Workplace Exposure Standard (WES) review

VANADIUM (AS V_2O_5)
(CAS NO: 1314-62-1)

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New Zealand Government

WORKSAFE
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CONTENTS

appendices

tables

1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for vanadium should be changed.

The WES review considers the potential for exposures to vanadium in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for vanadium, which is currently set at a **WES-TWA** of 0.05**mg/m³**, as V_2O_5 for respirable dust and fume, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: Vanadium: V.

Synonyms, Vanadium pentoxide: Divanadium pentoxide; Vanadic acid anhydride; **C.I.** 77938; Vanadium (V) oxide; Dioxovanadiooxy(dioxo)vanadium; V_2O_5; VP.

2.0 Chemical and physical properties

Vanadium is a light-grey or white, soft, ductile metal at room temperature with no odour (**NLM** PubChem, 2019a; **ATSDR**, 2012).

Vanadium pentoxide is a yellow to rust-brown crystalline solid at room temperature with no odour (NLM PubChem, 2019b; **ACGIH**®, 2009).

Vanadium can exist in the environment in one of several oxidation states, -2 to +5, but generally vanadium **V**$^{3+}$ [III] and vanadyl V4+ [IV] predominate in body tissues and vanadate, V^{5+} [V] in plasma (**DFG**, 2009). The different oxidation states allow vanadium to form a large range of different substances.

Chemical and physical properties vanadium and vanadium pentoxide include:

	VANADIUM	**VANADIUM PENTOXIDE**
CAS No.:	7440-62-2	1314-62-1
Molecular weight	50.94**g/mol**	181.88g/mol
Formula	V	V_2O_5
Specific gravity	6.11 at 18.7°C	3.357 at 18.7°C
Melting point	1,910°C	690°C
Boiling point	3,407°C	1,750°C [decomposes]
Vapour pressure	2.34 x 10^{-2}**mmHg** at 1,916°C [extrapolated]	Approximately 0mmHg at 20°C
Solubility	Soluble in nitric, hydrofluoric, and concentrated sulphuric acids; attacked by alkali forming water soluble vanadates	Soluble in concentrated acids, alkalis; insoluble in alcohol; in water, 0.8g/100mL
Conversion factors		1**mg/m**^{3} = 0.134**ppm** 1ppm = 7.44mg/m^3 [Calculated]

NLM PubChem, 2019a; ATSDR, 2012; ACGIH®, 2009

TABLE 1: Physicochemical properties of vanadium and vanadium pentoxide

Health-related hazard classifications for vanadium (V) pentoxide, vanadium (IV) oxide acetylacetonate and vanadium (III) chloride:

	HSNO CLASSIFICATION		
Substance	**Vanadium (III) chloride**	**Vanadium (IV) oxide acetylacetonate**	**Vanadium (V) pentoxide**
CAS No.:	7718-98-1	3153-26-2	1314-62-1
Classification	6.1D (All); 6.1D (O); 6.3A; 6.4A	6.4A	6.1D (All); 6.1D (O); 6.1D (I); 6.6B; 6.8B; 6.9A (All); 6.9A (I)

TABLE 2:
HSNO hazard classifications of vanadium (V) pentoxide, vanadium (IV) oxide acetylacetonate and vanadium (III) chloride (**EPA**, 2019a, 2019b, 2019c)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.

[O] Oral exposure route.

[D] Derman exposure route.

[I] Inhalation exposure route.

3.0
Uses

Vanadium is an important carbide stabiliser and used, most often as ferrovanadium, in producing rust-resistant, spring, and high-speed tool steels (ATSDR, 2012).

Vanadium foil is used as a bonding agent in cladding titanium to steel (ATSDR, 2012).

Vanadium pentoxide is the principal starting material for the production of vanadium compounds, and used as a chemical intermediate in the production of vanadium and steel alloys; a catalyst in the oxidation of sulphide to sulphate and alcohol to acetaldehyde; in catalytic converters; for the manufacture of yellow glass that inhibits transmission of ultraviolet light; in photographic developing solutions; in the production of aniline black dye; to dye ceramics; and, as a mordant in colouring textiles (**NTP**, 2002).

