Vanadium oxide (V2O5): Human health tier II assessment

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CAS Number: 1314-62-1

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

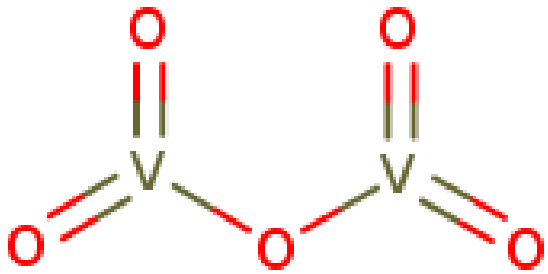
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	vanadium pentoxide divanadium pentaoxide vanadic acid anhydride C.I. 77938 dioxovanadiooxy(dioxo) vanadium
Structural Formula	
Molecular Formula	O5V2
Molecular Weight (g/mol)	181.88
Appearance and Odour (where available)	Odourless, yellow to rust-brown orthorhombic crystals
SMILES	O([V](=O)=O)[V](=O)=O

Import, Manufacture and Use

Australian

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was <100 tonnes. No use information has been identified.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments (The World Health Organisation's (WHO) Concise International Chemical Assessment Document (CICAD) 29, 2001; National Toxicology Program (NTP) Technical Report 507, 2002; International Agency for Research on Cancer (IARC) monograph 86, 2006; Environment Canada (EC) Screening Assessment for the Challenge Vanadium Oxide, 2010; Agency for Toxic Substances and Disease Registry (ATSDR), Toxicological Profile for Vanadium, 2012).

The chemical has reported commercial uses as:

- a component of developing agents in photography;
- a mordant (dye-binding agent) in textile dyeing; and
- an anti-corrosion agent.

The chemical has reported site-limited uses, including:

- as a catalyst in reactions producing other chemicals;
- in production of steels and alloys;
- in manufacturing yellow glass to inhibit ultraviolet light transmission;
- in production of superconductive magnets; and
- in producing ceramic pigments.

Restrictions

Australian

The chemical is listed in the Victorian Occupational Health and Safety Regulations—Schedule 9: Materials at Major Hazard Facilities (And Their Threshold Quantity) Table 2. A threshold quantity of 200 tonnes for 'Materials that meet the criteria for Toxic in Table 3 except, in relation to mines, sodium cyanide' applies (Galleria Chemica).

The chemical is a food and water contaminant that was analysed as part of the Food Standards Australia New Zealand (FSANZ) 23rd Australian Total Diet Study. It was not detected in any analyses, therefore estimates of dietary exposure and risk characterisation to determine a maximum limit could not be conducted (FSANZ, 2011).

International

The chemical is listed on the following (European Commission Cosmetic Ingredients and Substances (CosIng) database; Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products; and
- Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles: Limits for finished articles (0.1 mg/kg vanadium from vanadium compounds).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xn; R20/22 (acute toxicity)
- Xi; R37 (irritation)
- T; R48/23 (repeat dose toxicity)
- R68 Mut. Cat 3 (mutagenicity)
- R63 Repr. Cat 3 (reproductive toxicity)

Exposure Standards

Australian

The chemical has an exposure standard of 0.05 mg/m^3 time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

- a TWA of 0.01–0.05 mg/m³ in different countries such as Bulgaria, Canada, China, Denmark, France, Germany, Greece, Hungary, Indonesia, Ireland, Japan, Malaysia, Netherlands, Poland, Singapore, South Africa, Spain, Switzerland, the United Kingdom (UK) and the United States of America (USA);
- a TWA of 0.1–0.5 mg/m³ in different countries such as Egypt, Estonia, Iceland, Mexico, Philippines, Sweden and Taiwan;
- a TWA of 1–4 mg/m³ in different countries such as Latvia and Russia; and
- short-term exposure limit (STEL) values of 0.03, 0.05, 0.15 and 0.20 mg/m³ in the Netherlands, Switzerland, Canada and Hungary, respectively.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed following exposure via the inhalation route, but poorly absorbed through the oral (measured as 2.6 % in the rat) and dermal routes. Distribution of the chemical following inhalation exposure is mainly to the bone, liver and kidneys; and to the kidneys, spleen, bone and testes following oral exposure. The chemical is excreted in the urine following absorption after inhalation exposure, and via faeces following oral exposure (WHO, 2001; NTP, 2002; IARC, 2006; EC, 2010; ATSDR, 2012).

