets (Myron *et al.*, 1978; Byrne & Kucera, 1991a). Considering consumption of about 500 g (dry mass) total diet, daily dietary vanadium intake in the general population has been estimated at 10–30 µg per person per day, although it can reach 70 µg per day in some countries (Byrne & Kucera, 1991a).

An increased daily intake of vanadium may result from the consumption of some wild-growing mushrooms (Byrne & Kosta, 1978b) and some beverages (Minoia *et al*., 1994), especially beer. Contamination of the marine environment with oil in the Gulf War resulted in increased concentrations of vanadium in certain seafood (WHO, 2001).

Considering the poor absorption of vanadium from the gastrointestinal tract, dietary habits can be expected to have only a minor influence on vanadium concentrations in body fluids (WHO, 1988; Sabbioni *et al*., 1996) (see Section 4.1).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for vanadium pentoxide in workplace air are presented in Table 3.

ACGIH Worldwide® (2003) recommends a semi-quantitative BEI for vanadium in urine of 50 µg/g creatinine. ACGIH recommends monitoring vanadium in urine collected at the end of the last shift of the work week as an indicator of recent exposure to vanadium pentoxide. Germany recommends a biological tolerance value for occupational exposure for vanadium in urine of 70 µg/g creatinine. Germany also recommends monitoring vanadium in urine collected at the end of the exposure, for example at the end of the shift or, for long-term exposures, after several shifts (Deutsche Forschungsgemeinschaft, 2002).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

3.1.1 *Mouse*

In a study undertaken by the National Toxicology Program (2002), groups of 50 male and 50 female B6C3F$_1$ mice, 6–7 weeks of age, were exposed to vanadium pentoxide particulate (light orange, crystalline solid; purity, ≈ 99%; MMAD, 1.2–1.3 µm; GSD, 1.9 µm) at concentrations of 0, 1, 2 or 4 mg/m^3 by inhalation for 6 h per day on 5 days per week for 104 weeks. Survival was significantly decreased in males exposed to 4 mg/m^3 compared with chamber controls (survival rates: 39/50 (control), 33/50 (low concentration), 36/50 (mid concentration) or 27/50 (high concentration) in males and 38/50, 32/50 30/50 or 32/50 in females, respectively; mean survival times, 710, 692, 704 or 668 days in males and 692, 655, 653 or 688 days in females, respectively). Mean body weights were decreased in females exposed to ≥ 1 mg/m^3 and in males exposed to ≥ 2 mg/m^3. Exposure to vanadium pentoxide caused an increase in the incidence of alveolar/bronchiolar neoplasms, but did not cause an increased incidence of neoplasms in other tissues. The incidence of neoplasms and non-neoplastic lesions of the respiratory system

Table 3. Occupational exposure limits and guidelines for vanadium (as V_2O_5 unless otherwise specified)

Country or region	Concentration (mg/m^3)	Classification[a]	Interpretation[b]
Australia	0.05 (respirable dust and fume)		TWA
Belgium	0.5		TWA
Canada			
Alberta	0.05 (respirable dust and fume)		TWA
	0.15 (respirable dust and fume)		STEL
Quebec	0.05 (respirable dust and fume)		TWA
China	0.05 (dust and fume, as V)		TWA
	0.15 (dust and fume, as V)		STEL
Finland	0.05 (dust, as V)		TWA
	0.5 (fume, as V)		TWA
France	0.05 (respirable dust and fume)		TWA
Germany	0.05 (respirable fraction)		TWA (MAC)
	0.05 (respirable fraction)		STEL
Hong Kong SAR	0.05 (respirable dust and fume)	A4	TWA
Ireland	0.04 (respirable dust, as V)		TWA
	0.05 (fume, as V)		TWA
	0.5 (total inhalable dust, as V)		TWA
Japan	0.1 (fume)		TWA
	0.5 (dust)		TWA (JSOH)
Malaysia	0.05		TWA
Mexico	0.5 (dust and fume)	A4	TWA
Netherlands	0.01		TWA
	0.03		STEL
New Zealand	0.05 (respirable dust and fume)		TWA
Poland	0.05 (dust and fume)		TWA
	0.1 (fume); 0.5 (dust)		STEL
Russian Federation	0.1 (fume)		MAC
	0.5 (dust)		NG
South Africa	0.05 (respirable dust and fume)		TWA (DOL-RL)
	0.5 (total inhalable dust)		TWA
Spain	0.05 (respirable dust and fume)		TWA
Sweden	0.2 (total dust, as V)		TWA
	0.05 (respirable dust, as V)		Ceiling
Switzerland	0.05		TWA
	0.05		STEL
United Kingdom	0.05		TWA (MEL)

Table 3 (contd)

Country or region	Concentration (mg/m^3)	Classification[a]	Interpretation[b]
USA[c]			
ACGIH	0.05 (respirable dust and fume)	A4	TWA (TLV)
NIOSH	0.05 (total dust and fume, as V)		Ceiling (REL)
OSHA	0.1 (fume); 0.5 (respirable dust)		Ceiling (PEL)

From Sokolov (1981); INRS (1999); Työsuojelusäädöksiä (2002); ACGIH Worldwide® (2003); Suva (2003)

[a] A4, not classifiable as a human carcinogen; the absence of any classification does not necessarily mean that vanadium pentoxide has been evaluated by individual organizations as non-carcinogenic to humans.

[b] TWA, time-weighted average; STEL, short-term exposure limit; MAC, maximum allowed concentration; JSOH, Japanese Society for Occupational Health; NG, not given; DOL-RL, Department of Labour-Recommended Limit; MEL, maximum exposure limit; TLV, threshold limit value; REL, recommended exposure limit; PEL, permissible exposure limit.

are reported in Table 4. Alveolar/bronchiolar adenomas were typical of those that occur spontaneously in mice. Carcinomas had one or more of the following histological features; heterogeneous growth pattern, cellular pleomorphism and/or atypia, and local invasion or metastasis. A number of exposed males and females had multiple alveolar/bronchiolar neoplasms. This last finding is an uncommon response in mice and, in some cases, it was difficult to distinguish between multiplicity and metastases from other lung neoplasms. Mice are generally not considered to respond to particulate exposure by the development of lung neoplasms, even at high concentrations. There was a significantly-increased incidence of alveolar epithelial hyperplasia and bronchiolar epithelial hyperplasia in the lungs of exposed male and female mice. The hyperplasia was essentially a diffuse change with proliferation of epithelium in the distal terminal bronchioles and the immediately associated alveolar ducts and alveoli. The hyperplasia of the alveolar epithelium was pronounced and increased in severity with increasing exposure concentration, while the hyperplasia of the distal bronchioles was minimal to mild. Histiocytic infiltration occurred primarily within alveoli in close proximity to alveolar/bronchiolar neoplasms, particularly carcinomas (National Toxicology Program, 2002; Ress *et al*., 2003).

3.1.2 *Rat*

In a study undertaken by the National Toxicology Program (2002), groups of 50 male and 50 female Fischer 344/N rats, 6–7 weeks of age, were exposed to vanadium pentoxide particulate (light orange, crystalline solid; purity, ≈ 99%; MMAD, 1.2–1.3 μm; GSD, 1.9 μm) at concentrations of 0, 0.5, 1 or 2 mg/m^3 by inhalation for 6 h per day on 5 days per week for 104 weeks. No adverse effects on survival were observed in treated males or females compared with chamber controls (survival rates: 20/50 (control), 29/50 (low

Table 4. Incidence of neoplasms and non-neoplastic lesions of the respiratory system and bronchial lymph nodes in mice in a 2-year inhalation study of vanadium pentoxide

	No. of mice exposed to vanadium pentoxide at concentrations (mg/m^3) of			
	0 (chamber control)	1	2	4
Males				
Lung				
Total no. examined	50	50	50	50
No. with:				
Alveolar epithelium, hyperplasia	3 (3.0)[a]	41[b] (2.2)	49[b] (3.3)	50[b] (3.9)
Bronchiole epithelium, hyperplasia	0	15[b] (1.0)	37[b] (1.1)	46[b] (1.7)
Inflammation, chronic	6 (1.5)	42[b] (1.5)	45[b] (1.6)	47[b] (2.0)
Alveolus, infiltration cellular, histiocyte	10 (2.4)	36[b] (2.4)	45[b] (2.6)	49[b] (3.0)
Interstitial fibrosis	1 (1.0)	6 (1.7)	9[b] (1.2)	12[b] (1.7)
Alveolar/bronchiolar adenoma, multiple	1	1	11[b]	5
Alveolar/bronchiolar adenoma (includes multiple)	13	16	26[b]	15
Alveolar/bronchiolar carcinoma, multiple	1	10[b]	16[b]	13[b]
Alveolar/bronchiolar carcinoma (includes multiple)	12	29[b]	30[b]	35[b]
Alveolar/bronchiolar adenoma or carcinoma	22	42[b]	43[b]	43[b]
Larynx				
Total no. examined	49	50	48	50
No. with:				
Respiratory epithelium, epiglottis, metaplasia, squamous	2 (1.0)	45[b] (1.0)	41[b] (1.0)	41[b] (1.0)
Nose				
Total no. examined	50	50	50	50
No. witth:				
Inflammation, suppurative	16 (1.3)	11 (1.4)	32[b] (1.2)	23[c] (1.3)
Olfactory epithelium, atrophy	6 (1.0)	7 (1.6)	9 (1.3)	12 (1.2)
Olfactory epithelium, degeneration, hyaline	1 (1.0)	7[c] (1.0)	23[b] (1.1)	30[b] (1.2)
Respiratory epithelium, degeneration, hyaline	8 (1.1)	22[b] (1.0)	38[b] (1.2)	41[b] (1.4)
Respiratory epithelium, metaplasia, squamous	0	6[c] (1.2)	6[c] (1.3)	2 (1.5)
Lymph node, bronchial				
Total no. examined	40	38	36	40
No. with:				
Hyperplasia	7 (2.1)	7 (2.4)	12 (2.1)	13 (2.2)

Table 4 (contd)

	No. of mice exposed to vanadium pentoxide at concentrations (mg/m^3) of			
	0 (chamber control)	1	2	4
Females				
Lung				
Total no. examined	50	50	50	50
No. with:				
Alveolar epithelium, hyperplasia	0	31[b] (1.6)	38[b] (2.0)	50[b] (3.3)
Bronchiole epithelium, hyperplasia	0	12[b] (1.0)	34[b] (1.0)	48[b] (1.5)
Inflammation, chronic	4 (1.0)	37[b] (1.3)	39[b] (1.8)	49[b] (2.0)
Alveolus, infiltration cellular, histiocyte	0	34[b] (2.4)	35[b] (2.4)	45[b] (2.7)
Interstitial fibrosis	0	1 (2.0)	4[c] (2.5)	8[b] (1.5)
Alveolar/bronchiolar adenoma, multiple	0	3	5[c]	6[c]
Alveolar/bronchiolar adenoma (includes multiple)	1	17[b]	23[b]	19[b]
Alveolar/bronchiolar carcinoma, multiple	0	9[b]	5[c]	5[c]
Alveolar/bronchiolar carcinoma (includes multiple)	0	23[b]	18[b]	22[b]
Alveolar/bronchiolar adenoma or carcinoma	1	32[b]	35[b]	32[b]
Larynx				
Total no. examined	50	50	50	50
No. with:				
Respiratory epithelium, epiglottis, metaplasia, squamous	0	39[b] (1.0)	45[b] (1.0)	44[b] (1.1)
Nose				
Total no. examined	50	50	50	50
No. with:				
Inflammation, suppurative	19 (1.1)	14 (1.2)	32[b] (1.2)	30[b] (1.3)
Olfactory epithelium, atrophy	2 (1.5)	8[c] (1.3)	5 (1.0)	14[b] (1.3)
Olfactory epithelium, degeneration, hyaline	11 (1.2)	23[b] (1.0)	34[b] (1.2)	48[b] (1.3)
Respiratory epithelium, degeneration, hyaline	35 (1.3)	39 (1.5)	46[b] (1.7)	50[b] (1.8)
Respiratory epithelium, metaplasia, squamous	0	3 (1.3)	7[b] (1.1)	8[b] (1.1)
Respiratory epithelium, necrosis	0	0	1 (2.0)	7[b] (1.4)
Lymph node, bronchial				
Total no. examined	39	40	45	41
No. with:				
Hyperplasia	3 (2.0)	13[b] (1.8)	14[b] (2.3)	20[b] (2.3)

From National Toxicology Program (2002)
[a] Average severity grade of lesions in affected animals: 1, minimal; 2, mild; 3, moderate; 4, marked
[b] Significantly different ($p \leq 0.01$) from the chamber control group by the Poly-3 test
[c] Significantly different ($p \leq 0.05$) from the chamber control group by the Poly-3 test

concentration), 26/50 (mid concentration) or 27/50 (high concentration) in males and 33/50, 24/50, 29/50 or 30/50 in females, respectively; mean survival times: 668, 680, 692 or 671 days in males and 688, 678, 679 or 683 days in females, respectively). Mean body weights were slightly decreased in females exposed to 2.0 mg/m^3 throughout the study compared with chamber controls. Although there was a marginally increased incidence of alveolar/bronchiolar neoplasms in female rats, the increase was not statistically significant, did not occur in a concentration-related fashion and was in the historical control range. Thus, it was uncertain whether the increased incidence observed was exposure-related. Exposure to vanadium pentoxide caused an increase in the incidence of alveolar/bronchiolar neoplasms in male rats. Although not statistically significant, the incidence of alveolar/bronchiolar adenoma in males exposed to 0.5 mg/m^3 and of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) in males exposed to 0.5 and 2 mg/m^3 exceeded the historical ranges in controls (all routes) given NTP-2000 diet and inhalation controls given NIH-07 diet. This response was considered to be related to exposure to vanadium pentoxide. However, exposure to vanadium pentoxide did not cause increased incidence of neoplasms in other tissues. The incidence of neoplasms and non-neoplastic lesions of the respiratory system in male rats is reported in Table 5. Alveolar bronchiolar adenomas, typical of those occurring spontaneously, were generally distinct masses that compressed surrounding tissue. Component epithelial cells were generally uniform in appearance and were arranged in acinar and/or irregular papillary structures and occasionally in a solid cellular pattern. Alveolar/bronchiolar carcinomas had similar cellular patterns but were generally larger and had one or more of the following histological features; heterogeneous growth pattern, cellular pleomorphism and/or atypia, and local invasion or metastasis. Three male rats exposed to 0.5 mg/m^3, one male rat exposed to 1 mg/m^3 and three male rats exposed to 2 mg/m^3 developed alveolar/bronchiolar carcinomas, one of which metastasized. There were no primary lung carcinomas in the chamber control rats. Alveolar/bronchiolar adenomas and especially carcinomas with metastases from the site of origin are uncommon in rats (Hahn, 1993). Exposure to vanadium pentoxide caused a spectrum of inflammatory and proliferative lesions in the lungs that were similar in male and female rats. There was a significantly-increased incidence of alveolar epithelial hyperplasia in the lungs of males exposed to 0.5 mg/m^3 or greater and females exposed to 1 or 2 mg/m^3. Squamous metaplasia of the alveolar epithelium occurred in 21/50 male and 6/50 female rats exposed to 2.0 mg/m^3 vanadium pentoxide. Squamous epithelium is not a normal component of the lung parenchyma. It is a more resilient epithelium and its occurrence in the lung generally represents a response to injury (National Toxicology Program, 2002; Ress *et al.*, 2003).

3.1.3 *Comparison of findings from the rat and mouse inhalation studies*

A wide range of proliferative lesions in the lungs were observed in rats and mice exposed to vanadium pentoxide for 2 years. The incidence of hyperplasia of the alveolar and bronchiolar epithelium was increased in exposed rats and mice. Although given

Table 5. Incidence of neoplasms and non-neoplastic lesions of the respiratory system and bronchial lymph nodes in male rats in a 2-year inhalation study of vanadium pentoxide

	No. of rats exposed to vanadium pentoxide at concentrations (mg/m^3) of			
	0 (chamber control)	0.5	1	2
Lung				
Total no. examined	50	49	48	50
No. with:				
Alveolar epithelium, hyperplasia	7 (2.3)[a]	24[b] (2.0)	34[b] (2.0)	49[b] (3.3)
Bronchiole epithelium, hyperplasia	3 (2.3)	17[b] (2.2)	31[b] (1.8)	49[b] (3.3)
Alveolar epithelium, metaplasia, squamous	1 (1.0)	0	0	21[b] (3.6)
Bronchiole epithelium, metaplasia, squamous	0	0	0	7[b] (3.7)
Inflammation, chronic active	5 (1.6)	8 (1.8)	24[b] (1.3)	42[b] (2.4)
Interstitial fibrosis	7 (1.4)	7 (2.0)	16[c] (1.6)	38[b] (2.1)
Alveolus, infiltration cellular, histiocyte	22 (1.3)	40[b] (2.0)	45[b] (2.3)	50[b] (3.3)
Alveolus, pigmentation	1 (2.0)	0	2 (1.5)	28[b] (2.1)
Alveolar/bronchiolar adenoma, multiple	0	2	0	0
Alveolar/bronchiolar adenoma (includes multiple)	4	8	5	6
Alveolar/bronchiolar carcinoma, multiple	0	1	0	0
Alveolar/bronchiolar carcinoma (includes multiple)	0	3	1	3
Alveolar/bronchiolar adenoma or carcinoma	4	10	6	9
Larynx				
Total no. examined	49	50	50	49
No. with:				
Inflammation, chronic	3 (1.0)	20[b] (1.1)	17[b] (1.5)	28[b] (1.6)
Respiratory epithelium, epiglottis, degeneration	0	22[b] (1.1)	23[b] (1.1)	33[b] (1.5)
Respiratory epithelium, epiglottis, hyperplasia	0	18[b] (1.5)	34[b] (1.5)	32[b] (1.9)
Respiratory epithelium, epiglottis, metaplasia, squamous	0	9[b] (1.7)	16[b] (1.8)	19[b] (2.1)
Nose				
Total no. examined	49	50	49	48
No. with:				
Goblet cell, respiratory epithelium, hyperplasia	4 (1.8)	15[b] (1.8)	12[c] (2.0)	17[b] (2.1)

From National Toxicology Program (2002)

[a] Average severity grade of lesions in affected animals: 1, minimal; 2, mild; 3, moderate; 4, marked

[b] Significantly different ($p \leq 0.01$) from the chamber control group by the Poly-3 test

[c] Significantly different ($p \leq 0.05$) from the chamber control group by the Poly-3 test

distinct diagnoses, the lesions were considered to be one pathogenic process. The authors concluded that this hyperplastic change was striking and appeared more prominent than had been observed in other National Toxicology Program inhalation studies. Although the exact pathogenesis was not determined in this study, the hyperplasia of the alveolar and bronchiolar epithelium was consistent with bronchiolization, a process in which bronchiolar epithelium proliferates and migrates down into alveolar ducts and adjacent alveoli. Although there was clearly proliferation, it was thought primarily to represent a metaplastic change. Whether this represented a precursor lesion for development of pulmonary neoplasms is not known. The lung tumour response in rats and mice following exposure to vanadium pentoxide was not concentration-related; there was a flat dose response. Several dose metrics and lung-burden data were used to aid in interpretation of lung pathology in exposed rats and mice. In the case of all dose metrics, rats received more vanadium than mice. In mice, the total 'dose' was similar in the groups exposed to 1 mg/m^3 and 2 mg/m^3 and this may help explain the flat dose response in the lung neoplasms in male and female mice. The total dose does not explain the differences in neoplasms in rats compared with mice. However, when the total dose is corrected for body weight, mice received a three- to five-fold higher dose of vanadium than rats at comparable exposure concentrations of 1 and 2 mg/m^3. Therefore, on a body weight basis, mice received considerably more vanadium than rats, and this may help explain the differences in responses between the species (National Toxicology Program, 2002; Ress *et al*., 2003).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Deposition, retention, clearance and metabolism

Vanadium pentoxide (V_2O_5) is a poorly soluble oxide which, in water or body fluids, releases some vanadium ions which may speciate either in cationic (VO_2^+) or anionic (HVO_4^{2-}) forms [at physiological pH: $H_2VO_4^-$].