Vanadium is predominantly recovered from ores through a series of acid-leaching processes or a roast-quench-leach process that produces red cake which is 85% to 90% pure vanadium pentoxide (NTP, 2002).

Vanadium has been used in human nutritional supplements and multivitamins (ATSDR, 2012).

Occupational exposure to vanadium can occur during production, storage, transportation and end-use. Fossil fuels such as oil and coal can contain vanadium and consequently combustion by-products, as solid residues, soot and fly ash can contain vanadium pentoxide (Environment Canada, 2010), which become potential sources of occupational exposure particularly during equipment cleaning or maintenance. Occupational exposure to vanadium pentoxide can also occur during the re-cycling of spent catalysts (Environment Canada, 2010) and catalytic converters (NTP, 2002).

Workers can be exposed to vanadium, vanadium pentoxide and other vanadium compounds mainly via inhalation (**SCOEL**, 2004).

The number of workers exposed or potentially exposed to vanadium, vanadium pentoxide and other vanadium compounds in New Zealand workplaces is unknown.

Statistics New Zealand 2019 data indicate that 5,205 New Zealand workers were working in the areas of:

- iron ore mining
- other metal ore mining
- petroleum refining and petroleum and coal product manufacturing
- glass and glass product manufacturing
- other ceramic product manufacturing
- basic ferrous metal manufacturing
- basic ferrous metal product manufacturing (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The DFG review of vanadium and its inorganic compounds summarised the toxicity in humans after single exposures:

> "As regards short-term exposure, no exposure levels were specified in four single-case reports. In two workers who had been shovelling ammonium vanadate powder for two to three or six hours, and in two others who had been working in refineries for several hours, coughing with and without production of mucus, dyspnoea, whistling rales, swollen nasal mucosa, sore throat and hoarse voice as well as nausea occurred after several hours up to three days. A green discolouration of the tongue occurred in all four exposed persons and, in addition, on the skin of the fingers, the upper thigh and the scrotum in one worker. Two of the exposed persons complained of eye irritation. The irritation in the respiratory tract lasted from several days to weeks, recurring when exposure was repeated (**HSE** 2003).
>
> "After exposure to vanadium pentoxide fume and dust (particle size: 98% <5**µm**; exposure duration not specified) a concentration-effect relationship could be derived in eleven volunteers: whereas the inhalation of 0.4mg vanadium pentoxide fume/m^3 (0.22mg vanadium/m^3) resulted in pronounced irritation in all participants, only five persons reacted with moderate irritation at 0.16mg/m^3 (0.08mg vanadium/m^3), and 0.08mg/m^3 (0.04mg vanadium/m^3) were no longer perceived (SCOEL 2003). Inhalation of 1mg vanadium pentoxide dust/m^3 (particle size: 98% <5µm; 0.56mg vanadium/m^3) for eight hours resulted in sporadic coughing after five hours, which increased after seven hours. At 0.25mg/m^3 (0.14mg vanadium/m^3), moderate coughing occurred the following morning and, at 0.1mg/m^3 (0.056mg vanadium/m^3), the participants had an increased production of mucus, which was easily cleared by slight coughing. No subjective signs of irritation were reported either during the exposure or immediately thereafter (HSE 2003)." (References cited in DFG, 2009).

The New Zealand EPA classifies vanadium (III) chloride and vanadium (V) pentoxide as 6.1D substances – substances that are acutely toxic (EPA, 2019).

The **NICNAS** review of vanadium oxide summarised the irritation/corrosion potential in exposed 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 >0.5mg/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 1mg/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 0.25mg/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 0.4mg/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**)." (Reference cited in NICNAS, 2016).

The New Zealand EPA classifies vanadium (III) chloride as a 6.3B substance – a substance that is mildly irritating to the skin (EPA, 2019)

The New Zealand EPA classifies vanadium (III) chloride and vanadium (IV) oxide acetylacetonate as 6.4A substances – substances that are irritating to the eye (EPA, 2019).