In an in vitro bioaccessibility study, the dissolution of the chemical was tested in artificial human body fluids. The chemical was added at 100 mg/L to flasks containing artificial sweat (to mimic dermal exposure), Gamble's solution (to mimic deep interstitial lung fluid), artificial lysosomal fluid (to mimic the intracellular lung environment, including phagocytosis), artificial gastric fluid (to mimic digestion) or phosphate-buffered saline (to mimic the ionic strength of human serum). The solutions were agitated (100 rpm) in flasks that were maintained at 37 ± 2 °C for 24 hours, and samples taken for analysis at two and 24 hours. The chemical was completely dissolved after two hours in all types of artificial human body fluids, indicating that vanadium ions are bioaccessible (REACH).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the Hazardous Substances Information System (HSIS) (Safe Work Australia). The available data support this classification. Although there are some data indicating a higher hazard classification, these data cannot be verified for their accuracy.

Oral median lethal dose (LD50) values of 221–658 and 314–716 mg/kg bw were reported in female and male Sprague Dawley (SD) rats, respectively, in studies performed according to the Organization for Economic Cooperation and Development (OECD) Test Guideline (TG) 401. Reported signs of toxicity included lethargy, ataxia (loss of control of movement), dyspnoea (shortness of breath), lacrimation (tearing), diarrhoea and coma (REACH).

Lower oral LD50 values have been reported (64 mg/kg bw in male rabbits; 5, 23 and 64–117 mg/kg bw in mice; 10 and 86–137 mg/kg bw in rats—WHO, 2001; NTP, 2002; IARC, 2006; EC, 2010; ChemIDPlus; HSDB), but the original data can not be verified.

Dermal

The chemical has low acute dermal toxicity in rats.

The LD50 in male and female SD rats was reported to be >2500 mg/kg bw in a study performed according to OECD TG 402 (REACH). Although a much lower dermal LD50 value has been reported in rabbits (50 mg/kg bw—EC, 2010), the original data can not be verified.

Inhalation

The chemical is classified as hazardous with the risk phrase 'Harmful by inhalation' (Xn; R20) in the HSIS (Safe Work Australia). The available data support this classification.

Median lethal concentration (LC50) values of 2.21–4.29 and 4.40–16.1 mg/L/4-hours were reported in female and male SD rats, respectively, following exposure to the chemical as a dust (REACH).

Although lower LC50 values have been reported in rats and rabbits, the original data can not be verified: 0.103 mg/L/4-hours in rabbits, calculated from the reported 205 mg/m^3/2-hours; 0.018 mg/L/4-hours in albino rats, calculated from the reported 70 mg/m^3/1- hour; 0.189 mg/L/4-hours in rats, calculated from the reported 126 mg/m^3/6-hours (EC, 2010; HSDB).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in the HSIS (Safe Work Australia). The available animal data and human findings (see **Observation in humans)** support this classification.

In an inhalation study, male cynomolgus monkeys (*Macaca fascicularis*; n = 16) were exposed (whole body) to the chemical as a dust aerosol at 0.5 and 5.0 mg/m^3 for six hours, once at each concentration, one week apart. Lung function was assessed one day after each exposure and compared to the monkey's own baseline measurements prior to chemical exposure. Impaired lung function was observed in monkeys exposed at 5.0 mg/m^3, characterised by restricted and decreased air flow in central and peripheral airways, and a significant increase in inflammatory cells (polymorphonuclear (PMN) cells) in bronchoalveolar lavage (BAL) fluid (Knecht, et al., 1985; cited in ATSDR, 2012).

Single intratracheal instillations of the chemical at 0.042 or 0.420 mg/kg bw in female CD rats (n = 6–8/group) and at 1 mg/kg bw in male SD rats resulted in lung irritation characterised by increased neutrophils in the lungs, increased inflammatory cytokine mRNA expression in BAL macrophages or constricted airways. Animals were monitored for up to two weeks after administration; in females, increased neutrophils persisted for 48 hours before returning to control levels by day 5 and in males a marker of fibrosis (the appearance of peribronchiolar myofibroblasts) peaked by day 6 (WHO, 2001; NTP, 2002; IARC, 2006).

Skin Irritation

No animal data are available. Based on the results of an in vitro assay (which has been adopted into OECD TG 439 in July 2010), the chemical is not expected to be a skin irritant.