Toya *et al*. (2001) showed that vanadium pentoxide powder (geometric mean diameter, 0.31 μm) was eight times more soluble in an artificial biological fluid (Gamble's solution) than in water.

Elimination from the lung, and distribution to and elimination from tissues, is partly a function of solubility. Sodium vanadate is more soluble than vanadium pentoxide and is consequently cleared more rapidly from the lung (Sharma *et al*., 1987).

Vanadium (V) is reduced to vanadium (IV) in humans and other mammals. It is considered to be an essential element in chickens, rats and probably humans (Nielsen, 1991; French & Jones, 1993; Crans *et al*., 1998; Hamel, 1998; National Toxicology Program, 2002). The main source of vanadium intake for the general human population is food (see also Section 1.3.5).

4.1.1 *Humans*

Zenz and Berg (1967) studied responses in nine human volunteers exposed to 0.2 mg/m^3 vanadium pentoxide (particle size, 98% < 5 μm) for 8 h in a controlled environmental chamber. The highest concentration of vanadium was found in the urine (0.13 mg/L [2.6 μM/L]) 3 days after exposure; none of the volunteers had detectable concentrations 1 week after exposure.

Pistelli *et al*. (1991) studied 11 vanadium pentoxide-exposed workers 40–60 h after they had removed ashes from boilers of an oil-fired power station. Seven of the workers were smokers compared with eight of 14 controls. Vanadium concentrations in urine were determined by AAS and ranged between 1.4 and 27 μg/L in the exposed group. Four of the controls had detectable concentrations of vanadium in the urine (range, 0.5–1.0 μg/L).

Hauser *et al.* (1998) determined concentrations of vanadium by means of GF-AAS in the urine of workers overhauling an oil-fired boiler where concentrations of vanadium pentoxide in the air ranged from 0.36 to 32.2 μg/m^3 (mean, 19.1 μg/m^3). On the first day of work on the overhaul, the mean vanadium concentrations in urine were 0.87 mg/g creatinine before a shift and 1.53 mg/g creatinine after a shift. However, the vanadium concentrations in the start-of-shift urine samples on the last Monday of the study were not significantly different from the start-of-shift concentrations on the previous Saturday, a time interval of about 38 h between the end of exposure and sample collection. Spearman rank correlation between start-of-shift concentration of vanadium in urine and concentration of vanadium in workplace dust during the previous day was not strong (r = 0.35) due to incomplete and insufficient information on respirator usage as noted by the authors. These data support a rapid initial clearance of inhaled vanadium occurring on the first day of work followed by a slower clearance phase that was not complete 38 h after the end of exposure (Hauser *et al.*, 1998).

Kucera *et al*. (1998) analysed vanadium in biological samples from workers engaged in the production of vanadium pentoxide by a hydrometallurgical process and occupationally non-exposed controls. Average exposure time was 9.2 years (range, 0.5–33 years). Concentrations of vanadium in workplace air samples were high (range, 0.017–4.8 mg/m^3). Concentrations of vanadium in the blood of a subsample of workers was 12.1 ± 3.52 μg/L (geometric mean ± GSD) compared with 0.055 ± 1.41 μg/L among the non-exposed controls. Vanadium concentrations in morning urine were 29.2 ± 3.33 μg/L in exposed workers and 0.203 ± 1.61 μg/L for the non-exposed. The finding of high concentrations in morning urine is compatible with the fact that long-term exposure results in vanadium accumulation in the bone from which it can be released slowly.

Vanadium pentoxide was found to be rapidly absorbed following inhalation exposure, but poorly through dermal contact or when ingested as ammonium vanadyl tartrate (Dimond *et al.*, 1963; Gylseth *et al.*, 1979; Kiviluoto *et al.*, 1981; Ryan *et al*., 1999). When given orally, 0.1–1% is absorbed from the gut, although absorption of more soluble vanadium compounds is greater. About 60% of absorbed vanadium is excreted in the urine within 24 h (McKee, 1998). Based on samples from autopsies, vanadium was found to be distributed to

the lungs and the intestine. It was not detected in heart, aorta, brain, kidney, ovary or testes, although detection methods were reported to be insensitive (Schroeder *et al.*, 1963; Ryan *et al*., 1999).

Using AAS, Fortoul *et al*. (2002) analysed vanadium concentrations in lung tissue samples from autopsies of Mexico city residents in the 1960s and 1990s (n = 39 and 48, respectively). Vanadium concentrations were 1.04 ± 0.05 μg/g in lung samples from the 1960s and 1.36 ± 0.08 μg/g in samples from the 1990s, indicating an increase in ambient exposure to vanadium.

4.1.2 *Experimental systems*

(*a*) *In-vivo studies*

Absorption of vanadium compounds after oral administration is known to be strongly affected by such dietary components as type of carbohydrate, fibre protein concentration, other trace elements, chelating agents and electrolytes (Nielsen, 1987). Associated pathology or physiological state may also affect vanadium absorption and hence may render a consistent determination of a lethal dose (e.g. LD_{50}) by the oral route very difficult (Thompson *et al*., 1998).

In general, the absorption, distribution and elimination of vanadium pentoxide and other vanadium compounds are similar. There are, however, variations depending on the solubility of the administered compound, the route of exposure and the form of vanadium administered (National Toxicology Program, 2002).

(i) *Inhalation studies*

Mice

In a National Toxicology Program tissue burden study (2002), male and female $B6C3F_1$ mice were exposed to 1, 2, or 4 mg/m^3 vanadium pentoxide by inhalation for 104 weeks (for details, see Section 3.1.1). Tissue burden analyses were performed on days 1, 5, 12, 26, 54, 171, 362 and 535 after the start of treatment. Lung weights increased throughout the study, most markedly in the group exposed to the highest concentration. The mean lung weights of the two lower-dose groups were similar. Lung vanadium burden increased roughly in proportion to the exposure concentration, with strong indications of linear toxicokinetics. As with the rats (see below), lung burdens in the mice did not reach a steady state in the groups exposed to 2 and 4 mg/m^3; they peaked near day 54 (at 5.9 and 11.3 μg, respectively), and then declined until day 535. In the low-dose group (1 mg/m^3), the lung burden reached a steady state around day 26 at a level of 3 μg vanadium. The same toxicokinetic model could be applied to both mice and rats (see below), with an initial deposition rate increasing with increasing exposure concentration, and a decline in deposition rate over the course of the study. In the group exposed to 4 mg/m^3, the deposition rate decreased from 0.62 to 0.27 μg/day between day 1 and day 535 and in the group exposed to 2 mg/m^3 it decreased from 0.41 to 0.22 μg/day. However, in the group exposed to the lowest dose there was a minimal decline in deposition rate between

days 1 and 535 (0.31 to 0.26 µg/day). Lung clearance half-lives in mice were 6, 11 and 14 days for the 1, 2 and 4 mg/m^3 exposure groups, respectively. Total vanadium lung doses were estimated to have been 153, 162 and 225 µg, respectively, while normalized lung doses were 153, 80.9 and 56.2 µg vanadium per mg vanadium pentoxide per m^3 exposure. On day 535, mice had retained approximately 2–3% of the total estimated lung doses (National Toxicology Program, 2002).

In an inhalation model described by Sánchez *et al.* (2003; abstract only), male CD-1 mice were exposed to an aerosol of 0.02 M vanadium pentoxide for 2 h twice a week for 4 weeks. Concentrations of vanadium (determined by AAS) in lung, liver, kidney, testes and brain increased after the first week of inhalation in all the organs examined and remained at almost the same values at the end of the fourth week. The organ with the highest concentrations of vanadium was the liver followed by the kidney. The lowest concentrations were found in testes. However, at the fourth week, a decrease in concentrations of vanadium was observed in the kidney.

Rats

In a study undertaken by the National Toxicology Program (2002), blood and lung concentrations, lung clearance half-life of vanadium, and the onset and extent of vanadium pentoxide-induced lung injury were determined in female Fischer 344 rats exposed to 0, 1 or 2 mg/m^3 vanadium pentoxide for 16 days. Lung weights of exposed rats were significantly greater than those of control animals on days 0, 1 and 4 post-exposure but were similar on day 8 post-exposure. There was little difference in lung weights between exposed groups. AUC analysis showed that lung burdens were proportional to exposure concentration throughout the recovery period. The results suggested linear toxicokinetics. Lung clearance half-lives during the 8-day recovery period were similar among exposed groups (range, 4.42–4.96 days). Concentrations of vanadium in blood were similar among exposed groups, but several orders of magnitude lower than the concentrations in lung tissue, and showed only marginal increases with increasing exposure doses.

In the 2-year inhalation study (National Toxicology Program, 2002), tissue burden analyses were performed on female Fischer 344 rats on days 1, 5, 12, 26, 54, 173, 360 and 540 after the start of exposure to 0.5, 1 or 2 mg/m^3 vanadium pentoxide. Lung weights increased throughout the study, with similar increases in the two lower-dose groups. When lung burden data were integrated over all time points, they did appear to be approximately proportional to exposure concentrations. During the two years, lung burdens in the two higher-dose groups (1 and 2 mg/m^3) did not reach a steady state, but showed an increase until day 173 followed by a decline until day 542. In contrast, the lung burden in the group exposed to 0.5 mg/m^3 increased with time and reached a steady state at 173 days. The data fitted a model in which the rate of deposition of vanadium in the lung decreased with time, while the initial deposition rates increased with the exposure concentration. Between days 1 and 542, the calculated deposition rate decreased from 0.41 to 0.25 µg/day in the 1-mg/m^3 exposure group and from 0.68 to 0.48 µg/day in the 2-mg/m^3 exposure group. There was no such change in deposition rate in the group

exposed to the lowest dose (approximately 0.22 μg/day). These results are likely to be explained by altered pulmonary function in the higher-dose groups, resulting in lung clearance rates that were lower than in the low-dose group. Lung clearance half-lives were 37, 59 and 61 days for the high, medium and low exposure groups, respectively, i.e. much longer than in the 16-day study (see above). Apparently, vanadium is cleared more rapidly from the lungs of rats exposed to vanadium pentoxide for short periods of time or at low concentrations repeatedly for longer periods. From the deposition curves over the 542 days of the study, the estimated total vanadium lung doses were 130, 175 and 308 μg for the 0.5-, 1- and 2-mg/m^3 exposure groups, respectively. Normalized lung doses (μg vanadium/mg vanadium pentoxide per m^3) were not constant but decreased with increasing exposure, i.e., 260, 175 and 154 μg per mg/m^3 for low, medium and high dose groups, respectively. This decrease was due to the reduced deposition of vanadium with increasing exposure concentration. Rats retained approximately 10–15% of the estimated lung dose on day 542. Concentrations of vanadium in blood were much lower than in lung and were only marginally higher in exposed rats than in controls. Vanadium concentrations in blood of exposed animals peaked on days 26 or 54, then declined throughout the rest of the study. Because the changes were small, it was difficult to distinguish between decreased absorption from the lung, resulting from reduced deposition, and increased elimination from the blood (National Toxicology Program, 2002).

Kyono *et al.* (1999) showed that the health status of the lung influences the deposition and retention of vanadium. In an experimental model for nickel-induced bronchiolitis in rats, bronchiolitic rats and control animals were exposed to vanadium pentoxide (2.2 mg/m^3; MMAD, 1.1 μm) for 5 h. The vanadium content in the lungs of controls was higher (about 100%) than in bronchiolitic rats after 1 day of exposure, but 2 days later the retention was 20% in controls and 80% in bronchiolitic rats. Elimination of vanadium was found to be much slower in bronchiolitic rats.

(ii) *Intratracheal instillation*

Several studies have shown that after intratracheal instillation of vanadium pentoxide in rats there was generally a rapid initial clearance of up to 50% during the first hour, a second phase with a half-life of about 2 days and a third phase during which vanadium remained in the lung for up to 63 days (Oberg *et al*., 1978; Conklin *et al*., 1982; Rhoads & Sanders, 1985).

(iii) *Oral administration*

Administration of vanadium pentoxide by gavage resulted in absorption of 2.6% of the dose through the gastrointestinal tract 3 days after the treatment (Conklin *et al.*, 1982). Distribution was mainly to bone, liver, muscle, kidney, spleen and blood. Chronic treatment with inorganic vanadium salts or organic vanadium has been shown to result in significant accumulation in the bone, spleen and kidney (Mongold *et al*., 1990; Thompson & McNeil, 1993; Yuen *et al.*, 1993).

Studies with non-diabetic and streptozotocin-diabetic rats given vanadyl sulfate in their drinking-water (0.5–1.5 mg/mL) for 1 year showed concentrations of vanadium to be in the following order [of distribution]: bone > kidney > testis > liver > pancreas > plasma > brain. Vanadium was found to be retained in these organs 16 weeks after cessation of treatment while the concentrations in plasma were below the limits of detection at this time (Dai *et al*., 1994).

(*b*) *Cellular studies*

Edel and Sabbioni (1988, 1989) showed accumulation of vanadium in hepatocytes and kidney cells (in the nucleus, cytosol and mitochondria) in rats exposed to vanadium as radioactive ^{48}V (V) pentavanadate ions and ^{48}V (IV) tetravalent ions by intratracheal instillation, oral administration or intravenous injection.

Cell cultures (human Chang liver cells, bovine kidney cells), incubated in medium supplemented with vanadium in the form of vanadate, have been shown to accumulate this element in the nucleus and mitochondria (Bracken *et al*., 1985; Stern *et al*., 1993; Sit *et al*., 1996). In BALB/3T3 C1A31-1-1 cells incubated in the presence of sodium vanadate and vanadyl sulfate, the cellular retention of both compounds was similar. After exposure to a non-toxic dose (1 μM for 48 and 72 h), nearly all vanadium was present in the cytosol, but at a toxic dose (10 μM for 48 and 72 h), 20% of the vanadium was found in cellular organelles (Sabbioni *et al*., 1991).

4.2 Toxic effects

4.2.1 *Humans*

In humans, acute vanadium poisoning can manifest itself in a number of symptoms including eye irritation and tremors of the hands (Lewis, 1959). In addition, a greenish colouration of the tongue has been observed in humans exposed to high concentrations of vanadium pentoxide and is probably due to the formation of trivalent and tetravalent vanadium complexes (Wyers, 1946). The green colour disappears within 2–3 days of cessation of exposure (Lewis, 1959).

(*a*) *Studies with volunteers*

Zenz and Berg (1967) studied the effects of vanadium pentoxide in nine male volunteers exposed in an inhalation chamber to concentrations of vanadium pentoxide of 0.1, 0.25, 0.5 or 1.0 mg/m^3 (particle size, 98% < 5 μm) for 8 h, with follow-up periods of 11–19 months. Acute respiratory irritation was reported, which subsided within 4 days after exposure (see also Section 4.1.1).

No skin irritation was reported in 100 human volunteers after skin patch testing with 1, 2 and 10% vanadium pentoxide in petrolatum (Motolese *et al*., 1993).

(*b*) *Studies of workers exposed to vanadium*

There is an extensive published literature concerning the development of 'boilermakers bronchitis' in persons cleaning boilers in which fuel oils containing high concentrations of vanadium were used (Hudson, 1964; Levy *et al.*, 1984). The clinical picture is characterized by dyspnoea which is largely reversible. Levy *et al*. (1984) studied 100 workers exposed to vanadium pentoxide (0.05–5.3 mg/m^3) during the conversion of a utility company power plant and found severe respiratory tract irritation in 74 individuals. Expiratory flow rates and forced vital capacity were decreased in about 50% of a subsample (35 individuals) of the workers studied.

Eye irritation has been reported in workers exposed to vanadium (Lewis, 1959; Zenz *et al*., 1962; Lees, 1980; Musk & Tees, 1982). Skin patch testing in workforces produced two isolated reactions (but none in unexposed volunteers; see Section 4.2.1). The underlying reason for the skin responses in these workers is unclear (Motolese *et al*., 1993).

Lewis (1959) investigated 24 men exposed to vanadium pentoxide for at least 6 months from two different centres, and age-matched with 45 control subjects from the same areas. Exposure to vanadium pentoxide was between 0.02 and 0.92 mg/m^3. In the exposed group, 62.5% complained of eye, nose, and throat irritation (6.6% in control), 83.4% had a cough (33.3% in control), 41.5% produced sputum (13.3% in control), and 16.6% complained of wheezing (0% in control). Physical findings included wheezes, rales, or rhonchi in 20.8% (0% in controls), hyperaemia of the pharynx and nasal mucosa in 41.5% (4.4% in controls), and 'green tongue' in 37.5% (0% in controls).

Zenz *et al*. (1962) reported on 18 workers exposed to varying concentrations of vanadium pentoxide dust (mean particle size, < 5 μm) in excess of 0.5 mg/m^3 during a pelletizing process. Three of the men most heavily exposed developed symptoms, including sore throat and dry cough. Examination of each on the third work day revealed markedly inflamed throats and signs of intense persistent coughing, but no evidence of wheezing. The three men also reported 'burning eyes' and physical examination revealed slight conjunctivitis. Upon resumption of work after a 3-day exposure-free period, the symptoms returned within 0.5–4 h, with greater intensity than before, despite the use of respiratory protective equipment. After the process had been operating for 2 weeks, all 18 workers, including those primarily assigned to office and laboratory duties, developed symptoms and signs to varying degrees, including nasopharyngitis, hacking cough, and wheezing. This study confirms that vanadium pentoxide exposure can produce irritation of the eye and respiratory tract.

Lees (1980) reported signs of respiratory irritation (cough, respiratory wheeze, sore throat, rhinitis, and nosebleed) and eye irritation in a group of 17 boiler cleaners. As there was no control group and it was unclear whether there was exposure to compounds other than vanadium, no conclusions can be drawn regarding the cause or significance of these symptoms. However, the findings are compatible with those of other studies on inhalation of vanadium pentoxide.