The DFG review of vanadium and its inorganic compounds summarised the sensitisation potential in exposed humans:

Skin sensitisation

"One of 190 workers of five ceramics factories potentially exposed to vanadium pentoxide reacted to 10% vanadium pentoxide in petrolatum (the clinical relevance of the reaction was not specified). As controls, preparations containing 1%, 2% and 10% vanadium pentoxide in petrolatum were examined in 100 consecutively tested patients as well as in 92 healthy volunteers; no reaction was produced in any of these cases (Motolese *et al*. 1993). In a later publication, a reaction was reported in one of 50 workers, who were examined from a total collective of 250 (Gaddoni *et al*. 1993). It is not clear, however, whether a case of double reporting is involved or not.

"In another study, eczematous skin changes were reported in nine of 36 workers exposed to vanadium pentoxide dust. One of the nine persons tested reacted to a 2% sodium vanadate solution in the patch test, two other reactions were questionably positive (Sjöberg 1950).

"After epicutaneous testing of 520 patients with mucosal changes possibly caused by dental prostheses, 17 reactions to 1% "vanadium chloride" were observed. Clinical relevance was reported for 13 of these reactions, though more details are lacking (Vilaplana and Romaguera 2000). Seven out of 66 patients with a hip prosthesis reacted to 2% or 5% vanadium trichloride in petrolatum (no further details) in the epicutaneous test. An irritative reaction to 5% vanadium trichloride in petrolatum was observed in 17 other patients (Cancilleri *et al*. 1992; Lodi *et al*. 1995).

"One 54-year-old female patient suffering from nickel sensitization, generalized dermatitis and a suspected intolerance to an osteosynthesis screw consisting of a cobalt/chromium/molybdenum alloy had not reacted after 48 hours of epicutaneous testing; however, reaction then set in after 72 hours with a strong reaction (+++) to 2.5% nickel sulfate and a marked reaction (++) to 0.5% potassium dichromate, 1% cobalt chloride, 1% ammonium molybdate, and 0.5% vanadium oxide (no other details) (Oleffe and Wilmet 1980).

"Reactions to 0.5% sodium metavanadate in 5 of 125 workers with cement eczema (Geiser 1968) as well as reactions to 0.1% ammonium metavanadate were reported in one out of 50 patients with joint prostheses in other investigations – though without any greater detail (Elves *et al*. 1975).

"None of 17 workers exposed to dust containing vanadium while cleaning boilers in an oil power plant reacted after 48 hours to 2% sodium vanadate in water in the epicutaneous test (Lees 1980).

"A contact sensitizing effect of vanadium compounds cannot be demonstrated from these findings."

Respiratory sensitisation

"About every 4 months, a 38-year-old worker cleaned reaction chambers in which maleic anhydride was produced via the catalysis of vanadyl pyrophosphate, after which he filled the reaction chambers with fresh catalyst. The work involved lasted about 3 weeks each time. The employee had symptoms of irritation in the upper respiratory tract (sore throat, nasal congestion, epistaxis) and asthenia already during the first filling operations. These were followed the next day by chest tightness, dyspnoea on exertion, productive cough, and wheezing. The symptoms resolved during two weeks off work, but recurred each time when he was undertaking this activity in the plant. Specific **IgE** antibodies against maleic anhydride were not detected, prick tests with common inhalant allergens were also negative, and there was no increase in non-specific airway reactivity ($\mathbf{PC_{20(histamine)}}$: 20.5mg/ml). A bronchial provocation test, in which the patient refilled the catalyst containing vanadium (30g diluted 1:10 in lactose powder) was performed. The exposure duration was gradually increased (5, 10, 15, 30 and 60 minutes). There was a clear decline in forced vital capacity (**FVC**) and forced expiratory volume in one second ($\mathbf{FEV_1}$) by 27% or 35% 4 hours post-challenge. The values became normal after administration of salbutamol, but were markedly reduced again after 24 hours (–29% and –31%) and after 48 hours (–23% and –20%). Five hours after challenge, the body temperature increased to 39.5°C, becoming normal again after 7 hours. Simultaneously, the leukocyte count increased from 9400/mm^3 to 15800/mm^3. There was no increase in non-specific airway reactivity ($PC_{20(histamine)}$: 16mg/ml) after 48 hours. The total cell count in the bronchioalveolar lavage was markedly increased (5900× 103/ml), including 60% neutrophils, 39% macrophages and 1% lymphocytes. The authors cited values of 13.6 (**inhalable fraction**) and 4.3mg/m^3 (respirable fraction) for the vanadium concentration determined in a simulated challenge test with personal sampling pumps (Vandenplas *et al*. 2002).