In an in vitro skin irritation study (according to OECD draft proposal for a new guideline, in vitro skin irritation: Reconstructed Human Epidermis (RhE) test method as at 11 December 2009, version 4), 15 mg of the chemical was applied to normal, human-derived epidermal keratinocytes that were grown in tissue culture as a model of the human epidermis. Cells were exposed for 15 ± 1 minutes and viability was assessed. The viability of treated cells was not significantly different compared to the negative control and it was concluded that the chemical was not irritating (REACH).

Eye Irritation

Based on the available animal data, the chemical is considered to be severely irritating to the eyes, warranting hazard classification (see **Recommendation** section).

In an eye irritation study (OECD TG 405), Himalayan rabbits (n = 3 males) were administered 100 mg of the chemical into the conjunctival sac and examined at one, 24, 48 and 72 hours after administration. The mean scores over 24, 48 and 72 hours for all animals were 2.5 for corneal opacity, 1.7 for iris lesions, 2.8 for conjunctival redness and 2 for chemosis. The study was discontinued on days five or six due to the character and severity of the lesions, as the effects were not reversible (REACH).

Observation in humans

Dermal irritation has not been observed in humans experimentally exposed to the chemical at concentrations up to 10 %. In skin patch testing in 100 volunteers administered the chemical in petrolatum at 1, 2 or 10 %, no skin irritation was observed (WHO, 2001; IARC, 2006). In workers exposed to the chemical (dose or concentration not available), skin rashes were observed in some, but the incidence of dermatitis was not increased (ATSDR, 2012). No further details were available.

Ocular irritation has been reported in humans exposed to dusts of the chemical in the workplace. Numerous reports have documented conjunctivitis and a burning sensation of the eyes in workers exposed to the chemical as dust or fumes (WHO, 2001; IARC, 2006; EC, 2010).

Irritation of the respiratory tract was a frequently reported effect of the chemical following occupational short-term inhalation exposure. In male workers (n = 18) exposed to the chemical dust at >0.5 mg/m^3 for up to two weeks acute respiratory symptoms (cough, sore and inflamed throat, wheezing,

nasopharyngitis) were observed, even after exposure had ceased. In volunteers (n = 9) exposed to the chemical dust at 0.1, 0.25 or 1 mg/m^3 for eight hours, signs of irritation included increased mucous production and coughing for three days at the low dose and dose-dependent upper respiratory tract irritation characterised by cough for 7–10 days at ≥0.25 mg/m^3; lung function was not affected at any dose compared with baseline measurements. In volunteers (n = 11) exposed to the chemical as a condensation aerosol at 0.08, 0.16 or 0.4 mg/m^3, irritant effects were reported in 0/11, 5/11 and 11/11 subjects, respectively, and consisted of an itchy and dry oropharyngeal region and tingling in the nose and pharynx (EC, 2010; HSDB).

Sensitisation

Skin Sensitisation

No data are available for the chemical. Based on the data available for another pentavalent vanadium compound, the chemical is not expected cause skin sensitisation.

In a guinea pig maximisation test (OECD TG 406), male Dunkin-Hartley guinea pigs (n = 5–20/group) were induced with sodium metavanadate at 0.01 % intracutaneously and at 1 % topically. Following topical challenge at 0.05 % for 24 hours, no reactions indicative of skin sensitisation were observed (REACH).

Repeated Dose Toxicity

Oral

The limited data available are insufficient to draw a conclusion on the repeated dose oral toxicity of the chemical.

Male albino rats (n = 5/group) were exposed to the chemical at 3 mg/kg bw/day for five days per week for the first week and at 4 mg/kg bw/day for five days per week for another two weeks. A lowest observed adverse effect level (LOAEL) of 3.7 mg/kg bw/day was reported, based on changes in L-ascorbic acid (vitamin C) biosynthesis, metabolism and use by the liver and kidneys (EC, 2010).

Groups of ICR mice (n = 10/sex/group) were exposed to the chemical by oral gavage at doses of 0 or 6 mg/kg bw, five days per week for 6 weeks. Immunotoxicity was observed in treated mice as indicated by activation of T and B cell immune responses, increased spleen weight but decreased spleen cellularity, increased peripheral leukocytes, decreased phagocytosis and increased mitogen responsiveness compared with control mice (WHO, 2001; NTP, 2002; EC, 2010).