Huang *et al.* (1989) conducted a clinical and radiological investigation of 76 workers who had worked in a ferrovanadium factory for 2–28 years. In the exposed group, out of 71 workers examined, 89% had a cough (10% in controls), expectoration was seen in 74% (15% in controls), 38% were short of breath (0% in controls), and 44% had respiratory harshness or dry sibilant rale (0% in controls). In 66 of the exposed group examined, hyposmia or anosmia was reported in 23% (5% in controls), congested nasal mucosa in 80% (13% in controls), erosion or ulceration of the nasal septum in 9% (0% in controls), and perforation of the nasal septum in one subject (1.5%) (0 in controls). Chest radiographs of all 76 exposed subjects revealed 68% with increased, coarsened, and contorted bronchovascular shadowing (23% in controls). [While exposure to vanadium compounds may have contributed to the clinical findings and symptoms reported, no firm conclusion can be drawn from this study in this regard, as mixed exposures are likely to have occurred.]

A prospective study (Hauser *et al*., 1995a) of pulmonary function in 26 boiler workers exposed to fuel oil ash showed decreased FEV_1 (forced expiratory volume in 1 s) values which were associated with PM_{10} exposure but not with vanadium exposure. There was no post-exposure change in non-specific airway responsiveness. Hauser *et al*. (1995b) used nasal lavage analysis to study upper airway responses in 37 utility workers exposed to fuel oil ash. Responses were examined in relation to vanadium concentrations and PM_{10} particles using personal samplers. A significant increase in polymorphonuclear cells in nasal lavage was observed in samples from nonsmokers but not in smokers, suggesting that exposure to vanadium dust is associated with upper airway inflammation. In both nonsmokers and smokers, a dose–response relationship between adjusted polymorphonuclear cell count and either PM_{10} or respirable vanadium dust exposure could not be found.

Woodin *et al*. (1998) studied the effects of vanadium exposure/PM_{10} concentrations in 18 boilermakers engaged in a utility boiler conversion; 11 utility workers acted as controls. The nasal lavage technique was used at various time points and interleukins (IL-6, IL-8), eosinophilic cationic protein (ECP) and myeloperoxidase (MPO) were investigated as biomarkers. Increases were observed in IL-8 and MPO concentrations but not IL-6 and ECP concentrations, in the exposed workers. The authors concluded that the changes observed in the upper airways were related to increased PM_{10} and upper airway vanadium concentrations. Subsequent studies in workers exposed to vanadium-rich fuel-oil ash (Woodin *et al*., 2000) also demonstrated lower (72% versus 27% for controls) and upper (67% versus 36% for controls) airway symptoms.

While the majority of the above studies have noted reversibility of these acute pulmonary effects, asthma [now possibly labelled ‘reactive airways disfunction syndrome’] has been reported to develop as a sequela to high, acute exposure to vanadium in some exposed workers (Musk & Tees, 1982).

(*c*) *Environmental exposure*

A single epidemiological study has been conducted (Lener *et al.*, 1998) assessing individual exposure in the general population to dusts generated by a plant processing vanadium-rich slag. It was estimated that an area with a radius of 3 km was exposed to the dust

from the plant in Mnisek in the Czech Republic. The population in this area at the time of the study was 4850. The two-year study concentrated on three groups of 10–12-year-old schoolchildren: 15 children (11 boys, four girls) from the localities of Cisovice and Lisnice (Group A), the area potentially most affected by the emission of vanadium; 28 children (14 boys, 14 girls) from the locality of Mnisek (Group B), an area of medium exposure; and 32 children (17 boys, 15 girls) from the locality of Stechovive (Group C), a control area not affected by any emission from vanadium production. Vanadium concentrations in venous blood, hair and fingernail clippings were determined. The mean vanadium concentration in blood was 0.10 ± 0.07 μg/L in the exposed Group A (Group B data not given) and 0.05 ± 0.05 μg/L in the control group. In hair, the concentrations were 96 ± 42 μg/kg and 181 ± 114 μg/kg in the exposed groups A and B, respectively, compared with 69 ± 50 μg/kg in controls. Concentrations in fingernails were 189 ± 41 μg/kg and 186 ± 38 μg/kg in the exposed groups A and B, respectively, compared with 109 ± 68 μg/kg in the controls. Vanadium concentrations in blood, hair and fingernails were elevated in children living close to the plant. In group B, those with parent(s) working at the plant had higher vanadium concentrations in hair than those whose parent(s) did not, suggesting a secondary exposure in the home from dust transferred on working clothes.

Health status of the children in the study was assessed based on haematological parameters, specific immunity, cellular immunity and cytogenetic analysis. Children from the exposed groups A and B had lower red blood cell counts and lower concentrations of serum and salivary secretory IgA than control group, and a seasonal decrease in IgG. Marked differences between exposed and control groups were seen in natural cell-mediated immunity, with significantly higher mitotic activity of T-lymphocytes in children living in the immediate vicinity of the plant. A higher incidence of viral and bacterial infections was registered in children from the exposed area. However, the study could not control for confounding by exposures to compounds other than vanadium. Cytogenetic analysis revealed no genotoxic effects (see Section 4.4.1). The overall conclusion was that long-term exposure to vanadium had no negative impact on health; the differences observed were within the range of normal values in all cases (Lener *et al*., 1998).

4.2.2 *Experimental systems*

(*a*) *In-vivo studies*

(i) *General toxicity*

The acute toxicity of vanadium is low when given orally, moderate when inhaled and high when injected. As a rule, the toxicity of vanadium increases as its valency increases, with vanadium (V), as in vanadium pentoxide, being the most toxic form (Lagerkvist *et al*., 1986; WHO, 1988; National Toxicology Program, 2002).

Studies in animals have shown that equivalent doses of vanadium pentoxide are better tolerated by small animals, including rats and mice, than by larger animals, such as rabbits

and horses (Hudson, 1964). The LD_{50} of vanadium pentoxide is highly species-dependent (Table 6). Differences in diet and route of vanadium administration may contribute to these discrepancies.

Table 6. Acute toxicity values for vanadium pentoxide in experimental animals

Species	Route of administration	Dose or concentration/ exposure	Parameter[a]	Reference
Mouse	Oral	23 mg/kg bw	LD_{50}	Lewis (2000)
	Subcutaneous	10 mg/kg bw	LD_{50}	Lewis (2000)
	Subcutaneous	87.5–117.5 mg/kg bw	LD	Hudson (1964)
	Subcutaneous	102 mg/kg bw	LD_{100}	Venugopal & Luckey (1978)
Rat	Oral	10 mg/kg bw	LD_{50}	Lewis (2000)
	Inhalation	70 mg/m^3/2 h	LC_{LO}	Lewis (2000)
	Subcutaneous	14 mg/kg	LD_{50}	Lewis (2000)
	Intraperitoneal	12 mg/kg bw	LD_{50}	Lewis (2000)
Guinea-pig	Subcutaneous	20–28 mg/kg bw	LD	Hudson (1964)
Rabbit	Intravenous	1–2 mg/kg bw	LD	Hudson (1964)
	Intravenous	10 mg/kg	LD_{LO}	Lewis (2000)
	Inhalation	205 mg/m^3/7 h	LC_{100}	Sjöberg (1950)
	Subcutaneous	20 mg/kg	LD_{LO}	Lewis (2000)
Cat	Inhalation	500 mg/m^3/23 min	LC_{LO}	Lewis (2000)

[a] LD_{100}: dose which is lethal to 100% of the animals; LD_{50}, dose which is lethal to 50% of the animals; LC_{100}, concentration in air which is lethal to 100% of the animals; LC_{LO}, lethal concentration low: the lowest concentration in air which is lethal to animals; LD, lethal dose

Ammonium metavanadate given to six weanling pigs at a dose of 200 mg/kg of feed (200 ppm) for 10 weeks was found to suppress growth and increase mortality (Van Vleet *et al*., 1981). In contrast, ammonium metavanadate was not markedly toxic when 200 mg/kg of feed (200 ppm) (approximately equivalent to 6.6 mg/kg bw) or less were fed to growing lambs for 84 days (Hansard *et al*., 1978).

(ii) *Respiratory effects*

Inhalation exposure

Male CD-1 mice exposed by inhalation to vanadium pentoxide (0.01-M and 0.02-M solution as aerosol, for 1 h) developed an increased mitochondrial matrix density and distorted nuclear morphology in non-ciliated bronchiolar Clara cells (Sánchez *et al*., 2001; abstract only).

In rats and mice exposed to vanadium pentoxide at concentrations up to 16 mg/m^3 for 3 months, inflammation and epithelial hyperplasia were observed in the nose and lung of rats and in the lung of mice at exposures ≥ 2 mg/m^3. Non-neoplastic lesions in the nose

and lung of rats were noted at all doses, and rats exposed to ≥ 4 mg/m^3 developed fibrosis (National Toxicology Program, 2002).

In addition, decreases in heart rate and in diastolic, systolic and mean blood pressure were seen in male and female F344/N rats exposed to 16 mg/m^3. These effects were not attributed to a direct cardiotoxic action of vanadium pentoxide but were considered to reflect the poor condition of the animals coupled with an effect of the anaesthesia (used to facilitate implantation of electrodes for electrocardiogram measurements). The overall pulmonary changes indicated the presence of restrictive lung disease in both sexes exposed to vanadium pentoxide concentrations of ≥ 4 mg/m^3, while an obstructive lung disease may have been present in the group exposed to 16 mg/m^3 (National Toxicology Program, 2002).

In a two-year study, F344/N rats and B6C3F$_1$ mice (50 animals per sex and per species) were exposed to vanadium pentoxide at concentrations of 0, 0.5, 1 or 2 (rats only), 1, 2 or 4 (mice only) mg/m^3, by inhalation for 2 years. Non-neoplastic proliferative and inflammatory lesions of the respiratory tract were observed in both species at increasing frequency with increased exposure concentration (see Tables 3.1.1 and 3.1.2, Section 3) (National Toxicology Program, 2002; Ress *et al.* 2003). The main differences observed between acute (3 months) and chronic (2 years) effects of exposure to vanadium pentoxide were the development by 2 years of chronic inflammation of the bronchi, septic bronchopneumonia, interstitial infiltration and proliferation, and emphysema (National Toxicology Program, 2002).

When rabbits were exposed to vanadium pentoxide by inhalation (8–18 mg/m^3, 2 h per day, 9–12 months) and rats to vanadium pentoxide condensation aerosol (3–5 mg/m^3, 2 h per day every 2 days, 3 months) or vanadium pentoxide dust (10–40 mg/m^3, 4 months), similar respiratory effects (sneezing, nasal discharge, dyspnoea and tachypnea) were produced in both species, which in some cases included attacks of bronchial asthma and a haemorrhagic inflammatory process (Roshchin, 1967b, 1968, cited by WHO, 1988).

In studies carried out by Sjöberg (1950), rabbits exposed to vanadium pentoxide dust (205 mg/m^3) developed tracheitis, pulmonary oedema and bronchopneumonia and died within 7 h. In another experiment, repeated inhalation of vanadium pentoxide (20–40 mg/m^3, 1 h per day, for several months) by rabbits produced chronic rhinitis and tracheitis, emphysema, patches of lung atelectasis and bronchopneumonia.

When adult male cynomolgus monkeys were exposed by inhalation to 0.5 or 5.0 mg/m^3 vanadium pentoxide dust aerosol for 1 week, significant air flow limitation was produced only at the 5.0 mg/m^3 dose in both central and peripheral airways, without changes in parenchymal function. However, analysis of BALF showed a significant increase in the absolute number and relative percentage of polymorphonuclear leukocytes, indicating that vanadium pentoxide induced pulmonary inflammatory effects (Knecht *et al*., 1985). In a study conducted to evaluate changes in pulmonary reactivity resulting from repeated vanadium pentoxide inhalation through the use of provocation challenges, and after different subchronic exposure regimens, one group of monkeys (n = 8) was exposed by inhalation (6 h per day, 5 days per week, for 26 weeks) to 0.1 mg/m^3 vanadium pentoxide on Mondays, Wednesdays and Fridays, with a twice-weekly peak exposure of

1.1 mg/m^3 on Tuesdays and Thursdays, and another group (n = 8) was exposed to a constant daily concentration of 0.5 mg/m^3; a control group (n = 8) received filtered, conditioned air. Pre-exposure challenges with vanadium pentoxide induced airway obstruction with a significant influx of inflammatory cells into the lung in both subchronic exposure groups. Inhalation of vanadium pentoxide with intermittent high exposure concentrations did not produce an increase in pulmonary reactivity to vanadium pentoxide, and cytological, immunological and skin test results indicated the absence of allergic sensitization (Knecht *et al*., 1992).

Intratracheal exposure

Zychlinski *et al.* (1991) investigated the toxic effects of vanadium pentoxide in rats exposed intratracheally to 0.56 mg vanadium pentoxide/kg bw once a month for 12 months. Body weight gain of exposed animals slowed following the 10th treatment when compared with control animals. Lung weights were significantly greater than in controls, but other organ weights were unchanged. The glucose concentrations in blood of treated animals were slightly decreased whereas total cholesterol concentrations were reduced markedly. In parallel to this in-vivo study, in-vitro experiments with isolated untreated rat lung microsomes and mitochondria in the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH) were performed to investigate the mechanism of the chronic toxic effects of vanadium. The results showed that vanadium(V) undergoes one-electron redox cycling (enzymatic reduction) in rat lung biomembranes and that non-enzymatic reoxidation of vanadium(IV) initiates lipid peroxidation under aerobic conditions. It was postulated that free-radical redox cycling of vanadium may be responsible for the observed pulmonary toxicity.

When female CD rats were instilled intratracheally with 42 or 420 µg/kg bw vanadium pentoxide and followed from 1 h to 10 days, pulmonary inflammation was induced in a dose-dependent manner, but neutrophil influx was not detected until 24 h after exposure. Expression of mRNA for two cytokines, macrophage inflammatory protein-2 (MIP-2) and KC protein was also detected in the bronchoalveolar macrophages (Pierce *et al*., 1996).

Bonner *et al*. (2000) reported that two weeks after a single intratracheal instillation of 1 mg/kg bw vanadium pentoxide, male Sprague-Dawley rats developed constrictive airway pathology including airway smooth muscle cell thickening, mucous cell metaplasia and fibrosis.

Evaluating the effects of a single intratracheal dose of residual oil fly ash in rats, Dreher *et al*. (1997), Kodavanti *et al*. (1998) and Silbajoris *et al*. (2000) concluded that vanadium compounds were the major toxic component inducing pulmonary injury, activation of alveolar macrophages and inflammatory changes. In addition, Silbajoris *et al*. (2000) described the induction of some mitogen-activated protein (MAP) kinases in the alveolar epithelium of the animals.

Rice *et al*. (1999) instilled Sprague-Dawley rats intratracheally with 1 mg/kg bw vanadium pentoxide and found proliferation of myofibroblasts, indicating pulmonary fibrosis. Toya *et al*. (2001), using the same model, found that intratracheal instillation

with 0.88, 3.0 or 13.0 mg/kg bw vanadium pentoxide for 4 weeks induced pathological lung lesions that developed dose-dependently, and were characterized by exudative inflammation, injury of alveolar macrophages, and swelling and mucous degeneration of the broncho-bronchiolar epithelium.

(iii) *Hepatic effects*

In mice exposed to vanadium pentoxide (0.02 M inhaled for 30 min), fatty degeneration, extramedullary haematopoietic activity and neutrophilic infiltration around the central veins were detected in the liver (Acevedo-Nava *et al*., 2001; abstract only).

In rats and rabbits, fatty changes with necrosis in the liver and a drastic reduction in liver tissue respiration have been observed as a result of long-term exposure to vanadium pentoxide by inhalation (10–70 mg/m^3, 2 h per day, 9–12 months) (Roshchin, 1968, cited by Lagerkvist, 1986). Livers and kidneys of rats treated with vanadium(V) showed an electron paramagnetic resonance signal characteristic of vanadium(IV) (Johnson *et al*., 1974).

The bioenergetic functions of liver mitochondria have been studied *in vivo* and *in vitro* following acute and chronic exposure of rats to vanadium pentoxide via the respiratory tract or exposure of isolated rat liver mitochondria to various vanadium pentoxide concentrations. *In vivo*, the mitochondrial respiration with glutamate (as nicotinamide adenine dinucleotide (NAD)-linked substrate) or succinate (as flavine adenine dinucleotide (FAD)-linked substrate) was inhibited significantly when compared with control animals. No inhibition was found with ascorbate as cytochrome c-linked substrate. The same effects were observed *in vitro*. These combined effects provide evidence that vanadium(V) acts as an inhibitor of respiration in rat liver mitochondria. It was postulated that significant amounts of vanadium(V) accumulated in the intermembrane space of liver mitochondria of exposed rats. The enzymatic process of detoxification, by reduction of vanadium(V) in the tissue, may be insufficient to prevent the deleterious action of this compound on liver mitochondria (Zychlinski & Byczkowski 1990).

(iv) *Renal effects*

Glomerular hyperaemia and necrosis of convoluted tubules in the kidney were observed in some early studies of acute toxicity of vanadium compounds in various mammalian species (Hudson, 1964; Pazhynich, 1966; WHO, 1988).

Intraperitoneal administration of sodium orthovanadate to rats resulted in inhibition of tubular reabsorption of sodium and hypokalaemic distal renal tubular acidosis with increased urinary pH (Bräunlich *et al*., 1989; Dafnis *et al*., 1992). Vanadium, in the form of ammonium metavanadate injected subcutaneously into rats, was found to be toxic to the kidney at doses of 0.6 and 0.9 mg/kg bw per day for 16 days. Histological changes were observed, including necrosis, cell proliferation and fibrosis. Vanadium was shown to be more toxic for the kidneys in rats when given by a parenteral route (Al-Bayati *et al*., 1989).

Chronic treatment of rats with vanadyl sulfate has been shown to result in significant accumulation of the element in the kidneys (Mongold *et al.*, 1990; Thompson & McNeill, 1993); however, most is probably bound to small peptides or macromolecules in the form

of vanadyl and thus is not available as vanadate, a more potent inhibitor of Na^+/K^+-ATPases (Cantley *et al.*, 1977; Rehder, 1991; Thompson *et al.*, 1998).

(v) *Nervous system effects*

Neurophysiological effects have been reported following acute exposure (by oral administration and subcutaneous injection) of dogs and rabbits to vanadium oxides and salts (vanadium trioxide, vanadium pentoxide, vanadium trichloride and ammonium metavanadate). These effects included disturbances of the central nervous system, such as impaired conditioned reflexes and neuromuscular excitability (Roshchin, 1967a). The animals behaved passively, refusing to eat, and lost weight. In cases of severe poisoning, diarrhoea, paralysis of the hind limbs and respiratory failure were followed by death (Hudson, 1964; Roshchin, 1967b, 1968).

In a study reported by Seljankina (1961 cited by Lagerkvist *et al.*, 1986 and WHO, 1988), solutions of vanadium pentoxide were administered orally to rats and mice at doses of 0.005–1 mg/kg bw per day for periods ranging from 21 days at the higher concentrations to 6 months at the lower concentrations. A dose of 0.05 mg/kg bw was found to be the threshold dose for functional disturbances in conditioned reflex activity in both mice and rats. Repeated exposure to aqueous solutions (0.05–0.5 mg/kg bw per day, for 80 days) of vanadium pentoxide impaired conditioned reflex mechanisms in rats.