"In a plant employing 375 workers treating ores containing vanadium, 40 employees were subjected to closer examination for 24 months on account of persistent respiratory symptoms. In 12 of these 40, a non-specific hyperreactivity was found ($PC_{20(histamine)}$: <1mg/ml or positive findings in the exercise challenge test). In 7 of these, the first symptoms occurred within the first 6 months of employment. No challenge tests or other immunological investigations, particularly challenge tests with vanadium compounds, were performed (Irsigler *et al*. 1999).

"Two other studies involving workers exposed to vanadium compounds reported increased, non-specific hyperreactivity in the airways or an increase in symptoms similar to those of asthma (Irsigler *et al*. 1999); however, no immunological investigations were performed.

"Sensitization of the respiratory tract by vanadium compounds cannot be established from these findings." (References cited in DFG, 2009).

The ATSDR review of vanadium summarised the repeated dose toxicity in exposed humans:

> "Although a number of studies have reported respiratory effects in humans exposed to vanadium, in particular vanadium pentoxide, very few provide reliable quantitative exposure data. In an experimental study, persistent coughing lasting 8 days after exposure termination was observed in two subjects exposed to 0.6mg vanadium/m^3 for 8 hours; no alterations in lung function (lung function parameters assessed: forced vital capacity, 0.5 and 1 second forced expiratory volume, maximal expiratory flow, 200–1,200cc flow rate, maximal midexpiratory time, and forced inspiratory vital capacity) were observed (Zenz and Berg 1967). At 0.1mg vanadium/m^3, five subjects reported productive coughing without other subjective complaints, alterations in lung function, or changes in daily activities; this concentration level was considered a **NOAEL**. Workers exposed to a range of vanadium pentoxide dust levels for as little as 1 day (Levy *et al*. 1984; Musk and Tees 1982; Thomas and Stiebris 1956; Zenz *et al*. 1962) or as long as ≥6 years (Irsigler *et al*. 1999; Lewis 1959; **NIOSH** 1983; Sjöberg 1956; Vintinner *et al*. 1955; Wyers 1946), show mild respiratory distress, such as cough, wheezing, chest pain, runny nose, or sore throat. One study of chronically-exposed workers showed increased neutrophils in the nasal mucosa (Kiviluoto 1980; Kiviluoto *et al*. 1979b, 1981a). More severe pathology has not been reported. Symptoms are reversible within days or weeks after exposure ceases. Data were not located to assess the relationship of exposure level or duration to severity of response. Chest x-rays and pulmonary function tests were normal in most cases. Chronic effects were infrequently reported. In a study of 40 vanadium pentoxide workers with persistent respiratory symptoms (Irsigler *et al*. 1999), 12 were found to have bronchial hyperresponsiveness to inhaled histamine or exercise challenge. No significant alterations in baseline lung function were found. The mean urine vanadium level (assessed via spot urine samples) in the hyperresponsive group was 52.7µg/g creatinine compared to 30.7µg/g creatinine in 12 matched subjects with persistent respiratory symptoms and without bronchial hyperreactivity; statistical comparisons of the two groups were not made. Five to 23 months after removal from exposure, bronchial hyperreactivity was still present in nine of the subjects, although the response was less severe in five of them and more severe in one subject." (ATSDR, 2012).

The New Zealand EPA classifies vanadium (V) pentoxide as a 6.9A substance – a substance that is toxic to human target organs or systems (EPA, 2019).

Li *et al*. (2013) reported neurobehavioural alterations in 463 vanadium exposed workers compared to 251 controls using a WHO-recommended neurobehavioural core test battery (**NCTB**) and event-related auditory evoked potentials test (**P300**) (Li *et al*., 2013). The vanadium smoke time-weighted average concentration in the exposed group was 0.216mg/m^3 and 0.013mg/m^3 in the control group. The exposed workers exhibited an increased anger-hostility, depression-dejection and fatigue-inertia on the profile of mood states ($p<0.05$). Performances in the simple reaction time, digit span, Benton visual retention and pursuit aiming were also poorer among exposed workers as compared to unexposed control workers ($p<0.05$). Some of these poor performances in tests were also significantly related to workers' exposure duration. P300 latencies were longer in the exposed group than in the control ($p<0.05$). Longer mean reaction times and more counting errors were also found in the exposed workers ($p<0.05$). The authors noted that air levels of lead and manganese had not been measured in either workplace (Li *et al*., 2013).