Male Wistar rats (n = 10/group) were exposed to the chemical at 0, 1 or 100 mg/L in drinking water for six months (equivalent to 0, 0.25 and 25 mg/kg bw/day, respectively). An LOAEL of 0.25 mg/kg bw/day was reported based on decreased phagocytosis in peritoneal cells. Other signs of immunotoxicity included increased mitogen responsiveness and increased spleen weight in the high dose group (WHO, 2001; NTP, 2002; EC, 2010).

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure through inhalation' (T; R48/23) in the HSIS (Safe Work Australia). The available animal data and human findings (see **Observation in humans** below) support this classification.

In a repeated dose study, Fischer 344 (F344)/N rats (n = 10/sex/dose) were exposed (whole body) to the chemical as a particulate aerosol at 0, 1, 2, 4, 8 or 16 mg/m^3 for six hours per day, five days per week for three months. Deaths of 7/10 males and 3/10 females at 16 mg/m^3 were reported. Body weight gain was significantly reduced in male rats at ≥4 mg/m^3 and in female rats at 16 mg/m^3. Lung weights were significantly increased in rats exposed at ≥4 mg/m^3, with significantly increased incidences of lung epithelial hyperplasia at ≥2 mg/m^3. The incidences of inflammation or fibrosis in the lungs were significantly increased in male rats at ≥2 mg/m^3 and in female rats at ≥4 mg/m^3. Lung function was affected at ≥4 mg/m^3, characterised by restricted function (including reduced lung elasticity, reduced diffusion of carbon monoxide, reduced lung volume) at 4 and 8 mg/m^3 and obstructed function (including changes in breathing mechanics, expiratory resistance due to bronchoconstriction) at 16 mg/m^3. Concentration-dependent increases in inflammatory cells in the BAL fluid were reported in treated rats up to 8 mg/m^3 (NTP, 2002).

In another study, B6C3F1 mice (n = 10/sex/dose) were exposed (whole body) to the chemical as a particulate aerosol at 0, 1, 2, 4, 8 or 16 mg/m^3 for six hours per day, five days per week for three months. One male died at 16 mg/m^3. Body weight gain was significantly reduced in males at ≥8 mg/m^3 and in females at ≥4 mg/m^3. Lung weights were significantly increased at ≥4 mg/m^3, with significantly increased lung inflammation at ≥2 mg/m^3. Epithelial hyperplasia increased with increasing levels of exposure (NTP, 2002).

In a study designed to assess tissue burden, female F344/N rats (n = 40–60/group) were exposed (whole body) to the chemical as a particulate aerosol at 0, 1, 2 or 4 mg/m^3 for six hours per day, five days per week for up to 16 days. Groups were euthanised on different study days for different measurements. Lung weight was similarly and significantly increased in all exposed animals immediately after exposure on day 16 and remained significantly higher, compared with controls, one and four days (but not eight days) after the final exposure. Alveolar and bronchiolar epithelium hyperplasia was observed in 3/10 animals at 1 mg/m^3 (on day 13) and in nearly all animals at ≥2 mg/m^3 on day six and 13. Alveolar inflammation (characterised by macrophage infiltration) was observed in nearly all animals exposed for 6 and 13 days. Minimal to mild interstitial inflammation (characterised by mononuclear cells localised around blood vessels in small airways or alveolar ducts) was observed in some animals at 1 mg/m^3 (3/10 on day six and 8/10 on day 13) and in all animals at ≥2 mg/m^3 on days six and 13. Fibrosis was observed in 6/10 animals exposed to 4 mg/m^3 for 13 days and 1/4 animals exposed to 4 mg/m^3 for 10 and 16 days (NTP, 2002).

In another study designed to assess tissue burden, female B6C3F1 mice (n = 40–60/group) were exposed (whole body) to the chemical as a particulate aerosol at 0, 2, 4 or 8 mg/m^3 for six hours per day, five days per week for up to 16 days. Groups were euthanised on different study days for different measurements. Lung weight was similarly and significantly increased in all exposed animals immediately after exposure on day 16; it remained significantly higher, compared with controls, one and four days (but not eight days) after the final exposure. Mild to minimal alveolar and bronchiolar epithelium hyperplasia was observed in nearly all exposed animals and increased in severity with increasing concentration and duration of exposure. Minimal to mild interstitial inflammation (characterised by mononuclear cells localised around blood vessels in small airways or alveolar ducts) was observed in most animals exposed for 13 days. Histological examination on days 1, 2, 5, 10 or 16 showed lesions from day 5 onwards (NTP, 2002).