In male CD-1 mice exposed by inhalation to 0.02 M vanadium pentoxide 2 h twice a week for 4 weeks, Golgi staining revealed a drastic reduction in dendritic spines in the striatum compared with controls, showing that the inhalation of vanadium causes severe neuronal damage in the corpus striatum (Montiel-Flores *et al*., 2003; abstract only). Using the same inhalation model, after 12 weeks of exposure, a decrease in dendritic spines of granule cells of the olfactory bulb was observed (Mondragón *et al*., 2003; abstract only). In addition, ultrastructural modifications in nuclear morphology of these cells were evident, Golgi apparatus was dilated and an increase in lipofucsin granules was observed, as well as necrosis of some cells (Colin-Barenque *et al*., 2003; abstract only). In the cerebellum, necrosis and apoptosis of the Purkinje and granule cell layers were seen (Meza *et al*., 2003; abstract only).

(vi) *Cardiovascular system effects*

Perivascular swelling, as well as fatty changes in the myocardium, were observed by Roshchin (1968, cited by WHO, 1988) following chronic exposure of rats and rabbits to vanadium pentoxide (10–70 mg/m^3, 2 h per day, 9–12 months) by inhalation.

(vii) *Skeletal alterations*

The effect of vanadium pentoxide on bone metabolism has been investigated in weanling rats. Vanadium pentoxide (10.0–200.0 µmol/kg bw [1.8–36.4 mg/kg bw]) was administered orally for 3 days. Low doses (10–100 µmol/kg bw [1.8–18 mg/kg bw]) caused increases in alkaline phosphatase activity and DNA content in the femoral diaphysis, indicating that vanadium pentoxide may play a role in the enhancement of bone

formation *in vivo*. However, high doses (over 150 μmol/kg bw [27 mg/kg bw] had toxic inhibitory effects (Yamaguchi *et al*., 1989).

(viii) *Immunological effects*

In the National Toxicology Program study (2002), a localized inflammatory response was seen in the lungs of male F344/N rats and female B6C3F$_1$ mice exposed by inhalation to 4, 8, or 16 mg/m^3 vanadium pentoxide in a 16-day study. Increases in cell numbers, protein, neutrophils and lysozymes in BALF were observed but the number of macrophages in lavage fluids of male rats and female mice exposed to 8 or 16 mg/m^3 was decreased. No effects were seen on systemic immunity in rats and mice.

When weanling and adult ICR mice were given 6 mg/kg bw vanadium pentoxide by gavage (5 days per week for 6 weeks), an increase in the number of leukocytes and plaque-forming cells, as well as enhanced phytohaemagglutinin responsiveness, increased spleen weight and depression of phagocytosis were observed in treated mice. In Wistar rats given vanadium pentoxide in drinking-water (1 or 100 mg/L for 6 months), the higher dose resulted in increased spleen weight and concanavalin-A responsiveness; a depression of phagocytosis was found in a dose-dependent manner. These results suggest activation of T- and B-cell immune responses (Mravcová *et al.*, 1993).

(ix) *Biochemical effects*

Chakraborty *et al*. (1977) gave male albino rats vanadium pentoxide orally at a dose of 3 mg/kg bw five times a week for the first week and 4 mg/kg bw for a further 2 weeks and found that it induced histological and enzymatic alterations including inhibition of biosynthesis, enhanced catabolism and increased use of L-ascorbic acid in the liver and kidney tissues of the rats.

(*b*) *In-vitro studies*

(i) *Organ culture*

Garcia *et al.* (1981) found that treatment with vanadium pentoxide (10^{-5}–10^{-2} M [1.82–1820 μg/mL]) produced dose-dependent contractions of the rat vas deferens organ cultures *in vitro*; a response that could be associated with the inhibition of Na^+/K^+-ATPase activity.

Schiff and Graham (1984) used organ cultures of hamster trachea to study the in-vitro effects of vanadium pentoxide (0.1, 1, 10 or 100 μg/mL) and oil-fired fly ash (10, 50, 100 or 250 μg/mL) on mucociliary respiratory epithelium following exposure for 1 h per day for 9 consecutive days. Vanadium pentoxide was found to decrease ciliary activity and produce ciliostasis in tracheal ring explants. The degree of change depended on the concentration and length of exposure; early morphological alterations consisted of vacuolization of both nuclei and cytoplasm of tracheal epithelium cells.

Preincubation of rat kidney brush border membrane vesicles with 1 mM [182 μg/mL] vanadium pentoxide for 8 h significantly inhibited citrate uptake in a time-dependent manner. This effect was attributed to a direct interaction of vanadium with the sodium

citrate cotransporter. The results suggest that vanadium pentoxide has nephrotoxic potential (Sato *et al*., 2002).

(ii) *Cell culture*

In cultures of bovine alveolar macrophages, Fisher *et al.* (1986) found that vanadium pentoxide was the most cytotoxic compound when compared with other metals or metalloids (zinc oxide, nickel sulfide, manganese oxide, sodium arsenite, sodium selenite) tested. Vanadium caused a reduction in phagocytosis by macrophages to 50% of control values after incubation for 20 h at a concentration of 0.3 μg/mL, but this concentration was also associated with a substantial (59%) loss of macrophage viability. The authors concluded that their results confirmed those of previous studies (Waters *et al.*, 1974) which demonstrated that vanadium is a unique macrophage toxicant.

Vanadium(V) and related compounds are known to exert potent toxic effects on a wide variety of biological systems. One of the pathways of vanadium(V) toxicity is thought to be mediated by oxygen-derived free radicals (Zychlinski *et al*., 1991; Shi *et al*., 1997; Ding *et al*., 1999).

Parfett and Pilon (1995) evaluated the effects of promoters such as vanadium compounds on oxidative stress-regulated gene expression and promotion of morphological transformation in C3H/10T1/2 cells. Promoters which elevate intracellular oxidant levels can be distinguished by a spectrum of induced gene expression which includes the oxidant-responsive murine proliferin gene family. Proliferin transcription was found to be induced 20-fold by 5 μM [0.9 μg/mL] vanadium pentoxide. Another pentavalent vanadium, ammonium metavanadate (5 μM [0.6 μg/mL]), added as promoter in two-stage morphological transformation assays, amplified yields of Type II and Type III foci in monolayers of 20-methylcholanthrene-initiated C3H/10T1/2 cells. These results suggest that pentavalent vanadium compounds could promote morphological transformation in these cells by creating a cellular state of oxidative stress, which induces the expression of proliferin. Proliferation of MCF-7 cells was found to be stimulated after 4-day treatments with 0.5–2 μM vanadium(V); the effect reached a plateau at 1 μM vanadium, declined at 3 μM and disappeared at 5 μM (Auricchio *et al.*, 1995; 1996).

To determine the effect of vanadium pentoxide on the release of two major immunoregulatory cytokines, mouse macrophage-like WEHI-3 cells were treated *in vitro* (Cohen *et al.*, 1993). Vanadium pentoxide decreased the release of IL-1 and TNFα stimulated with lipopolysaccharide endotoxin. Spontaneous release of the IL-1/TNF-regulating prostanoid prostaglandin E_2 (PGE_2) was significantly increased by the highest concentration of ammonium metavanadate tested, although lipopolysaccharide endotoxin-stimulated PGE_2 production was unaffected. These results showed that pentavalent vanadium could alter the host's immunocompetence. In another study with WEHI-3 cells treated with 100 μM or 100 nM vanadium pentoxide or ammonium metavanadate, the capacity of macrophage-like cells to bind and respond to interferon γ was altered (Cohen *et al*., 1996).

When mice and rat hepatocytes or human Hep G2 cells were treated *in vitro* with vanadium pentoxide (1, 10 or 100 μM), gene expression (after 2-h treatment) and

secretion of IL-8, MIP-2 chemokines and TNFα (after 18-h treatment) were increased. The induction of IL-8 and MIP-2 secretion was inhibited by antioxidants such as tetramethylthiourea and *N*-acetylcysteine, showing that the events responsible for this gene expression involve cellular redox changes (Dong *et al*., 1998). Vanadium pentoxide caused a several-fold increase in heparin-binding epidermal growth factor-like growth factor (HB-EGF) mRNA expression and protein in normal human bronchial epithelial cells and increased the release of HB-EGF mitogenic activity of these cells (Zhang *et al.*, 2001a).

Wang and Bonner (2000) showed that vanadium pentoxide activated extracellular signal-regulated kinases 1 and 2 (ERK-1/2) in rat pulmonary myofibroblasts. This activation was an oxidant-dependent event and required components of an epidermal growth factor-receptor signalling cascade.

Ingram *et al*. (2003) showed that vanadium pentoxide stimulated HB-EGF mRNA expression and hydrogen peroxide production by human lung fibroblasts. Both vanadium pentoxide and hydrogen peroxide activated ERK-1/2 and p38 MAP kinases. Inhibitors of these two kinase-pathways significantly reduced both vanadium and H_2O_2-induced HB-EGF expression. These data indicate that vanadium upregulates HB-EGF via ERK and p38 MAP kinases.

Evidence suggests that some forms of vanadium (sodium metavanadate, peroxovanadate and pervanadate) or vanadium-containing particles from environmental and occupational sources can trigger or potentiate apoptosis. The pentavalent form of vanadium has been shown to cause apoptosis in a JB6 P^+ mouse epidermal cell line (Cl 41) and in lymphoid cell lines, but may be anti-apoptotic in others such as malignant glioma cells (Hehner *et al.*, 1999; Chin *et al.*, 1999; Huang *et al*., 2000; Chen *et al*., 2001).

Rivedal *et al*. (1990) found that vanadium pentoxide exposure for 5 days promoted the induction of morphological transformation of hamster embryo cells pre-exposed to a low concentration of benzo[*a*]pyrene for 3 days. However, when vanadium pentoxide (0.25, 0.50 or 0.75 μg/mL) was tested in the Syrian hamster embryo (SHE) assay, the results were negative after a 24-h exposure, but significant morphological transformation was produced after a 7-day exposure. This pattern of response (24-h SHE negative/7-day SHE positive) has been seen with other chemicals (i.e., 12-*O*-tetradecanoylphorbol 13-acetate, butylbenzyl phthalate, methapyrilene) that have tumour promotion-like characteristics (Kerckaert *et al*., 1996a,b).

(iii) *Cell-free systems*

In cell-free systems, vanadium(V) caused the oxidation of thiols, including GSH and cysteine, and induced the formation of thiyl radicals (Shi *et al*., 1990; Byczkowski & Kulkarni, 1998). It has been shown that depletion of GSH not only decreases the antioxidant defence in the cytosol, but also prevents regeneration of a vital lipid-soluble antioxidant, α-tocopherol, thereby increasing the vulnerability of phospholipid-rich biomembranes to oxidative stress and lipid peroxidation (Byczkowski & Kulkarni, 1998).

Vanadium can inhibit a variety of enzymes such as heart adenyl cyclase and protein kinase, ribonucleases, phosphatases, and several adenosinetriphosphatases (ATPases), but it can stimulate a number of others. The enzymes inhibited include phosphoenzyme ion-transport ATPases, acid and alkaline phosphatases, Na^++K^+ATPase, H^++K^+ATPase, phosphotyrosyl protein phosphatase, dynein (contractile protein ATPase associated with microtubules of cilia and flagella), myosin ATPase, phosphofructokinase, adenylate kinase and cholinesterase (Nechay, 1984; WHO, 1988).

Vanadium(V) appears to undergo a redox cycling when the inner mitochondrial membrane permeability barrier to vanadate polyanions is broken. It has been proposed that vanadium(V) stimulates the oxidation of NAD(P)H by biological membranes and amplifies the initial generation of $O_2^{-\bullet}$ produced by membrane-associated NAD(P)H oxidase. This stimulatory effect is due to interaction of vanadium(V) with $O_2^{-\bullet}$ but not with the membrane-associated enzymes (Liochev & Fridovich, 1988).

Using ESR spin trapping, Shi and Dalal (1992) demonstrated that rat liver microsomes/NADH, in the absence of exogenous H_2O_2, generated hydroxyl ($^\bullet$OH) radicals from the reduction of vanadium(V) via a Fenton-like mechanism. This radical generation may play a role in vanadium(V)-induced cellular injury.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

(*a*) *In-vivo studies*

Several studies describe the reprotoxic (male or female reproductive capability) and developmental (teratological) effects of vanadium pentoxide (Lagerkvist *et al*., 1986; Domingo, 1994; Leonard & Gerber, 1994; Domingo, 1996; Leonard & Gerber, 1998; National Toxicology Program, 2002).

(i) *Toxicokinetics in pregnant animals*

Li *et al*. (1991) treated non-pregnant and pregnant Wistar rats with 5 mg/kg vanadium pentoxide intraperitoneally and reported the tissue distribution of this compound. Non-pregnant rats had significant concentrations of vanadium in kidney, ovary, uterus and liver, suggesting that female genital organs are important target organs in the distribution of vanadium. Treatment of pregnant rats gave similar results, including the presence of vanadium in the placenta. The authors suggested that vanadium could pass the blood–placenta barrier.

Zhang *et al*. (1991a) analysed the passage of vanadium across the placenta into the embryo/fetus of pregnant Wistar rats at different times after different dose regimens: 4 h

after treatment with a single intraperitoneal injection of vanadium pentoxide (5 mg/kg bw) on day 12 of gestation; 1, 4, 24 or 48 h after a single treatment (5 mg/kg bw) on days 16–18 of gestation; or 120 h after the final treatment with 0.33, 1 or 3 mg/kg bw given daily on days 6–15 of gestation. The concentrations of vanadium in maternal blood, placenta and fetus were elevated after these different treatments in comparison with those of the respective untreated groups. The vanadium concentration in fetuses increased with increasing doses, suggesting that the embryo/fetus accumulated vanadium (Zhang *et al*., 1991a).

(ii) *Effects on reproductive organs and fertility*

Male CD-1 mice were treated intraperitoneally with 8.5 mg/kg bw vanadium pentoxide once every 3 days for 60 days. Groups of five animals were killed every 10 days after the beginning of treatment. Twenty-four hours after the last injection, the males were mated with untreated females. A decrease in fertility rate, implantations, live fetuses and fetal weight, and an increase in the number of resorptions/dam was observed. In males, sperm count and motility were impaired as treatment advanced and the presence of abnormal sperm was observed on days 50 and 60 of treatment (Altamirano-Lozano & Alvarez-Barrera, 1996; Altamirano-Lozano *et al.*, 1996).

In a National Toxicology Program study (2002), reduced epididymal sperm motility was observed in $B6C3F_1$ mice exposed to vanadium pentoxide by inhalation (8- and 16 mg/m^3 dose groups) for 3 months. There were no effects on estrous cycle parameters in females. No effects were seen on reproductive parameters in male and female F344/N rats exposed by inhalation to 4, 8 or 16 mg/m^3 vanadium pentoxide (National Toxicology Program, 2002).

To evaluate the effect of vanadium pentoxide on the newborn rats, Altamirano *et al*. (1991) injected 12.5 mg/kg bw vanadium pentoxide intraperitoneally into male and female prepubertal CII-ZV rats every 2 days (from birth to 21 days), and into female rats from day 21 to the day of the first vaginal estrus. No changes in vaginal opening nor in the estrous cycle were observed in either prepubertal or adult female rats; however, the ovulation rate was reduced in the treated adult females. No differences were observed in the weights of ovaries, uterus, adrenal gland or pituitary gland, compared to those of untreated rats; the weights of thymus, liver, kidneys and submandibular glands of newborn treated females were similar to those of controls. However, when treatment began at 21 days of age, an increase in the weight of thymus, submandibular glands and liver was observed. In male prepubertal rats, an increase was observed in the weight of seminal vesicles, thymus and submandibular glands but not of testis and prostate of animals treated with vanadium from birth to 21 days. The results indicate that, as observed with other metals, the toxicological effects of vanadium pentoxide differ in males and females, with toxicity in prepubertal rats being higher in males than in females.

(iii) *Developmental effects*

To evaluate the effects of vanadium pentoxide on the embryonic and fetal development of mice, Wide (1984) injected pregnant albino NMRI mice via the tail veins with

1.5 mM/animal [273 µg/animal ~ 10 mg/kg bw] vanadium pentoxide on day 3 or day 8 of gestation. All animals were killed 2 days before parturition (17th day of pregnancy) and fetuses were dissected and examined. Treatment with vanadium pentoxide on day 8 of gestation did not induce teratogenic effects but reduced fetal skeletal ossification.

In a study of the developmental toxicity of vanadium pentoxide, Zhang *et al*. (1991b) injected pregnant female NIH mice intraperitoneally with 5 mg/kg bw vanadium pentoxide per day on different days of gestation (days 1–5, 6–15, 7, 8, 9, 10, 11 or 14–17 of pregnancy). No effects on pre-implantation were found, nor malformations nor premature birth. However, an increased frequency of resorptions or fetal death was observed in animals treated on days 7, 6–15, and 14–17 of gestation. Delayed skeletal ossification was noted in mice treated on days 6–15, 8, 10 and 14–17 of gestation. The authors suggested that vanadium pentoxide acted as a weak developmental toxicant but not a teratogen.

To evaluate the teratogenic effects of vanadium pentoxide, female CD-1 mice were injected intraperitoneally once daily on days 6–15 of gestation with 8.5 mg/kg bw. Vanadium did not cause significant adverse effects on the number of live and dead fetuses (including resorptions) nor on fetal implants; however, a decrease in fetal weight and a delay in skeletal ossification were observed. Limb shortening was the most frequent alteration. No maternal toxicity was detected (Altamirano-Lozano *et al*., 1993).

In female Wistar rats exposed to 0.33, 1 or 3 mg/kg bw vanadium pentoxide from days 6–15 of gestation, the highest dose was toxic. Increased fetal mortality and external or skeletal malformations with delay in ossification were also observed (Zhang *et al.*, 1993a). Similar results were found in one further study in Wistar rats (Zhang *et al*., 1993b).

(*b*) *In-vitro studies*

Li *et al.* (1995) investigated the toxicological effects of vanadium pentoxide (0.125, 0.25, 0.5, 2 or 3 mM) in rat Leydig cells *in vitro* and found no obvious relationship between testosterone secretion and the concentration of vanadium. The authors concluded that Leydig cells are not a target for vanadium pentoxide. This is in agreement with results of in-vivo studies previously reported by Altamirano *et al.* (1991) who had shown that the weight of the testis and prostate were not increased after vanadium treatment of rats (see Section 4.3.2(ii)).

Altamirano-Lozano *et al.* (1997, 1998a) tested the reprotoxic effects of various metal compounds on boar spermatozoa *in vitro*. Sperm were exposed to vanadium pentoxide (5.5, 16.5, 27.5, 55, 110 or 220 µM) and motility was analysed 0, 1, 2, 3, 4, 5 and 6 h after treatment. A dose- and time-dependent reduction in sperm motility was observed, in accordance with results obtained *in vivo* in mice by the same group (Altamirano-Lozano *et al.*, 1996).