The ATSDR review of vanadium summarised the reproductive/developmental toxicity in exposed humans, that no studies were located regarding the reproductive or developmental effects in humans after inhalation, oral or dermal exposure to vanadium (ATSDR, 2012).

The New Zealand EPA classifies vanadium (V) pentoxide as a 6.8B substance – a substance that is a suspected human reproductive or developmental toxicant (EPA, 2019).

The DFG review of vanadium and its inorganic compounds summarised the genotoxic potential in exposed humans:

> "The white blood cells in the peripheral blood of 49 male workers in vanadium production, who were found to have 5.38µg vanadium/l blood (range 2.18–46.35µg/l), were compared with those of 12 non-exposed control persons (no data on vanadium concentration). No increased incidence in **DNA** strand breaks (comet assay), oxidative DNA strand breaks (**8-OHdG**) or sister chromatid exchange were found (Ivancsits *et al*. 2002)." (Reference cited in DFG, 2009).

The ATSDR review of vanadium noted that an increase in micronuclei formation (x2.5) had been reported in the lymphocytes of workers exposed to vanadium pentoxide (Ehrlich *et al*., 2008 cited in ATSDR, 2012). Ehrlich *et al*. (2008) also reported increases in the oxidation of DNA bases; nucleoplasmic bridges (**NPB**s); nuclear buds; apoptosis; and, necrosis, with reduced DNA repair in lymphocytes from 52 vanadium exposed workers compared to 52 controls (Ehrlich *et al*., 2008). The vanadium levels in plasma were reported as 2.2 (1.54–3.89)µg/L in the exposed group; and, 0.3 (0.24–0.39)µg/L in the control group, even though the exposed workers were required to wear protective masks and gloves through the 8-hour shifts (Ehrlich *et al*., 2008).

The New Zealand EPA classifies vanadium (V) pentoxide as a 6.6B substance – a substance that is a suspected human mutagen (EPA, 2019).

Animals

The NICNAS review of vanadium oxide summarised the acute toxicity potential in experimental animals:

> **Inhalation**
>
> "Median lethal concentration (**LC50**) values of 2.21–4.29 and 4.40–16.1mg/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: 0.103mg/L/4-hours in rabbits, calculated from the reported 205mg/m^3/2-hours; 0.018mg/L/4-hours in albino rats, calculated from the reported 70mg/m^3/1-hour; 0.189mg/L/4-hours in rats, calculated from the reported 126mg/m^3/6-hours (EC, 2010; HSDB)."
>
> **Dermal**
>
> "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 (50mg/kg bw–EC, 2010), the original data can not be verified."

Oral

"Oral median lethal dose (LD50) values of 221–658 and 314–716mg/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 (64mg/kg bw in male rabbits; 5, 23 and 64–117mg/kg bw in mice; 10 and 86–137mg/kg bw in rats – WHO, 2001; NTP, 2002; IARC, 2006; EC, 2010; ChemIDPlus; HSDB), but the original data can not be verified." (References cited NICNAS, 2016).

The NICNAS review of vanadium oxide summarised the irritation/ corrosion potential in experimental animals:

Respiratory irritation

"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 5.0mg/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 5.0mg/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 0.420mg/kg bw in female CD rats (n = 6–8/group) and at 1mg/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."

Eye irritation

"In an eye irritation study (OECD TG 405), Himalayan rabbits (n = 3 males) were administered 100mg 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)." (References cited in NICNAS, 2016).

The NICNAS review of vanadium oxide summarised the sensitisation potential in experimental animals:

> "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)." (Reference cited in NICNAS, 2016).