Observation in humans

Based on observational studies in humans, respiratory effects have been reported in workers exposed to the chemical long-term, supporting the classification for repeated dose inhalation toxicity.

In 24 male workers exposed to the chemical at 0.2–0.9 mg/m^3 for at least six months, increased incidences of eye/nose/throat irritation, coughing, sputum production, wheezing and green discolouration of the tongue (likely from accumulation of chemical dusts on the tongue or the formation of tetravalent or trivalent vanadium complexes) were reported compared with 45 age-matched controls. In 40 male workers exposed to the chemical at <0.05–1.53 mg/m^3 for variable durations, but examined over a 24-month study period, bronchial hyperreactivity was diagnosed in 12 workers who had normal lung function previously and it persisted for up to 23 months even when exposure ceased (EC, 2010).

Genotoxicity

The chemical is classified as hazardous—Category 3 mutagenic substance—with the risk phrase ‘Possible risk of irreversible effects’ (Xn; R68) in the HSIS (Safe Work Australia). The available data support this classification.

There were mixed results from in vitro genotoxicity studies using the chemical (IARC, 2006; EC, 2010; ATSDR, 2012; REACH). Most assays were conducted without metabolic activation (unless otherwise indicated):

- *Bacillus subtilis* strains H17 and M45 tested positive for mutagenicity when exposed to the chemical at 100 mg/mL;
- *Escherichia coli* strains WP2, WPuvrA and CM891 tested positive for mutagenicity when exposed to the chemical at 1200 µg/plate;
- *E. coli* strains WP2 and WP2hcr, and strains ND160 and MR102, tested negative for mutagenicity when exposed to the chemical at 0.5 M and 1200 µg/plate, respectively;
- *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA1535, TA1537 and TA1538 tested negative for mutagenicity when exposed to the chemical at 0.5 M, 200 µg/plate or 333 µg/plate, with or without metabolic activation;
- Chinese hamster lung (V79) fibroblast cells tested positive for micronucleus formation and numerical chromosomal aberrations when exposed to the chemical at 1 µg/mL, but negative for gene mutation and sister chromatid exchanges (SCE) when exposed to the chemical at 4 µg/mL;
- Syrian hamster embryo cells tested negative for chromosomal aberrations when exposed to the chemical at 10–25 µg/mL;
- mouse lymphoma L5178Y cells tested negative for gene mutation when exposed to the chemical at 1–32 µg/mL, with or without metabolic activation;
- human fibroblasts tested positive for DNA damage (comet assay) when exposed to the chemical at 0.5 µM;

- human lymphocytes and human lymphoblastoid cells (TK6) tested positive for increased micronuclei when exposed to the chemical at 6–50 µg/mL and 3–60 µg/mL, respectively, with or without metabolic activation;
- human lymphocytes tested positive for DNA damage (comet assay), numerical chromosomal aberrations, aneuploidy, inhibition of microtubule formation and satellite association when exposed to the chemical at 0.3 µM, 2 µg/mL, 0.001 µM, 0.1 µM and 4 µg/mL, respectively;
- human lymphocytes tested negative for SCE and structural chromosomal aberrations when exposed to the chemical at 47 M and 6 µg/mL, respectively; and
- human peripheral lymphocytes tested positive and human mucosal epithelial cells tested negative for DNA damage (comet assay) when exposed to the chemical at 0.06–0.47 mM.

There were mixed results from in vivo genotoxicity studies using the chemical. Positive results were seen in one germ cell test (dominant lethal assay in mice) (IARC, 2006; EC, 2010; REACH):