4.4 Genetic and related effects

4.4.1 *Humans*

Lener *et al.* (1998) studied children exposed to vanadium in air in an area close to a plant processing vanadium-rich slag (see Section 4.2.3). Group A comprised 15 children from the area potentially most affected by vanadium emissions; Group B, 28 children from an area of medium exposure; and Group C, 32 children was the control group. No significant induction of chromosomal aberrations was found in the lymphocytes of exposed children (1.2 ± 1.2 in Group A; 1.3 ± 1.1 in Group B) compared with the control group (0.95 ± 0.97). Sister chromatid exchange was analysed in exposed children (4.6 ± 1.0 in Group A; 4.6 ± 0.87 in Group B) but no data were available from controls. However, the authors concluded that these results revealed no genotoxic effects of vanadium exposure.

Only one in-vivo study of the genotoxic action of vanadium pentoxide in adult humans has been reported. Ivancsigts *et al*. (2002) studied the effect of occupational exposure to vanadium pentoxide by measuring DNA strand breaks using the single-cell gel electrophoresis assay 'Comet Assay', formation of 8-hydroxy-2′-deoxyguanosine, and the frequency of sister chromatid exchange in whole blood or lymphocytes of 49 male workers in a vanadium-processing factory. Although there was significant vanadium uptake (mean vanadium concentration in serum, 5.38 μg/mL), no increase in cytogenetic end-points nor in oxidative DNA damage was observed in the cells from these workers.

4.4.2 *Experimental systems*

(*a*) *Biochemical assays*

Effects of vanadium compounds on DNA-metabolizing enzymes have been reported by Sabbioni *et al*. (1983). Vanadate(V) ions (10^{-7}–10^{-3} M) inhibited calf thymus terminal deoxynucleotidyl transferase (with an apparent Ki of 2.5 μM) and the catalytic activity of mammalian DNA polymerase α (at I_{50} of 60 μM), while bacterial DNA polymerase-I was inhibited when the concentration was increased to about 0.5 mM.

(*b*) *Mutagenicity* (see Table 7)

(i) *In-vitro studies*

The mutagenicity of vanadium compounds has been reviewed (Graedel *et al*., 1986; Léonard & Gerber, 1994; Altamirano-Lozano *et al*., 1998b; Léonard & Gerber, 1998; National Toxicology Program, 2002).

The majority of the results of mutagenic activity of vanadium have been shown in *Escherichia coli* and *Salmonella typhimurium* (Hansen & Stern, 1984; Graedel *et al.*, 1986; Leonard & Gerber, 1994); there is one study only with exogenous metabolic activation (National Toxicology Program, 2002).

Early studies demonstrated that vanadium pentoxide was more genotoxic in recombination-repair-deficient (rec^-) strains of *Bacillus subtilis* than in the wild-type rec^+

Table 7. Genetic and related effects of vanadium pentoxide

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli, spot test B/r WP2try$^-$, WP2hcr$^-$try$^-$	–	NT	0.5 M	Kanematsu *et al*. (1980)
Escherichia coli, WP_2, WP_2uvrA, CM_{891}, reversion assay	+	NT	1200 µg/plate	Si *et al.* (1982)[c]
Escherichia coli, ND160 and MR102, frameshift mutation	–		1200 µg/plate	Si *et al.* (1988)[c]
Bacillus subtilis, M45 recombination-repair-deficient (rec$^-$)	+	NT	0.5 M	Kanematsu & Kada (1978); Kada *et al*. (1980); Kanematsu *et al*. (1980)
Bacillus subtilis H17 (rec$^+$) and M45 (rec$^-$) recombination-repair-deficient	+	NT	100 000	Sun (1996)
Salmonella typhimurium, TA100, TA1535, TA1537, TA1538, (his$^-$)	–	NT	0.5 M	Kanematsu *et al*. (1980)
Salmonella typhimurium, TA100, TA98, TA102, TA1535 reverse mutation	–	–	333 µg/plate	National Toxicology Program (2002)
Salmonella typhimurium, TA97, TA98, TA100, TA102 reverse mutation	–	NT	200 µg/plate	Zen *et al.* (1988)[c]
Gene mutation, 6-thioguanine resistant mutation, Chinese hamster lung fibroblast cell line (V79) *in vitro*	–		4	Zhong *et al*. (1994)
Sister chromatid exchanges, Chinese hamster lung fibroblast cell line (V79) *in vitro*	–		4	Zhong *et al*. (1994)
Micronucleus formation in binucleated cells, cytochalasin-B assay, Chinese hamster lung fibroblast cell line (V79) *in vitro*	+	NT	1	Zhong *et al*. (1994)
Numerical chromosomal aberrations, endoreduplication, Chinese hamster lung fibroblast cell line (V79) *in vitro*	+		1	Zhong *et al*. (1994)

Table 7 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Numerical chromosomal aberrations, aneuploidy, kinetochore staining of micronuclei in binucleated cells, Chinese hamster lung fibroblast cells line (V79) *in vitro*	+		1	Zhong et al. (1994)
DNA strand breaks, alkaline 'Comet Assay', human lymphocytes *in vitro*	+	NT	0.3 µM	Rojas *et al*. (1996a, b)
Inhibition of double-strand DNA breaks repair, alkaline and neutral 'Comet Assay', human fibroblasts *in vitro*	+		UV (4.8 kJ/m^2) + V_2O_5 0.5 µM	Ivancsists *et al*. (2002)
	+		Bleomycin (1 µg/mL) + V_2O_5 0.5 µM	
Sister chromatid exchanges, human lymphocytes *in vitro*	–	NT	47 M	Sun *et al.* (1989)[c]
Sister chromatid exchanges, human lymphocytes *in vitro*	–	NT	6	Roldán & Altamirano (1990)
Sister chromatid exchanges, human lymphocytes *in vitro*	+	NT	4[d]	Roldán-Reyes *et al*. (1997)
Structural chromosomal aberrations, human lymphocytes *in vitro*	–	NT	6	Roldán & Altamirano (1990)
Numerical chromosomal aberrations, polyploidy, human lymphocytes *in vitro*	+	NT	2	Roldán & Altamirano (1990)
Aneuploidy, FISH centromeric probes, human lymphocytes *in vitro*	+	NT	0.001 µM	Ramírez *et al*. (1997)
Inhibition of microtubule polymerisation, immunostaining, human lymphocytes *in vitro*	+	NT	0.1 µM	Ramírez *et al*. (1997)
Chromosomes associated and satellite association, human lymphocyte *in vitro*	+	NT	4	Roldán & Altamirano (1990)

Table 7 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DNA strand breaks, alkaline 'Comet Assay', in several organs of CD-1 mice *in vivo*	+		5.75 ip	Altamirano-Lozano *et al*. (1996, 1999)
DNA synthesis, inhibition assay, mice testes, spleen, liver and lymphocytes *in vivo*	–		58.4 po	Zen *et al.* (1988)[c]
Sister chromatid exchanges, CD-1 mice, bone marrow, *in vivo*	-		23 ip	Altamirano-Lozano *et al*. (1993); Altamirano-Lozano & Alvarez-Barrera (1996)
Micronucleus formation, 615 and Kunming albino mice, bone marrow, *in vivo*	+		0.17 ip	Si *et al.* (1982)[c]
Micronucleus formation, 615 and Kunming albino mice, bone marrow, *in vivo*	+		0.25 sc	Si *et al.* (1982)[c]
Micronucleus formation, 615 and Kunming albino mice, bone marrow, *in vivo*	+		0.5 mg/m^3, inhal.	Si *et al.* (1982)[c]
Micronucleus formation, Kunming albino mice, bone marrow, *in vivo*	–		11.3 po	Sun *et al.* (1989)[c]
Micronucleus formation, Kunming albino pregnant mice, fetal liver, maternal bone marrow, maternal spleen, *in vivo*	+		0.2–5 ip[e]	Liu *et al.* (1992)[c]
Micronucleus formation, B6C3F1mice, peripheral blood erythrocytes, *in vivo*	–		16 mg/m^3, inhal.	National Toxicology Program (2002)
Structural chromosomal aberrations, CD-1 mice, bone marrow, *in vivo*	–		23 ip	Altamirano-Lozano & Alvarez-Barrera (1996)

Table 7 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Structural chromosomal aberrations, albino rat, bone marrow cells, *in vivo*	?		4 po	Giri *et al*. (1979)
Dominant lethal mutations, CD-1 mice *in vivo*	+		8.5 ip	Altamirano-Lozano *et al.* (1996)
Dominant lethal mutations, CD-1 mice *in vivo*	–		4 sc	Si *et al.* (1982)[c]

FISH, fluorescence in-situ hybridization

[a] +, positive; –, negative; (+), weak positive; NT, not tested;?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL, except where stated otherwise; in-vivo tests, mg/kg bw per day; po, orally, by gavage; sc, subcutaneously; ip, intraperitoneally; inhal., by inhalation

[c] Cited in Sun (1996)

[d] Combined with 20 μg of caffeine

[e] LED not given

(Kanematsu & Kada, 1978; Kanematsu *et al*., 1980). However, vanadium pentoxide was not mutagenic in several strains of *E. coli* or *S. typhimurium*. But Si *et al.* (1982) (cited by Sun *et al.*, 1996) demonstrated that vanadium pentoxide induced reverse mutations in *E. coli* WP2, WP2uvrA and CM-981, but not frameshift mutations in strains ND-160 or MR102. This compound showed negative results in *S. typhimurium* strains TA100, TA1535, TA1537, TA1538, TA97, and TA98.

Bis(cyclopentadienyl)vanadium chloride (1 to 33 μg/plate) was mutagenic or weakly mutagenic in strains TA97 and TA100 without exogenous metabolic activation system, but not mutagenic in strains TA1535 and TA98 with or without metabolic activation (Zeiger *et al.*, 1992).

In another series of studies, vanadium pentoxide (0.33 to 333.00 μg/plate) was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, TA102 or TA1535, with or without induced rat or hamster liver S9 enzymes (National Toxicology Program, 2002).

No increase in the frequency of micronucleated normochromatic erythrocytes was seen in peripheral blood samples from male or female $B6C3F_1$ mice exposed to vanadium pentoxide by inhalation in concentrations up to 16 mg/m^3 for 3 months. Furthermore, no effect was seen in the ratio of polychromatic erythrocytes/normochromatic erythrocytes in peripheral blood, indicating a lack of toxicity to the bone marrow by vanadium pentoxide (National Toxicology Program, 2002).

[The Working Group was aware of positive results on induction of mitotic recombination by vanadium pentoxide in *Drosophila*; the data were reported in BSc and MSc theses].

In Chinese hamster lung fibroblast cell lines, vanadium pentoxide induced endoreduplication and micronuclei which were shown to be kinetochore-positive, but did not induce gene mutation nor sister chromatid exchange.

In human lymphocytes cultured *in vitro*, positive genotoxic effects of vanadium pentoxide were demonstrated for the induction of DNA damage with the alkaline 'Comet Assay' (two studies from the same laboratory), sister chromatid exchange when the compound was given in combination with caffeine (one study out of three), chromosomes associated, satellite associations and polyploidy with Hoechst staining (a single study), aneuploidy with fluorescence in-situ hybridization staining and inhibition of microtubule polymerization with immunostaining (a single study).

Vanadium pentoxide was shown to inhibit repair of double-strand breaks induced in human fibroblasts by UV radiation or bleomycin in both the neutral and alkaline comet assays.

(ii) *In-vivo studies*

In CD-1 mice, induction of DNA damage by vanadium pentoxide administered intraperitoneally was demonstrated with the alkaline 'Comet Assay' in several organs. In the same mouse strain, a lack of sister chromatid exchange and chromosomal aberrations was reported in bone marrow; however, dominant lethal effects were observed after intraperitoneal injection of vanadium pentoxide (8.5 mg/kg bw).

In 615 and Kunming albino mice, micronuclei were induced in bone marrow by vanadium pentoxide administered by inhalation, by subcutaneous injection or by intraperitoneal injection. The results were negative following oral administration. Micronuclei were also seen in fetal liver after intraperitoneal injection of vanadium pentoxide into pregnant mice. No induction of dominant lethals was observed.

A single in-vivo study of the induction of chromosomal aberrations in albino rats was inconclusive (number of animals not reported).

(*c*) *Genetic changes in vanadium pentoxide-induced tumours*

In a National Toxicology Program study (2002), male and female B6C3F_1 mice were exposed by inhalation to 1, 2, or 4 mg/m^3 vanadium pentoxide for 2 years (see Section 3.1.1). The lung carcinomas that developed as a result of this exposure showed a high frequency of K-*Ras* mutation, loss of heterozygosity in the region of the K-*Ras* gene on chromosome 6 and activation of MAP kinase (Zhang *et al.*, 2001b; Devereux *et al.*, 2002; National Toxicology Program, 2002). The authors concluded that these genetic alterations played an important role in vanadium pentoxide-induced lung carcinogenesis. On the other hand, there was no evidence of overexpression of mutant p53 suggesting no evidence of a role for altered p53 function in the lung carcinomas due to exposure to vanadium pentoxide (Devereux *et al.*, 2002; National Toxicology Program, 2002).

4.5 Mechanistic considerations

Vanadium pentoxide is considered to induce oxidative damage leading to DNA alkali-labile sites and DNA strand breakage.

Inhibition of microtubule polymerization may explain the aneugenic effects of vanadium pentoxide. Whether these spindle disturbances are related to oxidative damage or to direct interaction with vanadium cations is unclear. Indirect effects of vanadium pentoxide through inhibition of various enzymes involved in DNA synthesis and DNA repair also contribute to its genotoxicity.

Induction of dominant lethal mutations in mice may result from one, or a combination, of the modes of action mentioned above.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Vanadium is widely distributed in the earth's crust in a wide range of minerals and in fossil fuels. Vanadium pentoxide, the major commercial product of vanadium, is mainly used in the production of alloys with iron and aluminium. It is also used as an oxidation catalyst in the chemical industry and in a variety of minor applications. Exposure to vana-

dium pentoxide in the workplace occurs during the refining and processing of vanadium-rich mineral ores, during the burning of fossil fuels, especially petroleum, during the handling of vanadium catalysts in the chemical manufacturing industry and during the cleaning of oil-fired boilers and furnaces. Exposure to vanadium can also occur from ambient air contaminated by the burning of fossil fuels and, at much lower levels, from contaminated food and drinking-water.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Vanadium pentoxide was tested for carcinogenicity in a single study in mice and rats by inhalation exposure. In both male and female mice, the incidences of alveolar/bronchiolar neoplasms were significantly increased, and there were also increases in male rats. It was uncertain as to whether a marginal increase in alveolar/bronchiolar neoplasms in female rats was related to exposure to vanadium pentoxide.

5.4 Other relevant data

Vanadium pentoxide is rapidly absorbed following inhalation, but poorly through dermal contact or ingestion. Elimination from the lung is initially fast, but complete only after several days. Lung retention can increase due to impaired health status of the lung. Distribution of vanadium pentoxide is mainly to the bone and kidney.

The major non-cancer health effect associated with inhalation exposure to vanadium pentoxide involves acute respiratory irritation, characterized as 'boilermakers bronchitis'. This clinical effect appears to be reversible. Green coloration of the tongue is another frequently observed clinical manifestation of intoxication with vanadium pentoxide.

Vanadium has been recognized as an essential nutritional requirement in animals of high order, but its function is not clear. Vanadium pentoxide has important effects on a broad variety of cellular processes. It stimulates cell differentiation, it causes cell and DNA injury via generation of reactive oxygen species and it alters gene expression. The many biochemical effects induced by vanadium pentoxide, such as the inhibition of a number of different enzymes, can explain many of the metabolic effects observed in experimental animals treated with this compound.

Vanadium pentoxide can pass the blood–placenta barrier. It has been reported to be teratogenic in rodents and it affects sexual development in pre-pubertal animals, the toxicity in males being greater than that in females. The reduced fertility seen in male mice was confirmed by a reduction in sperm motility *in vitro*.

Vanadium pentoxide is mutagenic *in vitro* and possibly *in vivo* in mice. It shows clastogenic and aneugenic activity in cultured mammalian cells, the latter effect probably being due to disturbance of spindle formation and chromosome segregation. Vanadium pentoxide has been reported to inhibit enzymes involved in DNA synthesis and repair of DNA damage. Data on genetic effects in humans exposed to vanadium pentoxide are scarce.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of vanadium pentoxide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of vanadium pentoxide.

Overall evaluation

Vanadium pentoxide is *possibly carcinogenic to humans (Group 2B)*.