The NICNAS review of vanadium oxide summarised the repeated dose toxicity in experimental animals:

> "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 16mg/m^3 for six hours per day, five days per week for three months. Deaths of 7/10 males and 3/10 females at 16mg/m^3 were reported. Body weight gain was significantly reduced in male rats at 4mg/m^3 and in female rats at 16mg/m^3. Lung weights were significantly increased in rats exposed at 4mg/m^3, with significantly increased incidences of lung epithelial hyperplasia at 2mg/m^3. The incidences of inflammation or fibrosis in the lungs were significantly increased in male rats at 2mg/m^3 and in female rats at 4mg/m^3. Lung function was affected at 4mg/m^3, characterised by restricted function (including reduced lung elasticity, reduced diffusion of carbon monoxide, reduced lung volume) at 4 and 8mg/m^3 and obstructed function (including changes in breathing mechanics, expiratory resistance due to bronchoconstriction) at 16mg/m^3. Concentration-dependent increases in inflammatory cells in the BAL fluid were reported in treated rats up to 8mg/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 16mg/m^3 for six hours per day, five days per week for three months. One male died at 16mg/m^3. Body weight gain was significantly reduced in males at 8mg/m^3 and in females at 4mg/m^3. Lung weights were significantly increased at 4mg/m^3, with significantly increased lung inflammation at 2mg/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 4mg/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 1mg/m^3 (on day 13) and in nearly all animals at 2mg/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 1mg/m^3 (3/10 on day six and 8/10 on day 13) and in all animals at 2mg/m^3 on days six and 13. Fibrosis was observed in 6/10 animals exposed to 4mg/m^3 for 13 days and 1/4 animals exposed to 4mg/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 8mg/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)." (References cited in NICNAS, 2016).

The ATSDR review of vanadium noted:

> "Severe lung inflammation and mucous cell metaplasia were observed in mice exposed to vanadium pentoxide via laryngeal aspiration (Rondini *et al*. 2010; Yu *et al*. 2011) and lung inflammation and interstitial fibrosis were observed in mice administered vanadium pentoxide via intranasal administration (Turpin *et al*. 2010). Bronchoalveolar lavage fluid from rats nose-only exposed to 2mg vanadium/m^3 as ammonium metavanadate 8 hours/day for 4 days contained higher levels of neutrophils, small macrophages, and protein levels and increased lactate dehydrogenase activity than air-exposed controls (Cohen *et al*. 1996); these alterations are suggestive of lung inflammation. Vanadium exposure also resulted in alterations in the ability of pulmonary alveolar macrophages to respond to immunoregulating cytokines.
>
> "The nasal effects observed in rats consisted of hyperplasia and squamous metaplasia of respiratory epithelium at 2.2mg vanadium/m^3 for 13 weeks, inflammation at 9.0mg vanadium/m^3 for 13 weeks, and goblet cell hyperplasia of the respiratory epithelium at 0.28mg vanadium/m^3 for 2 years. In mice exposed to vanadium pentoxide for 2 years, the nasal effects included suppurative inflammation at 1.1mg vanadium/m^3, olfactory epithelium atrophy at 0.56mg vanadium/m^3, hyaline degeneration of olfactory and respiratory epithelium at 0.56mg vanadium/m^3, and squamous metaplasia of respiratory epithelium at 0.56mg vanadium/m^3. Chronic exposure also resulted in damage to the larynx; degeneration and hyperplasia of the epiglottis epithelium were observed in rats exposed to 0.28mg vanadium/m^3 and squamous metaplasia of epiglottis epithelium was observed in rats exposed to 1.1mg vanadium/m^3 and mice exposed to 0.56mg vanadium/m^3." (References cited in ATSDR, 2012).

Ngwa *et al*. (2014) reported that intranasal instillation of 182µg of vanadium pentoxide 3 times per week for one month decreased olfactory bulb volume and the loss of dopaminergic neurotransmission to the olfactory bulb in C57BL/6 mice. The authors noted that in addition to inhalation being the main route for vanadium exposure, the olfactory nerves bypass the blood brain barrier allowing absorbed chemicals direct transport to the brain (Ngwa *et al*., 2014).

The Wilk *et al*. (2017) review of the toxicity of vanadium on gastrointestinal, urinary and reproductive systems highlighted the potential for hepato-, nephro- and reproductive toxicity in experimental species after oral or intraperitoneal administration (Wilk *et al*., 2017). Wilk *et al*. (2017) also noted that vanadium administered to experimental species can cross the blood-placenta barrier with a tendency to accumulate in the foetus causing adverse developmental effects including visceral abnormalities and skeletal defects (Wilk *et al*., 2017).