- DNA damage (comet assay) in testes, liver, kidney, lung, spleen and heart (but not bone marrow) of male CD-1 mice exposed to the chemical by one intraperitoneal (i.p.) injection at 5.75, 11.5 or 23 mg/kg bw;
- micronucleus formation in bone marrow cells of albino mice (615 and Kunming strains) exposed to the chemical by inhalation at 0.5, 2 or 8 mg/m^3 or by i.p injection at 0.2, 2 or 6 mg/kg bw/day for five days or by subcutaneous (s.c.) injection at 0.25, 1 or 4 mg/kg bw/day six days per week for five weeks;
- micronucleus formation in foetal liver, maternal bone marrow and maternal spleen when pregnant Kunming Albino mice were exposed to the chemical by i.p. injection at 0.2–5 mg/kg bw/day;
- negative results for SCE in bone marrow cells of male CD-1 mice exposed to the chemical at 5.75, 11.5 or 23 mg/kg bw by one i.p. injection;
- no micronucleus formation in bone marrow cells of albino mice (615 and Kunming strains) exposed to the chemical by oral gavage at 1, 3, 6 or 11 mg/kg bw/day for six weeks;
- no micronucleus formation in peripheral blood cells of male and female B6C3F1 mice exposed to the chemical by inhalation at 1, 2, 4, 8 or 16 mg/m^3 for six hours per day, five days per week for three months;
- negative results in a comet assay in BAL fluid and pulmonary cells of female B6C3F1 mice exposed to the chemical by inhalation at 0.25, 1, or 4 mg/m^3 for six hours per day for 16 days;
- no micronucleus formation in polychromatic erythrocytes of bone marrow from male SD rats exposed to the chemical once, at 30, 60 or 120 mg/kg bw by oral gavage; and
- positive results in a dominant lethal assay in male CD-1 mice exposed to the chemical by i.p. injection at 8.5 mg/kg bw every third day for 60 days; but negative results when exposed to the chemical by one s.c. injection at 4 mg/kg bw/day.

Carcinogenicity

Based on the available data, there is some evidence of a carcinogenic effect, warranting hazard classification (see **Recommendation** section).

The IARC has classified the chemical as ‘Possibly carcinogenic to humans’ (Group 2B), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity in animal testing. 'The lung tumour response in rats and mice following exposure to vanadium pentoxide was not concentration-related; there was a flat dose response' (IARC, 2006). This was attributed to similar total dose exposure in the 1 and 2 mg/m^3 groups for mice. The differences in response in mice compared with rats may be related to a 3–5 fold higher total dose in mice when corrected for body weight (NTP, 2002; IARC, 2006).

In a carcinogenicity study, B6C3F1 mice (n = 50/sex/group) were exposed (whole body) to the chemical as a particulate aerosol (mass median aerodynamic diameter (MMAD) = 1.2–1.3 µm) at 0, 1, 2 or 4 mg/m^3 for six hours per day, five days per week for two years. There was a decreased survival rate in male mice at the highest dose, and body weights were generally lower in all mice at the highest dose. Based on clinical observations, breathing was deemed abnormal in animals exposed at ≥2 mg/m^3. There were increased incidences of alveolar/bronchiolar carcinoma and adenoma in all exposed groups (22/50, 42/50, 43/50 and 43/50 in males and 1/50, 32/50, 35/50 and 32/50 in females at 0, 1, 2 and 4 mg/m^3, respectively). Non-neoplastic changes included significantly increased incidences of alveolar and bronchiolar epithelial hyperplasia in all exposed groups; significantly increased incidences of minimal to mild chronic inflammatory lesions and histiocytic cellular infiltrate in lungs of all exposed groups; significantly increased incidences of interstitial fibrosis in lungs of animals exposed at ≥2 mg/m^3; increased incidences of mild to minimal suppurative (pus forming) nasal inflammation in animals exposed at ≥2 mg/m^3; significantly increased incidences of olfactory epithelium atrophy in females exposed at 1 or 4 mg/m^3; and significantly increased incidences of bronchial lymph node hyperplasia in all exposed female groups, likely as secondary effects due to the lung inflammation and/or neoplasms (NTP, 2002).

In another 2-year study, F344/N rats (n = 50/sex/group) were exposed (whole body) to the chemical as a particulate aerosol (MMAD = 1.2–1.3 µm) at 0, 0.5, 1 or 2 mg/m^3 for six hours per day, five days per week for two years. There were increased incidences of alveolar/bronchiolar adenoma and

carcinoma in males (4/50, 10/49, 6/48 and 9/50 at 0.5, 1 and 2 mg/m^3, respectively). Non-neoplastic changes included significantly increased incidences of alveolar and bronchiolar epithelial hyperplasia in all exposed male groups and in female groups at ≥1 mg/m^3; significantly increased incidences of alveolar squamous metaplasia in animals exposed at 2 mg/m^3; significantly increased incidences of minimal to mild chronic inflammatory lesions and interstitial fibrosis in lungs of males exposed at ≥1 mg/m^3 and in females exposed at 2 mg/m^3; and significantly increased incidences of histiocytic cellular infiltrate in alveoli of all exposed groups (NTP, 2002).

Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 3 substance toxic to reproduction—with the risk phrase 'Possible risk of harm to the unborn child' (T; R63) in the HSIS (Safe Work Australia). The available data support this classification for developmental toxicity. Based on the reproductive toxicity effects observed in female rats (significantly increased oestrus cycle) and male mice (significantly reduced sperm motility), hazard classification is also warranted for reproductive toxicity (see **Recommendation** section).

Pregnant Wistar rats (n = 18–21) were exposed to the chemical by oral gavage at 0, 1, 3, 9 or 18 mg/kg bw/day on gestation day (GD) 6–15 and euthanised on GD 20. Maternal body weight gain was significantly reduced by 25–60 % in groups exposed at ≥9 mg/kg bw/day. Foetal body weight, body length and tail length were significantly reduced in pups from dams exposed to the chemical at 18 mg/kg bw/day. There were significantly increased skeletal abnormalities in pups from dams exposed at ≥9 mg/kg bw/day (WHO, 2001; IARC, 2006; EC, 2010).

In a three-month study, F344/N rats (n = 10/sex/dose) were exposed (whole body) to the chemical as a particulate aerosol at 0, 1, 2, 4, 8 or 16 mg/m^3 for six hours per day, five days per week. Oestrus cycle length was significantly increased in females at 8 mg/m^3 and the number of cycling rats (time spent in pro-oestrus, oestrus and metoestrus stages) was decreased in females exposed at 16 mg/m^3 (NTP, 2002).

In another three-month study, B6C3F1 mice (n = 10/sex/dose) were exposed (whole body) to the chemical as a particulate aerosol at 0, 1, 2, 4, 8 or 16 mg/m^3 for six hours per day, five days per week. Epididymal sperm motility was significantly reduced in males exposed to the chemical at ≥ 8 mg/m^3 (NTP, 2002).

Although i.p. injection is not a relevant route of exposure for humans, given the low oral bioavailability of the chemical, these studies have been considered appropriate for simulating chemical bioavailability by inhalation exposure (WHO, 2001) and are summarised below.

In pregnant mice and rats exposed to the chemical by i.p. injection at up to 8 mg/kg bw on different GD, both maternal and foetal toxicity have been reported. Maternal toxicity included decreased body weight and implantation rates. Foetal toxicity, in the absence of maternal toxicity, included death, reduced body weight, reduced crown-rump length, reduced or delayed bone ossification, limb shortening, visceral abnormalities and external malformations (NTP, 2002; IARC, 2006).

In male CD-1 mice (n = 15–20/group) exposed to the chemical by i.p. injection at 0 or 8.5 mg/kg bw/day every third day for up to 60 days before mating, treated animals had decreased body weight, sperm count and impaired sperm motility. In females mated with treated males, there were reduced pregnancy rates, increased resorptions per litter and decreased live births. Foetal body weight was also reduced (WHO, 2001; NTP, 2002; IARC, 2006; EC, 2010).

Other Health Effects

Neurotoxicity

In an observational study in 49 male workers exposed to the chemical (concentration not available) for a mean duration of 12.2 years (range 0.5–31 years), urinary and serum vanadium concentrations were significantly increased compared with 49 control workers from a steel plant with no exposure to the chemical or other known neurotoxins. In neurobehavioural tests, the exposed workers scored lower for visuospatial ability and attention compared with the control workers, and scores correlated with urinary and serum vanadium concentrations (EC, 2010).

Scores in four other neurobehavioural tests (including reaction time and short-term memory) were not affected by vanadium exposure between the workers (EC, 2010).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include the systemic long-term effects of mutagenicity, carcinogenicity, reproductive and developmental toxicity, and toxic effects following repeated inhalation exposure.

The chemical is a severe eye irritant and a respiratory irritant. It can also cause harmful systemic effects following a single exposure through the oral and inhalation routes.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41) Irritating to respiratory system (Xi; R37)*	Causes serious eye damage - Cat. 1 (H318) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)*	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62) Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)*	Suspected of damaging fertility or the unborn child - Cat. 2 (H361fd)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from oral, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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