6. References

Acevedo-Nava, S., López, I., Bizarro, P., Sánchez, I., Pasos, F., Delgado, V., Vega, M.I., Calderón, N. & Fortoul, T.I. (2001) Alteraciones morfológicas en el hígado de ratón por inhalacion de vanadio. In: *Proceedings of the IV Congreso Mexicano de Toxicología, Mérida, Yucatán, México*

ACGIH Worldwide® (2003) *Documentation of the TLVs® and BEIs® with other Worldwide Occupational Exposure Values — CD-ROM — 2003*, Cincinnati, OH

Al-Bayati, M.A., Giri, S.N., Raabe, O.G., Rosenblatt, L.S. & Shifrine, M. (1989) Time and dose-response study of the effects of vanadate on rats: Morphological and biochemical changes in organs. *J. environ. Pathol. Toxicol. Oncol*., **9**, 435–455

Altamirano, M., Ayala, M.E., Flores, A., Morales, L. & Dominguez, R. (1991) Sex differences in the effects of vanadium pentoxide administration to prepubertal rats. *Med. Sci. Res.*, **19**, 825–826

Altamirano-Lozano, M.A. & Alvarez-Barrera, L. (1996) Genotoxicity and reprotoxic effects of vanadium and lithium. In: Collery, P., Corbella, J., Domingo, J.L., Etienne, J.C. & Llobert, J.M., eds, *Metal Ions in Biology and Medicine*, Vol. 4, Paris, John Libbey Eurotext, pp. 423–425

Altamirano-Lozano, M., Alvarez-Barrera, L. & Roldán-Reyes, E. (1993) Cytogenetic and teratogenic effects of vanadium pentoxide on mice. *Med. Sci. Res.*, **21**, 711–713

Altamirano-Lozano, M., Alvarez-Barrera, L., Basurto-Alcántara, F., Valverde, M. & Rojas, E. (1996) Reprotoxic and genotoxic studies of vanadium pentoxide in male mice. *Teratog. Carcinog. Mutag.*, **16**, 7–17

Altamirano-Lozano, M., Roldán-Reyes, E., Bonilla, E. & Betancourt, M. (1997) Effect of some metal compounds on sperm motility *in vitro. Med. Sci. Res.*, **25**, 147–150

Altamirano-Lozano, M., Roldán, E., Bonilla, E. & Betancourt, M. (1998a) Effect of metal compounds on boar sperm motility in vitro. *Adv. exp. Med. Biol.*, **444**, 105–111

Altamirano-Lozano, M.A., Roldán-Reyes, M.E. & Rojas, E. (1998b) Genetic toxicology of vanadium compounds. In: Nriagu, J.O., ed., *Vanadium in the Environment. Part 2: Health Effects*, Vol. 31, New York, John Wiley & Sons, pp. 159–179

Altamirano-Lozano, M., Valverde, M., Alvarez-Barrera, L., Molina, B. & Rojas, E. (1999) Genotoxic studies of vanadium pentoxide (V_2O_5) in male mice. II. Effects in several mouse tissues. *Teratog. Carcinog. Mutag*., **19**, 243–255

American Elements (2003) *Vanadium*, Los Angeles, CA (http://www.americanelements.com.vv.html, accessed 19.09.2003)

Arbouine, M. & Smith, N.J. (1991) The determination of vanadium in urine and its application to the biological monitoring of occupationally exposed workers. *Atomic Spectr.*, **12**, 54–58

Atomix (2003) *Product Data Sheet: Vanadium Pentoxide (V_2O_5)*, Hohokus, NJ (http://www.atomixinc.com/vanadiumpentoxide.htm, accessed 19.09.2003)

Auricchio, F., Di Domenico, M., Migliaccio, A., Castoria, G. & Bilancio, A. (1995) The role of estradiol receptor in the proliferative activity of vanadate on MCF-7 cells. *Cell Growth Differ.*, **6**, 105–113

Auricchio, F., Migliaccio, A., Castoria, G., Di Domenico, M., Bilancio, A. & Rotondi, A. (1996) Protein tyrosine phosphorylation and estradiol action. *Ann. N.Y. Acad. Sci*., **784**, 149–172

AVISMA titanium-magnesium Works (2001) *Vanadium Pentoxide*, Berezniki (http://www.avisma.ru/eng/produkts, accessed 19.09.2003)

Barisione, G., Fontana, L. & Pasquarelli, P. (1993) [Acute exposure to vanadium pentoxide: Critical review and clinical investigation.] *Archiv. Sci. Lav*., **8**(2), 111–115 (in Italian)

Bauer, G., Güther, V., Hess, H., Otto, A., Roidl, O., Roller, H. & Sattelberger, S. (2003) Vanadium and vanadium compounds. In: Bohnet *et al.*, eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 6th rev. Ed., Vol. 38, Weinheim, Wiley-VCH Verlag GmbH & Co., pp. 1–21

Blotcky, A.J., Duckworth, W.C., Ebrahim, A., Hamel, F.K., Rack, E.P. & Sharma, R.B. (1989) Determination of vanadium in serum by pre-irradiation and post-irradiation chemistry and neutron activation analysis. *J. radioanal. nucl. Chem.*, **134**, 151–160

Bonner, J.C., Rice, A.B., Moomaw, C.R. & Morgan, D.L. (2000) Airway fibrosis in rats induced by vanadium pentoxide. *Am. J. Physiol. Lung Cell mol. Physiol*., **278**, L209–L216

Bracken, W.N., Sharma, R.P. & Elsner, Y.Y. (1985) Vanadium accumulation and subcellular distribution in relation to vanadate induced cytotoxicity in vitro. *Cell Biol. Toxicol.*, **1**, 259–268

Bräunlich, H., Pfeifer, R., Grau, P. & Reznik, L. (1989) Renal effects of vanadate in rats. *Biomed. biochim. Acta*, **48**, 457–464

Buchet, J.P., Knepper, E. & Lauwerys R. (1982) Determination of vanadium in urine by electrothermal atomic absorption spectrometry. *Anal. chim. Acta*, **136**, 243–248

Buratti, M., Pellegrino, O., Caravelli, G., Calzaferri, G., Bettinelli, M., Colombi, A. & Maroni, M. (1985) Sensitive determination of urinary vanadium by solvent extraction and atomic absorption spectroscopy. *Clin. Chem. Acta*, **150**, 53–58

Byczkowski, J.Z. & Kulkarni, A.P. (1998) Oxidative stress and pro-oxidant biological effects of vanadium. In: Nriagu, J.O., ed., *Vanadium in the Environment. Part 2: Health Effects*, Vol. 31, New York, John Wiley & Sons, pp. 235–264

Byerrum, R.U., Eckardt, R.E., Hopkins, L.L., Libsch, J.F., Rostoker, W., Zenz, C., Gordon, W.A., Mountain, J.T., Hicks, S.P. & Boaz, T.D. (1974) *Vanadium*, Washington DC, National Academy of Sciences, pp. l–117

Byrne, A.R. (1993) Review of neutron activation analysis in the standardization and study of reference materials, including its application to radionuclide reference materials. *Fresenius J. anal. Chem.*, **345**, 144–151

Byrne, A.R. & Kosta, L. (1978a) Determination of vanadium in biological materials at nanogram level by neutron activation analysis. *J. Radioanal. Chem.*, **44**, 247–264

Byrne, A.R. & Kosta, L. (1978b) Vanadium in foods and in human body fluids and tissues. *Sci. total Environ*., **10**, 17–30

Byrne, A.R. & Kucera, J. (1991a) New data on levels of vanadium in man and his diet. In: Momcilovic, B., ed., *Proceedings of the 7th International Symposium on Trace Elements in Man and Animals*, pp. 25-18–25-20

Byrne, A.R. & Kucera, J. (1991b) Radiochemical neutron activation analysis of traces of vanadium in biological samples: A comparison of prior dry ashing with post-irradiation wet ashing. *Fresenius J. anal. Chem.*, **340**, 48–52

Byrne, A.R. & Versieck, J. (1990) Vanadium determination in the ultratrace level in biological reference materials and serum by radiochemical neutron activation analysis. *Biol. trace Elem. Res.*, **27**, 529–540

Cantley, L.C., Jr, Josephson, L., Warner, R., Yanagisawa, M., Lechene, C. & Guidotti, G. (1977) Vanadate is a potent (Na,K)-ATPase inhibitor found in ATP derived from muscle. *J. biol. Chem.*, **252**, 7421–7423

Carsey, T.P. (1985) Quantitation of vanadium oxides in airborne dusts by X-ray diffraction. *Anal. Chem.*, **57**, 2125–2130

Chakraborty, D., Bhattacharyya, A., Majumdar, K. & Chatterjee, G.C. (1977) Effects of chronic vanadium pentoxide administration on L-ascorbic acid metabolism in rats: Influence of L-ascorbic acid supplementation. *Int. J. Vitam. Nutr. Res*, **47**, 81–87

Chemical Information Services (2003) *Directory of World Chemical Producers (Version 2003)*, Dallas, TX (http://www.chemical.info.com, accessed 18.09.2003)

Chen, F., Vallyathan, V., Castranova, V. & Shi, X. (2001) Cell apoptosis induced by carcinogenic metals. *Mol. cell. Biochem*., **222**, 183–188

Chin, L.S., Murray, S.F., Harter, D.H., Doherty, P.F. & Singh, S.K. (1999) Sodium vanadate inhibits apoptosis in malignant glioma cells: A role for Akt/PKB. *J. Biomed. Sci.*, **6**, 213–218

Cohen, M.D., Parsons, E., Schlesinger, R.B. & Zelikoff, J.T. (1993) Immunotoxicity of *in vitro* vanadium exposures: Effects on interleukin-1, tumor necrosis factor-α, and prostaglandin E_2 production by WEHI-3 macrophages. *Int. J. Immunopharmacol*., **15**, 437–446

Cohen, M.D., McManus, T.P., Yang, Z., Qu, Q., Schlesinger, R.B. & Zelikoff, J.T. (1996) Vanadium affects macrophage interferon-γ-binding and -inducible responses. *Toxicol. appl. Pharmacol*., **138**, 110–120

Colin-Barenque, L., Avila-Costa, M.R., Sánchez, I., López, I., Niño-Cabrera, G., Pasos, F., Delgado, V. & Fortul, T.I. (2003) Muerte neuronal en el bulbo olfatorio de ratón inducida por exposición subaguda y crónica de vanadio. In: *Proceedings of the XLVI Congreso Nacional de la Sociedad de Ciencias Fisiológicas, A.C., Aguascalientes, Ags. México*

Conklin, A.W., Skinner, C.S., Felten, T.L. & Sanders, C.L. (1982) Clearance and distribution of intratracheally instilled ^{48}vanadium compounds in the rat. *Toxicol. Lett.*, **11**, 199–203

Cornelis, R., Versieck, J., Mees, L., Hoste, J. & Barbier, F. (1980) Determination of vanadium in human serum by neutron activation analysis. *J. radioanal. Chem*., **55**, 35–43

Cornelis, R., Versieck, J., Mees, L., Hoste, J. & Barbier, F. (1981) The ultratrace element vanadium in human serum. *Biol. trace Elem. Res.*, **3**, 257–263

Crans, D.C., Amin, S.S. & Keramidas, A.D.(1998) Chemistry of relevance to vanadium in the environment. In: Nriagu, J.O. ed., *Vanadium in the Environment. Part One. Chemistry and Biochemistry,* New York, John Wiley & Sons, 73–96

Dafnis, E., Spohn, M., Lonis, B., Kurtzman, N.A. & Sabatini, S. (1992) Vanadate causes hypokalemic distal renal tubular acidosis. *Am. J. Physiol.*, **262**, F449–F453

Dai, S., Thompson, K.H., Vera, E. & McNeill, J.H. (1994) Toxicity studies on one-year treatment of non-diabetic and streptozotocin-diabetic rats with vanadyl sulphate. *Pharmacol. Toxicol.*, **75**, 265–273

Deutsche Forschungsgemeinschaft (2002) *List of MAK and BAT Values 2002 — Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area* (Report No. 38), Weinheim, Wiley-VCH Verlag GmbH, pp. 109, 189

Devereux, T.R., Holliday, W., Anna, C., Ress, N., Roycroft, J. & Sills, R.C. (2002) Map kinase activation correlates with k-*ras* mutation and loss of heterozygosity in chromosome 6 in alveolar bronchiolar carcinomas from B6C3F1 mice exposed to vanadium pentoxide for 2 years. *Carcinogenesis*, **23**, 1737–1743

Dimond, E.G., Caravaca, J. & Benchimol, A. (1963) Vanadium. Excretion, toxicity, lipid effect in man. *Am. J. clin. Nutr.*, **12**, 49–53

Ding, M., Li, J.-J., Leonard, S.S., Ye, J.-P., Shi, X., Colburn, N.H., Castranova, V. & Vallyathan, V. (1999) Vanadate-induce activation of activator protein-1: Role of reactive oxygen species. *Carcinogenesis*, **20**, 663–668

Domingo, J.L. (1994) Metal-induced developmental toxicity in mammals: A review. *J. Toxicol. environ. Health*, **42**, 123–141

Domingo, J.L. (1996) Vanadium: A review of the reproductive and developmental toxicity. *Reprod. Toxicol*., **10**, 175–182

Dong, W., Simeonova, P.P., Gallucci, R., Matheson, J., Flood, L., Wang, S., Hubbs, A. & Luster, M.I. (1998) Toxic metals stimulate inflammatory cytokines in hepatocytes through oxidative stress mechanisms. *Toxicol. appl. Pharmacol*., **151**, 359–366

Dreher, K.L., Jaskot, R.H., Lehmann, J.R., Richards, J.H., McGee, J.K., Ghio, A.J. & Costa, D.L. (1997) Soluble transition metals mediate residual oil fly ash induced acute lung injury. *J. Toxicol. environ. Health*, **50**, 285–305

Edel, J. & Sabbioni, E. (1988) Retention of intratracheally instilled and ingested tetravalent and pentavalent vanadium in the rat. *J. trace Elem. Electrolytes Health Dis.*, **2**, 23–30

Edel, J. & Sabbioni, E. (1989) Vanadium transport across placenta and milk of rats to the fetus and newborn. *Biol. trace. Elem. Res.*, **22**, 265–275

Environmental Protection Agency (1977) *Scientific and Technical Assessment Report on Vanadium*, Washington DC, US Environmental Protection Agency (STAR Series, EPA-600/6-77-002)

Environmental Protection Agency (1985) *Health and Environmental Effects Profile for Vanadium Pentoxide* (EPA/600/X-85/114, 53), Cincinnati, OH, US Environmental Protection Agency, Environmental Criteria and Assessment Office

ESPI (1994) *Material Safety Data Sheet: Vanadium Pentoxide*, Ashland, OR (http://www.espimetals.com/msds's/vanadiumoxidev2o5.pdf, accessed 18.09.2003)

Fassett, J.D. & Kingston, H.M. (1985) Determination of nanogram quantities of vanadium in biological material by isotope dilution thermal ionization mass spectrometry with ion counting detection. *Anal. Chem.*, **57**, 2474–2478

Fisher, G.L., McNeill, K.L. & Democko, C.J. (1986) Trace element interactions affecting pulmonary macrophage cytotoxicity. *Environ. Res*., **39**, 164–171

Fortoul, T.I., Quan-Torres, A., Sánchez, I., Lopez, I.E., Bizarro, P., Mendoza, M.L., Osorio, L.S., Espejel-Maya, G., Avila-Casado M.D.C., Avila-Costa, M.R., Colin-Barenque, L., Villanueva, D.N. & Olaiz-Fernandez, G. (2002) Vanadium in ambient air: Concentrations in lung tissue from autopsies of Mexico City residents in the 1960s and 1990s. *Arch. environ. Health*, **57**, 446–449

French, R.J. & Jones, P.J.H. (1993) Minireview. Role of vanadium in nutrition: Metabolism, essentiality and dietary considerations. *Life Sci.*, **52**, 339–346

Garcia, A.G., Jurkiewicz, A. & Jurkiewicz, N.H. (1981) Contractile effect of vanadate and other vanadium compounds on the rat vas deferens. *Eur. J. Pharmacol.*, **70**, 17–23

GfE mbH (2003) *Products by Product Groups: Vanadium Chemicals*, Nuremburg (http://www.gfe-online.de, accessed 19.09.2003)

Giri, A.K., Sanyal, R., Sharma, A., & Talukder, G. (1979) Cytological and cytochemical changes induced through certain heavy metals in mammalian systems. *Natl. Acad Sci. Lett*., **2**, 391–394

Graedel, T.E., Hawkins, D.T., & Claxton, L.D. (1986) *Atmospheric Chemical Compounds, Sources, Occurrence and Bioassay*, New York, Academic Press

Greenberg, R.R., Kingston, H.M., Zeisler, R. & Woittiez, J. (1990) Neutron activation analysis of biological samples with a preirradiation separation. *Biol. trace Elem. Res.*, **26/27**, 17–25

Gylseth, B., Leira, H.L., Steinnes, E. & Thomassen, Y. (1979) Vanadium in the blood and urine of workers in a ferroalloy plant. *Scand. J. Work Environ. Health*, **5**, 188–194

Hahn, F.F. (1993) Chronic inhalation bioassays for respiratory tract carcinogenesis. In: Gardner, D.E., Crapo, J.D. & McClellan, R.O., eds, *Target Organ Toxicology Series: Toxicology of the Lung*, 2nd Ed., New York, Raven Press, p. 435

Hamel, F.G. (1998) Endocrine control of vanadium accumulation. In: Nriagu, J.O. ed., *Vanadium in the Environment. Part 2: Health Effects*, New York, John Wiley & Son, pp. 265–276

Hansard, S.L., Ammerman, C.B., Fick, K.R. & Miller, S.M. (1978) Performance and vanadium content of tissues in sheep as influenced by dietary vanadium. *J. Anim. Sci.* **46**, 1091–1095

Hansen, K. & Stern, R.M. (1984) A survey of metal-induced mutagenicity *in vitro* and *in vivo*. *Toxicol. environ. Chem*., **9**, 87–91

Hauser, R., Elreedy, S., Hoppin, J.A. & Christiani, D.C. (1995a) Airway obstruction in boilermakers exposed to fuel oil ash. A prospective investigation. *Am. J. respir. crit. Care Med.*, **152**, 1478–1484

Hauser, R., Elreedy, S., Hoppin, J.A. & Christiani, D.C. (1995b) Upper airway response in workers exposed to fuel oil ash: Nasal lavage analysis. *Occup. environ. Med.*, **52**, 353–358

Hauser, R., Elreedy, S., Ryan, P.B. & Christiani, D.C. (1998) Urine vanadium concentrations in workers overhauling an oil-fired boiler. *Am. J. ind. Med.*, **33**, 55–60

Hehner, S.P., Hofmann, T.G., Dröge, W. & Schmitz, M.L. (1999) Inhibition of tyrosine phosphatases induces apoptosis independent from the CD95 system. *Cell Death Differ.*, **6**, 833–841

Hery, M., Gerber, J.M., Hecht, G., Hubert, G., Elcabache, J.M. & Honnert, B. (1992) [Handling of catalysts in the chemical industry: Exposure assessment during operations carried out by outside contractors.] *Cahiers de Notes Documentaires*, **149**, 479–486 (in French)

Hery, M., Gerber, J.M., Diebold, F., Honnert, B., Hecht, G. & Hubert, G. (1994) [Exposure to chemical pollutants during the manufacture and reprocessing of inorganic catalysts] *Cahiers de Notes Documentaires*, **155**, 151–156 (in French)

Heydorn, K. (1990) Factors affecting the levels reported for vanadium in human serum. *Biol. trace Elem. Res.*, **27**, 541–551

Highveld Steel & Vanadium Corporation Ltd (2003) *Vanadium Pentoxide Powder*, Witbank, (http://www.highveldsteel.co.za/Marketing/Files/vanadium_pentoxide_powder_R_Grade.htm; http://www.highveldsteel.co.za/Marketing/Files/vanadium_pentoxide_powder_R_Granular.htm; accessed 19.09.2003)

Hilliard, H.E. (1994) *The Materials Flow of Vanadium in the United States* (Information Circular 9409), Washington DC, US Bureau of Mines

Hoffman, G.L., Duce, R.A. & Zoller, W.H. (1969) Vanadium copper, and aluminum in the lower atmosphere between California and Hawaii. *Environ. Sci. Technol.*, **3**, 1207–1210

Hope, B.K. (1994) A global biogeochemical budget for vanadium. *Sci. tot. Environ.*, **141**, 1–10

Huang, R.-T., Kang, J.F., Jin, H.E., Xue, H. & Wu, B.H. (1989) [Radiological observation on the workers exposed to vanadium]. *Zhonghua Yu Fang Yi Xue Za Zhi* [*Chin. J. Prev. Med.*, **23**, 283–285 (In Chinese)

Huang, C., Zhang, Z., Ding, M., Li, J., Ye, J., Leonard, S.S., Shen, H.-M., Butterworth, L., Lu, Y., Costa, M., Rojanasakul, Y., Castranova, V., Vallyathan, V. & Shi, X. (2000) Vanadate induces p53 transactivation through hydrogen peroxide and causes apoptosis. *J. biol. Chem*., **275**, 32516–32522

Hudson, T.G.F. (1964) Vanadium: Toxicology and biological significance. In: Browning, E., ed., *Elsevier Monographs on Toxic Agents*, Amsterdam, Elsevier Publishing Company, pp. 67–78