The NICNAS review of vanadium oxide summarised the reproductive/ developmental toxicity in experimental animals:

> "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 9mg/kg bw/day. Foetal body weight, body length and tail length were significantly reduced in pups from dams exposed to the chemical at 18mg/kg bw/day. There were significantly increased skeletal abnormalities in pups from dams exposed at 9mg/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 16mg/m^3 for six hours per day, five days per week. Oestrus cycle length was significantly increased in females at 8mg/m^3 and the number of cycling rats (time spent in pro-oestrus, oestrus and metoestrus stages) was decreased in females exposed at 16mg/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 16mg/m^3 for six hours per day, five days per week. Epididymal sperm motility was significantly reduced in males exposed to the chemical at 8mg/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 8mg/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 8.5mg/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)." (References cited in in NICNAS, 2016).

The Environment Canada review of vanadium oxide noted:

> "In a dominant lethal assay, the **LOAEL** for reproductive toxicity was 2.8mg/ kg-bw per day, the only dose tested, based on a decreased pregnancy rate (52%) in untreated females mated with male mice exposed intraperitoneally to vanadium pentoxide (Altamirano-Lozano *et al*. 1996). Other effects observed in treated males at this dose were a reduction in sperm motility with treatment for 20 days or longer, a marked reduction in sperm counts with the advancement of treatment and a significant increase in the percentage of morphological abnormalities in spermatozoa after 50–60 days of treatment. No parental LOAEL was reported. Although the dominant lethal assay provides limited information on reproductive toxicity, it is not a guideline reproductive toxicity study. No other reproductive studies were identified." (Reference cited in Environment Canada, 2010).

The NICNAS review of vanadium oxide summarised the genotoxic potential in experimental animals and *in vitro* test systems:

> "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)." (References cited in NICNAS, 2016).
>
> "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)." (References cited in NICNAS, 2016).

The DFG review of vanadium and its inorganic compounds noted:

> "The Commission has discussed the available studies thoroughly and concluded that vanadium compounds are to be considered genotoxic *in vitro* and *in vivo* (clastogenic and aneugenic). The underlying mechanisms of action show that enzyme inhibition is responsible for the aneugenic effect and the formation of radicals for the clastogenic effect. A dominant lethal effect has been demonstrated at high doses after intraperitoneal injection into mice und [sic] after oral administration to rats." (DFG, 2009).

4.2 Cancer

The International Agency for Research on Cancer [IARC] evaluation of vanadium pentoxide concluded that:

> 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.

With an overall evaluation that:

> Vanadium pentoxide is *possibly carcinogenic to humans (Group 2B)*. (IARC, 2006).

The US National Toxicology Program [NTP] Report on Carcinogens [**RoC**], Fourteenth Edition has no evaluation on the carcinogenic potential of vanadium pentoxide or other vanadium compounds (NTP RoC, 2019).

The NZ EPA has not classified vanadium (V) pentoxide, vanadium (IV) oxide acetylacetonate or vanadium (III) chloride as 6.7A or 6.7B substances – substances that are known or presumed, or suspected human carcinogens, respectively (EPA, 2019).

Humans

The ATSDR review of vanadium noted that they had found no studies on the carcinogenic potential in humans (Reference cited in ATSDR, 2012).

Animals

The NICNAS review of vanadium oxide summarised the carcinogenicity data in experimental animals:

> "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**) = 1.2–1.3µm) at 0, 1, 2 or 4mg/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 2mg/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 4mg/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 2mg/m^3; increased incidences of mild to minimal suppurative (pus forming) nasal inflammation in animals exposed at 2mg/m^3; significantly increased incidences of olfactory epithelium atrophy in females exposed at 1 or 4mg/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 = 1.2–1.3µm) at 0, 0.5, 1 or 2mg/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 2mg/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 1mg/m^3; significantly increased incidences of alveolar squamous metaplasia in animals exposed at 2mg/m^3; significantly increased incidences of minimal to mild chronic inflammatory lesions and interstitial fibrosis in lungs of males exposed at 1mg/m^3 and in females exposed at 2mg/m^3; and significantly increased incidences of histiocytic cellular infiltrate in alveoli of all exposed groups (NTP, 2002)." (References cited in NICNAS, 2016; NTP, 2002).