IARC (1989) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 45, *Occupational Exposures in Petroleum Refining; Crude Oil and Major Petroleum Fuels*, Lyon, IARC*Press*

INRS (1999) [Threshold limit values for occupational exposure to chemicals in France] In: *Cahiers de Notes Documentaires ND 2098-174-99*, Paris, Hygiène et Sécurité du Travail (in French)

Ingram, J.L., Rice, A.B., Santos, J., Van Houten, B. & Bonner, J.C. (2003) Vanadium-induced HB-EGF expression in human lung fibroblast is oxidant dependent and requires MAP kinases. *Am. J. Physiol. Lung Cell mol. Physiol*., **284**, L774–L782

Ishida, O., Kihira, K., Tsukamoto, Y. & Marumo, F. (1989) Improved determination of vanadium in biological fluids by electrothermal atomic absorption spectrometry. *Clin. Chem.*, **35**, 127–130

Ivancsists, S., Pilger, A., Diem, E., Schaffer, A. & Rüdiger, H.W. (2002) Vanadate induces DNA strand breaks in cultured human fibroblasts at doses relevant to occupational exposure. *Mutat. Res*., **519**, 25–35

Johnson, J.L., Cohen, H.J. & Rajagopalan, K.V. (1974) Studies of vanadium toxicity in the rat: Lack of correlation with molybdenum utilization. *Biochem. biophys. Res. Commun*., **56**, 904–946

Kada, T., Hirano, K. & Shirasu, Y. (1980) Screening of environmental chemical mutagens by the rec-assay system with *Bacillus subtilis*. In: de Serres, F.J. & Hollaender, A., eds, *Chemical Mutagens: Principles and Methods for their Detection*, Vol. 6, New York, Plenum Press, pp. 149–173

Kanematsu, K. & Kada, T. (1978) Mutagenicity of metal compounds. *Mutation. Res*., **53**, 207–208

Kanematsu, N., Hare, M., & Kada, T. (1980) Rec assay and mutagenicity studies on metal compounds. *Mutat. Res*., **77**, 109–116

Kawai, T., Seiji, K., Watanabe, T., Nakatsuka, H. & Ikeda, M. (1989) Urinary vanadium as a biological indicator of exposure to vanadium. *Int. Arch. occup. environ. Health*, **61**, 283–287

Kerckaert, G.A., LeBoeuf, R.A. & Isfort, R.J. (1996a) Use of the Syrian hamster embryo cell transformation assay for determining the carcinogenic potential of heavy metal compounds. *Fundam. appl. Toxicol*., **34**, 67–72

Kerckaert, G.A., Brauninger, R., LeBoeuf, R.A. & Isfort, R.J. (1996b) Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ. Health Perspect.*, **104** (Suppl. 5), 1075–1084

Kiviluoto, M., Pyy, L. & Pakarinen, A. (1979) Serum and urinary vanadium of vanadium-exposed workers. *Scand. J. Work Environ. Health*, **5**, 362–367

Kiviluoto, M., Pyy, L. & Pakarinen, A. (1981) Serum and urinary vanadium of workers processing vanadium pentoxide. *Int. Arch. occup. environ. Health,* **48**, 251–256

Knecht, E.A., Moorman, W.J., Clark, J.C., Lynch, D.W. & Lewis, T.R. (1985) Pulmonary effects of acute vanadium pentoxide inhalation in monkeys. *Am. Rev. respir. Dis.*, **132**, 1181–1185

Knecht, E.A., Moorman, W.J., Clark, J.C., Hull, R.D., Biagini, R.E., Lynch, D.W., Boyle, T.J. & Simon, S.D. (1992) Pulmonary reactivity to vanadium pentoxide following subchronic inhalation exposure in a non-human primate animal model. *J. appl. Toxicol.*, **12**, 427–434

Kodavanti, U.P., Hauser, R., Christiani, D.C., Meng, Z.H., McGee, J., Ledbetter, A., Richards, J. & Costa, D.L. (1998) Pulmonary responses to oil fly ash particles in the rat differ by virtue of their specific soluble metals. *Toxicol. Sci.*, **43**, 204–212

Kucera, J. & Sabbioni, E. (1998) Baseline vanadium levels in human blood, serum, and urine. In: Nriagu, J.O., ed., *Vanadium in the Environment. Part 2: Health Effects*, New York, John Wiley & Sons, pp. 75–89

Kucera, J., Byrne, A.R., Mravcová, A. & Lener, J. (1992) Vanadium levels in hair and blood of normal and exposed persons. *Sci. total Environ.*, **15**, 191–205

Kucera, J., Lener, J. & Mnuková, J. (1994) Vanadium levels in urine and cystine levels in fingernails and hair of exposed and normal persons. *Biol. Trace Element Res.*, **43–45**, 327–334

Kucera, J., Lener, J., Mnuková, J. & Bayerová, E. (1998) Vanadium exposure tests in humans: Hair, nails, blood, and urine. In: Nriagu, J.O., ed., *Vanadium in the Environment. Part 2: Health Effects*, New York, John Wiley & Sons, pp. 55–73

Kuzelova, M., Havel, V., Popler, A. & Stepanek, O. (1977) [The problems of occupational medicine in the work of chimney sweeps] *Prac. Lek*., **29**, 225–228 (in Czech)

Kyono, H., Serita, F., Toya, T., Kubota, H., Arito, H., Takahashi, M., Maruyama, R., Homma, K., Ohta, H., Yamauchi, Y., Nakakita, M., Seki, Y., Ishihara, Y. & Kagawa, J. (1999) A new model rat with acute bronchiolitis and its application to research on the toxicology of inhaled particulate matter. *Ind. Health*, **37**, 47–54

Lagerkvist, B., Nordberg, G.F. & Vouk, V. (1986) Vanadium. In: Friberg, L., Nordberg, G.F. & Vouk, V.B., eds, *Handbook on the Toxicology of Metals, Vol. II, Specific Metals*, 2nd Ed., Amsterdam, Elsevier, pp. 638–663

Lees, R.E.M. (1980) Changes in lung function after exposure to vanadium compounds in fuel oil ash. *Br. J. ind. Med.*, **37**, 253–256

Lener, J., Kucera, J., Kodl, M. & Skokanová, V. (1998) Health effects of environmental exposure to vanadium. In: Nriagu J, ed. *Vanadium in the Environment. Part 2: Health Effects,* New York, John Wiley & Sons, Inc., pp. 1–19

Leonard, A. & Gerber, G.B. (1994) Mutagenicity, carcinogenicity and teratogenicity of vanadium compounds. *Mutat. Res.*, **317**, 81–88

Leonard, A. & Gerber, G.B. (1998) Mutagenicity, carcinogenicity, and teratogenicity of vanadium. In: Nriagu, J.O., ed., *Vanadium in the environment. Part Two: Health Effects*, New York, John Wiley & Sons, Inc., pp. 39–51

Levy, B.S., Hoffman, L. & Gottsegen, S. (1984) Boilermakers' bronchitis. Respiratory tract irritation associated with vanadium pentoxide exposure during oil-to-coal conversion of a power plant. *J. occup. Med*., **26**, 567–570

Lewis, C.E. (1959) The biological effects of vanadium. II. The signs and symptoms of occupational vanadium exposure. *Arch. ind. Health*, **19**, 497–503

Lewis, R.J., Sr (2000) Sax's Dangerous Properties of Industrial Materials, 10th Ed., New York, John Wiley and Sons, Inc., pp. 3657–3660

Li, S., Zhang, T., Yang, Z. & Gou, X. (1991) [Distribution of vanadium in tissues of nonpregnant and pregnant Wistar rats]. *Hua Xi Yi Ke Da Xue Xue Bao*, **22**, 196–200 (in Chinese)

Li, H., Yang, Z. & Zhang, T. (1995) [Toxicity of vanadium to Leydig cells in vitro]. *Hua Xi Yi Ke Da Xue Xue Bao*, **26**, 433–435 (in Chinese)

Lide, D.R., ed. (2003) *CRC Handbook of Chemistry and Physics*, 84th Ed., Boca Raton, FL, CRC Press LLC, p. 4-93

Liochev, S. & Fridovich, I. (1988) Superoxide is responsible for the vanadate stimulation of NAD(P)H oxidation by biological membranes. *Arch. Biochem. Biophys*., **263**, 299–304

Liu, G. *et al.* (1992) The measure of cytogenic effects of vanadium pentaoxide on pregnant mice and embryo. *J. environ. Health*, **9**, 119 (cited in Sun, 1996)

Magyar, M.J. (2002) *Minerals Yearbook: Vanadium*, Reston, VA, US Geological Survey (http://minerals.usgs.gov/minerals/pubs/commodity/vanadium/index.html, accessed 19.09.2003)

Mamane, Y. & Pirrone, N. (1998) Vanadium in the atmosphere. In: Nriagu, J.O., ed., *Vanadium in the Environment. Part 1: Chemistry and Biochemistry*, New York, John Wiley & Sons, pp. 37–71

Martens, C.S., Wesolowski, J.J., Kaifer, R., John, W. & Harriss, R.C. (1973) Sources of vanadium in Puerto Rican and San Francisco Bay area aerosols. *Environ. Sci. Technol.*, **7**, 817–820

McKee, J.M. (1998) Vanadium. In: Wexler, P., ed., *Encyclopedia of Toxicology*, Vol. 3, San Diego, CA, Academic Press, pp. 386–387

Meza, P., Colin-Barenque, L., Mondragón, A., Avila-Costa, M.R., Sánchez, I., López, I., Niño-Cabrera, G., Pasos, F., Delgado, V. & Fortoul, T. (2003) Efecto de la inhalación subaguda y crónica de vanadio sobre la ultraestructura del cerebelo de ratón. In: *Proceedings of the XLVI Congreso Nacional de la Sociedad de Ciencias Fisiológicas, A.C., Aguascalientes, Ags. México*

Minoia, C., Sabbioni, E., Apostoli, P., Pietra, R., Pozzoli, L., Gallorini, M., Nicolaou, G., Alessio, L. & Capodaglio, E. (1990) Trace element reference values in tissues from inhabitants of the European community. I. A study of 46 elements in urine, blood and serum of Italian subjects. *Sci. total Environ.*, **95**, 89–105

Minoia, C., Pietra, R., Sabbioni, E., Ronchi, A., Gatti, A., Cavalleri, A. & Manzo, L. (1992) Trace element reference values in tissues from inhabitants of the European Community. III. The control of preanalytical factors in the biomonitoring of trace elements in biological fluids. *Sci. total Environ*., **120**, 63–79

Minoia, C., Sabbioni, E., Ronchi, A., Gatti, A., Pietra, R., Nicolotti, A., Fortaner, S., Balducci, C., Fonte, A. & Roggi, C. (1994) Trace element reference values in tissues from inhabitants of the European Community. IV. Influence of dietary factors. *Sci. total Environ.*, **141**, 181–195

Moens, L. & Dams, R. (1995) NAA and ICP-MS: A comparison between two methods for trace and ultra-trace element analysis. *J. radioanal. nucl. Chem.*, **192**, 29–38

Moens, L., Verrept, P., Dams, R., Greb, U., Jung, G. & Laser, B. (1994) New high-resolution inductively coupled plasma mass spectrometry technology applied for the determination of V, Fe, Cu, Zn and Ag in human serum. *J. anal. Atom. Spectr.*, **9**, 1075–1078

Mondragón, A., Colin-Barenque, L., Meza, P., Avila-Costa, M.R., Sánchez, I., López, I., Niño-Cabrera, G., Pasos, F., Delgado, V., Ordóñez, J., Gutiérrez, A., Aley, P. & Fortoul, T. (2003) Efectos de la inhibición crónica de vanadio sobre la citología del bulbo olfatorio de ratón. In: *Proceedings of the XLVI Congreso Nacional de la Sociedad de Ciencias Fisiológicas, A.C., Aguascalientes, Ags. México*

Mongold, J.J., Cros, G.H., Vian, L., Tep, A., Ramanadham, S., Siou, G., Diaz, J., McNeill, J.H. & Serrano, J.J. (1990) Toxicological aspects of vanadyl sulphate on diabetic rats: Effects on vanadium levels and pancreatic B-cell morphology. *Pharmacol. Toxicol.*, **67**, 192–198

Montiel-Flores, E., Avila-Costa, M., Aley, P., López, I., Acevedo, S., Saldivar, L., Espejel, G., González, A., Avila-Casado, M., Niño, G., Bizarro, P., Mussali, P., García-Morales, D., Colin-Barenque, L., Delgado, V. & Fortoul, T. (2003) Vanadium inhalation induces neuronal alterations in *corpus striatum*. An experimental model in mice. In: *Proceedings of the 42nd Annual Meeting of the Society of Toxicology, Salt Lake City, Utah, USA*

Motolese, A., Truzzi, M., Giannini, A. & Seidenari, S. (1993) Contact dermatitis and contact sensitization among enamellers and decorators in the ceramics industry. *Contact Derm.*, **28**, 59–62

Mravcová, A., Jírová, D., Janci, H. & Lener, J. (1993) Effects of orally administered vanadium on the immune system and bone metabolism in experimental animals. *Sci total Environ.*, **Suppl.**, 663–669

Musk, A.W. & Tees, J.G. (1982) Asthma caused by occupational exposure to vanadium compounds. *Med. J. Aust.*, **1**, 183–184

Myron, D.R., Gvand, S.H. & Nielsen, F.H. (1977) Vanadium content of selected foods as determined by flameless atomic absorption spectroscopy. *J. agric. food Chem.*, **25**, 297–300

Myron, D.R., Zimmerman, T.J., Shuler, T.R., Klevay, L.M., Lee, D.E. & Nielsen, F.H. (1978) Intake of nickel and vanadium by humans. A survey of selected diets. *Am. J. clin. Nutr.*, **31**, 527–531

National Institute for Occupational Safety and Health (1976) *National Occupational Hazard Survey (1970) Database*, Cincinnati, OH

National Institute for Occupational Safety and Health (1984) *National Occupational Exposure Survey (1980–1983) Database*, Cincinnati, OH

National Institute for Occupational Safety and Health (1994) Vanadium oxides — Method 7504, Issue 2. In: *NIOSH Manual of Analytical Methods (NMAM)*, 4th Ed., dated August 15, 1994

National Institute for Occupational Safety and Health (2005) Vanadium dust. In: *NIOSH Pocket Guide to Chemical Hazard* (DHHS (NIOSH) Publication No. 2005-149), Cincinnati, OH, Department of Health and Human Services, p. 328

National Library of Medicine (2003) ChemIDplus (http://chem2.sis.nlm.nih.gov/chemidplus/chemidlite.jsp, accessed 11.10.2003)

National Toxicology Program (2002) *Toxicology and Carcinogenesis Studies of Vanadium Pentoxide (CAS No. 1314-62-1) in F3344/N rats and B6C3F1 mice (Inhalation Studies)* (Technical Report series No. 507; NIH Publication No. 03-4441) Research Triangle Park, NC

Nechay, B.R. (1984) Mechanisms of action of vanadium. *Am. Rev. Pharmacol. Toxicol.*, **24**, 501–524

Nielsen, F.H. (1987) Vanadium. In: Mertz, W., ed., *Trace Elements in Human and Animal Nutrition*, 5th Ed., Vol. 1, San Diego, Academic Press, pp. 275–300

Nielsen, F.H. (1991) Nutritional requirements for boron, silicon, vanadium, nickel, and arsenic: Current knowledge and speculation. *FASEB J.*, **5**, 2661–2667

Nriagu, J.O. (1998) History, occurrence, and uses of vanadium. In: Nriagu, J.O., ed., *Vanadium in the Environment. Part 1: Chemistry and Biochemistry*, John Wiley & Sons, Inc., pp. 1–24

Nriagu, J.O. & Pirrone, N. (1998) Emission of vanadium into the atmosphere. In: Nriagu, J.O., ed., *Vanadium in the Environment. Part 1: Chemistry and Biochemistry*, John Wiley & Sons, Inc., pp. 25–36

Oberg, S.G., Parker, R.D.R. & Sharma, R.P. (1978) Distribution and elimination of an intratracheally administered vanadium compound in the rat. *Toxicology*, **11**, 315–323

O'Neil, M.J., ed. (2001) *The Merck Index*, 13th Ed., Whitehouse Station, NJ, Merck & Co., Inc., p. 1767

Parfett, C.L.J. & Pilon, R. (1995) Oxidative stress-regulated gene expression and promotion of morphological transformation induced in C3H/10T1/2 cells by ammonium metavanadate. *Food chem. Toxicol.*, **33** , 301–308

Pazhynich, V.M. (1966) Maximum permissible concentration of vanadium pentoxide in the atmosphere. *Hyg. Sanit*., **31**, 6–11

Pazhynich, V.M. (1967) [Experimental basis for the determination of maximum allowable concentrations of vanadium pentoxide in atmospheric air]. In: Rjazanov, V.A., ed. [*The Biological Effect and Hygienic Importance of Atmospheric Pollutants*], Moscow, Medicina Publishing House, pp. 201–217 (in Russian)

Perron, L. (1994) *Canadian Minerals Yearbook: Vanadium*, Natural Resources Canada

Perron, L. (2001) *Canadian Minerals Yearbook: Vanadium*, Natural Resources Canada

Pierce, L.M., Alessandrini, F., Godleski, J.J. & Paulauskis, J.D. (1996) Vanadium-induced chemokine mRNA expression and pulmonary inflammation. *Toxicol. appl. Pharmacol*., **138**, 1–11

Pistelli, R., Pupp, N., Forastiere, F., Agabiti, N., Corbo, G.M., Tidei, F. & Perucci, C.A. (1991) [Increase of non-specific bronchial responsiveness following occupational exposure to vanadium]. *Med. Lav.*, **82**, 270–275 (in Italian)

Plunkett, E.R. (1987) *Handbook of Industrial Toxicology*, 3rd Ed., New York, Chemical Publishing Co., pp. 563–564

Pyy, L., Hakala, E. & Lajunen, L.J. (1984) Screening for vanadium in urine and blood serum by electrothermal atomic absorption spectrometry and d.c. plasma atomic emission spectrometry. *Anal. chim. Acta*, **158**, 297–303

Ramírez, P., Eastmond, D.A., Laclette, J.P. & Ostrosky-Wegman, P. (1997) Disruption of microtubule assembly and spindle formation as a mechanism for the induction of aneuploid cells by sodium arsenite and vanadium pentoxide. *Mutat. Res*., **386**, 291–298

Reade Advanced Materials (1997) *Vanadium Oxide Powder*, Providence, RI (http://www.reade.com/Products/Oxides/vanadium_oxide.htm, accessed 19.09.2003)

Rehder, D. (1991) The bioinorganic chemistry of vanadium. *Angew. Chem. Int. Ed. Engl.*, **30**, 148–167

Ress, N.B., Chou, B.J., Renne, R.A., Dill, J.A., Miller, R.A., Roycroft, J.H., Hailey, J.R., Haseman, J.K. & Bucher, J.R. (2003) Carcinogenicity of inhaled vanadium pentoxide in F344/N rats and B6C3F$_1$ mice. *Toxicol. Sci*., **74**, 287–296

Rhoads, K. & Sanders, C.L. (1985) Lung clearance, translocation, and acute toxicity of arsenic, beryllium, cadmium, cobalt, lead, selenium, vanadium, and ytterbium oxides following deposition in rat lung. *Environ. Res.*, **36**, 359–378

Rice, A.B., Moomaw, C.R., Morgan, D.L. & Bonner, J.C. (1999) Specific inhibitors of platelet-derived growth factor or epidermal growth factor receptor tyrosine kinase reduce pulmonary fibrosis in rats. *Am. J. Phatol*., **155**, 213–221

Rivedal, E., Roseng, L.E. & Sanner, T. (1990) Vanadium compounds promote the induction of morphological transformation of hamster embryo cells with no effect on gap junctional cell communication. *Cell Biol. Toxicol*., **6**, 303–314

Rojas, E., Valverde, M., Sordo, M., Altamirano-Lozano, M. & Ostrosky-Wegman, P. (1996a) Single cell gel electrophoresis assay in the evaluation of metal carcinogenicity. In: Collery, P., Corbella, J., Domingo, J.L., Elienne, J.-C. & Llobet, J.M. eds, *Metal Ions in Biology and Medicine*, Vol. 4, Paris, John Libbey Eurotext, pp. 375–377

Rojas, E., Valverde, M., Herrera, L.A., Altamirano-Lozano, M. & Ostrosky-Wegman, P. (1996b) Genotoxicity of vanadium pentoxide evaluated by the single cell gel electrophoresis assay in human lymphocytes. *Mutat. Res*., **359**, 77–84

Roldán, R.E. & Altamirano, L.M.A. (1990) Chromosomal aberrations, sister-chromatid exchanges, cell-cycle kinetics and satellite associations in human lymphocyte cultures exposed to vanadium pentoxide. *Mutat. Res*., **245**, 61–65

Roldán-Reyes, E., Aguilar-Morales, C., Frías-Vásquez, S. & Altamirano-Lozano, M. (1997) Induction of sister chromatid exchanges in human lymphocytes by vanadium pentoxide in combination with caffeine. *Med. Sci. Res*., **25**, 501–504

Roshchin, A.V. (1967a) Toxicology of vanadium compounds used in modern industry. *Hyg. Sanit.*, **32**, 345–352

Roshchin, A.V. (1967b) Vanadium. In: Izraelson, Z.I., ed., *Toxicology of the Rare Metals (AEC-tr-6710)*, Jerusalem, Israel Program for Scientific Translations, Washington, DC, pp. 52–59

Roschin, A.V. (1968) [*Vanadium and its Compounds*], Moscow, Medicina Publishing House (in Russian)

Ryan, R. P., Terry, C. E., & Leffingwell, S. S., eds (1999) *Toxicology Desk Reference: The Toxic Exposure and Medical Monitoring Index,* Taylor and Francis, pp. 1211–1217

Sabbioni, E., Clerici, L. & Brazzelli, A. (1983) Different effects of vanadium ions on some DNA-metabolizing enzymes. *J. Toxicol. environ. Health*, **12**, 737–748

Sabbioni, E., Pozzi, G., Pintar, A., Casella, L. & Garattini, S. (1991) Cellular retention, cytotoxicity and morphological transformation by vanadium(IV) and vanadium(V) in BALB/3T3 cell lines. *Carcinogenesis*, **12**, 47–52

Sabbioni, E., Kucera, J., Pietra, R. & Vesterberg, O. (1996) A critical review on normal concentrations of vanadium in human blood, serum, and urine. *Sci. total Environ.*, **188**, 49–58

Sánchez, G.I., López, I.E., Acevedo, S., Bizarro, P., Pasos, F., Delgado, V., Rondán, A. & Fortoul, T.I. (2001) Cambios ultraestructurales en pulmón causados por la inhalación aguda de V_2O_5: Modelo en ratón. In: *Proceedings of the IV Congreso Mexicano de Toxicología, Mérida, Yucatán, México*

Sánchez, G.I., López, I., Mussali, P., Bizarro, N.P., Niño, G., Saldivar, L., Espejel, G., Avila, M., Morales, D., Colin, L., Delgado, V., Acevedo, S., González, A., Avila-Costa, M.R. & Fortoul, T.I. (2003) Vanadium concentrations in lung, liver, kidney, testes and brain, after the inhalation

of 0.02M of V_2O_5. An experimental model in mice. In: *Proceedings of the 42nd Annual Meeting of the Society of Toxicology, Lake City, Utah, USA*

Sato, K., Kusaka, Y., Akino, H., Kanamaru, H. & Okada, K. (2002) Direct effect of vanadium on citrate uptake by rat renal brush border membrane vesicles (BBMV). *Ind. Health*, **40**, 278–281

Schiff, L.J. & Graham, J.A. (1984) Cytotoxic effect of vanadium and oil-fired fly ash on hamster tracheal epithelium. *Environ. Res*., **34**, 390–402

Schroeder, H.A., Balassa, J.J. & Tipton, I.H. (1963) Abnormal trace metals in man — Vanadium. *J. chron. Dis.*, **16**, 1047–1071

Seiler, H.G. (1995) Analytical procedures for the determination of vanadium in biological materials. In: Sigel, H. & Sigel, A., eds, *Metal Ions in Biological Systems, Vol. 31, Vanadium and its Role in Life*, New York, Marcel Dekker, pp. 671–688

Seljankina, K.P. (1961) [Data for determining the maximum permisible content of vanadium in water basins.] *Gig. Sanit*., **26**, 6–12 (in Russian)

Sharma, R.P., Flora, S.J.S., Drown, D.B. & Oberg, S.G. (1987) Persistence of vanadium compounds in lungs after intratracheal instillation in rats. *Toxicol. ind. Health*, **3**, 321–329

Shi, X. & Dalal, N.S. (1992) Hydroxyl radical generation in the NADH/microsomal reduction of vanadate. *Free Rad. Res. Commun.*, **17**, 369–376

Shi, X., Sun, X. & Dalal, N.S. (1990) Reaction of vanadium(V) with thiols generates vanadium(IV) and thiyl radicals. *FEBS Lett*., **271**, 185–188

Shi, X., Flynn, D.C., Liu, K. & Dalal, N. (1997) Vanadium (IV) formation in the reduction of vanadate by glutathione reductase/NADPH and the role of molecular oxygen. *Ann. clin. Lab. Sci*., **27**, 422–427

Si, R. *et al.* (1982) Studies on the mutagenicity and teratogenicity of vanadium pentaoxide. Weisheng Zhuanye Cankao Ziliao. School of Public Health, Sichuan Medical College, **22**, 36 [cited in Sun, 1996]

Silbajoris, R., Ghio, A.J., Samet, J.M., Jaskot, R., Dreher, K.L. & Brighton, L.E. (2000) *In vivo* and *in vitro* correlation of pulmonary MAP kinase activation following metallic exposure. *Inhalat. Toxicol*., **12**, 453–468

Sit, K.H., Paramanantham, R., Bay, B.H., Wong, K.P., Thong, P. & Watt, F. (1996) Induction of vanadium accumulation and nuclear sequestration causing cell suicide in human Chang liver cells. *Experientia*, **52**, 778–785

Sjöberg, S.G. (1950) Vanadium pentoxide dust: A clinical and experimental investigation on its effect after inhalation. *Acta med. scand*., **138** (Suppl. 238), 1–188

Smith, M.M., White, M.A. & Ide, C. (1992) *The Biological Monitoring of Occupational Exposure to Vanadium in Boiler Cleaners*. Health and Safety Executive (Research Report IR/L/TM/92/1), Sudbury, Suffolk

Sokolov, S.M. (1981) Experimental data for establishing time differentiated maximum permissible concentrations of vanadium pentoxide in the atmosphere. *Gig. Sanit.*, 17–19

Stern, A., Yin, X., Tsang, S.-S., Davison, A. & Moon, J. (1993) Vanadium as modulator of cellular regulatory cascades and oncogene expression. *Biochem. Cell Biol.*, **71**, 103–112

STN International (2003) STN International Registry file (http://stnweb.cas.org/html/english/a_index.html, accessed 19.09.2003)

Strategic Minerals Corp. (2003) *Vanadium pentoxide (V_2O_5)*, Danbury, CT (http://www.stratcor.com/products/vanadium_pentoxide.html, accessed 19.09.2003)

Sun, M. *et al.* (1989) *Study on the Maximum Allowable Concentration of Vanadium in Surface Water*, *Report on the National Technical Committee of Environmental Health Standard* [reference cited in Sun, 1996]

Sun, M.-L. (1996) Toxicity of vanadium and its environmental health standard. *J. Health Toxicol.*, **10**, 25–31

Suva (2003) *Grenzwerte am Arbeitsplatz 2003*, Luzern [Swiss OELs]

Thompson, K.H. & McNeill, J.H. (1993) Effect of vanadyl sulfate feeding on susceptibility to peroxidative change in diabetic rats. *Res. Comm. chem. Pathol. Pharmacol.*, **80**, 187–200

Thompson, K.H., Battell, M. & McNeill, J.H. (1998) Toxicology of vanadium in mammals. In: Nriagu, J.O., ed., *Vanadium in the Environment. Part Two: Health Effects*, New York, John Wiley & Sons, pp. 21–37

Todaro, A., Bronzato, R., Buratti, M. & Colombi, A. (1991) [Acute exposure to vanadium-containing dusts: Health effects and biological monitoring in a group of boiler maintenance workers.] *Med. Lav.*, **82**, 142–147 (in Italian)

Toya, T., Fukuda, K., Takaya, M. & Arito, H. (2001) Lung lesions induced by intratracheal instillation of vanadium pentoxide powder in rats. *Ind. Health*, **39**, 8–15

TRI (1987–2001) *Toxic Release Inventory Database*, Bethesda, MD, National Library of Medicine (http://www.epa.gov/triexplorer/chemical.htm, accessed 19.09.2003)

Tsukamoto, Y., Saka, S., Kumano, K., Iwanami, S., Ishida, O. & Marumo, F. (1990) Abnormal accumulation of vanadium in patients on chronic hemodialysis therapy. *Nephron*, **56**, 368–373

Työsuojelusäädöksiä (2002) *HTP arvot 2002*, Sosiali-ja terveysministeriö [Finnish OELs]

Usutani S., Nishiama, K., Sato, I., Matsura, K., Sawada, Y., Hosokawa, Y. & Izumi, S. (1979) [An investigation of the environment in a certain vanadium refinery]. *Jpn. J. ind. Health*, **21**, 11–20 (in Japanese)

Van Vleet, J.F., Boon, G.D. & Ferrans, V.J. (1981) Induction of lesions of selenium-vitamin E deficiency in weanling swine fed silver, cobalt, tellurium, zinc, cadmium, and vanadium. *Am. J. vet. Res*., **42**, 789–799

Venugopal, B. & Luckey, T.D. (1978) *Chemical Toxicity of Metals and Metalloids*, Vol. 2, *Metal Toxicity in Mammals*, New York, Plenum Press

Versieck, J. & Cornelis, R. (1980) Normal levels of trace elements in human blood plasma or serum. *Anal. chim. Acta*, **116**, 217–254

Versieck, J., Vanballenberghe, L., de Kesel, A., Hoste, J., Wallaeys, B., Vandenhaute, J., Baeck, N., Steyaert, H., Byrne, A.R. & Sunderman, F.W., Jr (1988) Certification of a second-generation biological reference material (freeze-dried human serum) for trace element determinations. *Anal. Chim. Acta*, **204**, 63–75

Wang, Y.-Z. & Bonner, J.C. (2000) Mechanism of extracellular signal-regulated kinase (ERK)-1 and ERK-2 activation by vanadium pentoxide in rat pulmonary myofibroblasts. *Am. J. resp. Cell mol. Biol*., **22**, 590–596

Waters, M.D. (1977) Toxicology of vanadium. In: Goyer R.A. & Melhman M.A., eds, *Advances in Modern Toxicology*, Vol. 2, *Toxicology of Trace Elements*, New York, Halsted Press, pp. 147–189

Waters, M.D., Gardner, D.E. & Coffin, D.L. (1974) Cytotoxic effects of vanadium on rabbit alveolar macrophages in vitro. *Toxicol. appl. Pharmacol.*, **28**, 253–263

White, M.A., Reeves, G.D., Moore, S., Chandler, H.A. & Holden, H.J. (1987) Sensitive determination of urinary vanadium as a measure of occupational exposure during cleaning of oil fired boilers. *Ann. occup. Hyg.*, **31**, 339–343

WHO (1988) *Vanadium* (Environmental Health Criteria 81), Geneva, International Programme on Chemical Safety

WHO (2000) *Air Quality Guidelines for Europe* (European Series No. 91), 2nd Ed., Copenhagen, Regional Office for Europe

WHO (2001) *Vanadium Pentoxide and Other Inorganic Vanadium Compounds (Concise International Chemical Assessment Document 29)*, Geneva, International Programme on Chemical Safety

Wide, M. (1984) Effect of short-term exposure to five industrial metals on the embryonic and fetal development of the mouse. *Environ. Res*., **33**, 47–53

Williams, N. (1952) Vanadium poisoning from cleaning oil-fired boilers. *Br. J. ind. Med*., **9**, 50–55

Woodin, M.A., Hauser, R., Liu, Y., Smith, T.J., Siegel, P.D., Lewis, D.M., Tollerud, D.J. & Christiani, D.C. (1998) Molecular markers of acute upper airway inflammation in workers exposed to fuel-oil ash. *Am. J. respir. crit. Care Med.*, **158**, 182–187

Woodin, M.A., Liu, Y., Hauser, R., Smith, T.J. & Christiani, D.C. (1999) Pulmonary function in workers exposed to low levels of fuel-oil ash. *J. occup. environ. Med*., **41**, 973–980

Woodin, M.A., Liu, Y., Neuberg, D., Hauser, R., Smith, T.J. & Christiani, D.C. (2000) Acute respiratory symptoms in workers exposed to vanadium-rich fuel-oil ash. *Am. J. Ind. Med.*, **37**, 353–363

Woolery, M. (1997) Vanadium compounds. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 24, New York, John Wiley & Sons, pp. 797–811

Wrbitzky, R., Göen, T., Letzel, S., Frank, F. & Angerer, J. (1995) Internal exposure of waste incineration workers to organic and inorganic substances. *Intern. Arch. occup. environ. Health*, **68**, 13–21

Wyers, H. (1946) Some toxic effects of vanadium pentoxide. *Br. J. ind. Med*., **3**, 177–182

Yamaguchi, M., Oishi, H. & Suketa, Y. (1989) Effect of vanadium on bone metabolism in weanling rats: Zinc prevents the toxic effect of vanadium. *Res. exp. Med*., **198**, 47–53

Yuen, V.G., Orvig, C., Thompson, K.H. & McNeill, J.H. (1993) Improvement in cardiac dysfunction in streptozotocin-induced diabetic rats following chronic oral administration of bis(maltolato)oxovanadium(IV). *Can. J. Physiol. Pharmacol.*, **71**, 270–276

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T. & Mortelmans, K. (1992) Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ. mol. Mutagen.*, **19** (Suppl. 21), 2–141

Zen, X. *et al.* (1988) Study on the mutagenicity of vanadium Pentaoxide, *Report on the National Symposium of Trace Element and Health* [cited in Sun, 1996]

Zenz, C., ed. (1994) *Occupational Medicine*, 3rd Ed., St Louis, MO, Mosby, pp. 584–594

Zenz, C. & Berg, B.A. (1967) Human responses to controlled vanadium pentoxide exposure. *Arch. Environ. Health*, **14**, 709–712

Zenz, C., Bartlett, J.P. & Thiede, W. (1962) Acute vanadium pentoxide intoxication. *Arch. environ. Health*, **5**, 542–546

Zhang, T., Yang, Z., Li, S. & Go, X. (1991a) [Transplacental passage of vanadium after treatment with vanadium pentoxide in Wistar rat]. *Hua Xi Yi Ke Da Xue Xue Bao*, **22**, 296–299 (in Chinese)

Zhang, T., Gou, X. & Yang, Z. (1991b) [A study on developmental toxicity of vanadium pentoxide in NIH mice]. *Hua Xi Yi Ke Da Xue Xue Bao*, **22**, 192–195 (in Chinese)

Zhang, T., Yang, Z., Zeng, C. & Gou, X. (1993a) [A study on developmental toxicity of vanadium pentoxide in Wistar rats]. *Hua Xi Yi Ke Da Xue Xue Bao*, **24**, 92–96 (in Chinese)

Zhang, T., Gou, X. & Yang, Z. (1993b) [Study of teratogenicity and sensitive period of vanadium pentoxide in Wistar rats]. *Hua Xi Yi Ke Da Xue Xue Bao*, **24**, 202–205 (in Chinese)

Zhang, L., Rice, A.B., Adler, K., Sannes, P., Martin, L., Gladwell, L., Koo, J.-S., Gray, T.E. & Bonner, J.C. (2001a) Vanadium stimulates human bronchial epithelial cells to produce heparin-binding epidermal growth factor-like growth factor: A mitogen for lung fibroblasts. *Am. J. respir. Cell mol. Biol*., **24**, 123–131

Zhang, Z., Wang, Y., Vikis, H.G., Johnson, L., Liu, G., Li, J., Anderson, M.W., Sills, R.C., Hong, H.L., Devereux, T.R., Jacks, T., Guan, K.-L. & You, M. (2001b) Wildtype *Kras2* can inhibit lung carcinogenesis in mice. *Nature Genetics*, **29**, 25–33

Zhong, B.-Z., Gu, Z.-W., Wallace, W.E., Whong, W.-Z. & Ong, T. (1994) Genotoxicity of vanadium pentoxide in Chinese hamster V79 cells. *Mutat. Res*., **321**, 35–42

van Zinderen Bakker, X. & Jaworski, J.F. (1980) *Effects of Vanadium in the Canadian Environment*, Ottawa, National Research Council Canada, Associate Committee Scientific Criteria for Environmental Quality, pp. 1–94

Zoller, W.H., Gordon, G.E., Gladney, E.S. & Jones, A.G. (1973) The sources and distribution of vanadium in the atmosphere. In: Kothy, E.L., ed., *Trace Elements in the Environment: Symposium* (Advances in Chemistry Series No. 123), Washington DC, American Chemical Society, pp. 31–47

Zoller, W.H., Gladney, E.S. & Duce, R.A. (1974) Atmospheric concentrations and sources of trace metals at the South Pole. *Science*, **183**, 198–200

Zychlinski, L. & Byczkowski, J.Z. (1990) Inhibitory effects of vanadium pentoxide on respiration of rat liver mitochondria. *Arch. environ. Contam. Toxicol*., **19**, 138–142

Zychlinski, L., Byczkowski, J.Z. & Kulkarni, A.P. (1991) Toxic effects of long-term intratracheal administration of vanadium pentoxide in rats. *Arch. environ. Contam. Toxicol*., **20**, 295–298