The Environment Canada review of vanadium oxide noted:

> "Although the increased incidence of lung tumours in both sexes of rats was not statistically significant, the incidence of carcinomas and combined adenomas and carcinomas in males exceeded historical control ranges at 0.5 and 2mg/m^3 (lung adenoma 4/50, 8/49, 5/48 and 6/50 at 0, 0.5, 1 or 2mg/m^3, respectively; lung carcinoma 0/50, 3/49, 1/48 and 3/50, respectively; lung adenoma/carcinoma combined 4/50, 10/49, 6/48 and 9/50, respectively), and the incidence of adenomas and combined adenomas and carcinomas in females was at the upper end of the range for historical controls at 0.5mg/m^3 (lung adenoma 0/49, 3/49, 1/50 and 0/50 at 0, 0.5, 1 or 2mg/m^3, respectively; lung carcinoma 0/50, 0/49, 0/50 and 1/50, respectively; lung adenoma/carcinoma combined 0/49, 3/49, 1/50 and 1/50, respectively) (NTP 2002; Ress *et al*. 2003). The NTP (2002) concluded that clear evidence of lung tumours was seen in mice in both sexes, while some evidence of carcinogenicity was seen in male rats and an equivocal response was

seen in female rats. The basis for the observed interspecies differences and differences between responses in male and female rats has not been articulated." (References cited in Environment Canada, 2010).

4.3 Absorption, distribution, metabolism and excretion

The Environment Canada review of vanadium oxide summarised the **ADME**:

"Toxicokinetic studies on vanadium pentoxide show that it is rapidly absorbed following inhalation, but poorly absorbed through the skin or following ingestion (in rats, approximately 3% of the ingested amount of vanadium pentoxide was absorbed from the gastrointestinal tract 3 days after exposure) (**IPCS** 2001; IARC 2006). Elimination from the lung is initially fast, but complete only after several days. Vanadium pentoxide distribution following inhalation exposure was mainly to the bone and kidney (IARC 2006). Similarly, oral rat studies in which vanadium pentoxide was given via drinking water have shown that vanadium is distributed mainly to the kidneys, spleen, tibia and testes (IPCS 2001). Excretion of ingested vanadium pentoxide occurs mostly through the feces, while urine is the main route of excretion for absorbed vanadium (ACGIH 2001)." (References cited in Environment Canada, 2010).

The DFG review of vanadium and its inorganic compounds noted:

"In workers exposed to a vanadium concentration between 0.36 and 32.19µg/m^3 (mean 19.1µg/m^3), the urine concentrations were at 0.83mg vanadium/g creatinine prior to start of shift and 1.52mg vanadium/g creatinine after the shift (Hauser *et al*. 1998)."

"In workers occupationally exposed to vanadium pentoxide, blood and urine levels were measured at the beginning and at the end of a holiday lasting three or 16 days. It could be shown that the vanadium absorbed via the lungs is eliminated with the urine in an initial rapid and a second, slow phase. After 16 days, the urine vanadium levels were higher in the workers with 48 ± 26nmol vanadium/mmol creatinine (22 ± 12µg vanadium/g creatinine) than in the control persons with 32 ± 17nmol vanadium/mmol creatinine (14 ± 8µg vanadium/g creatinine) (Kiviluoto *et al*. 1981)." (DFG, 2009).

The DFG review of vanadium and its inorganic compounds summarised the mechanistic data for toxicity:

"Under physiological conditions (at pH 7 in human tissues) only the vanadyl cation (VO^{2+}) and the vanadate anion (H_2VO_4–) are of importance. Other vanadium species like vanadium(III) only occur under physiological conditions in the form of coordination complexes. The vanadyl cation and the vanadate anion are readily and interchangeably transformed under physiological conditions by redox reactions (Rehder 1995).

"The biochemical reactions of vanadium compounds are very complex as a result of the different oxidation states and compound forms [cationic as vanadyl(IV) cation (VO^{2+}), anionic as vanadate(V) anions (VO_3^{1-} or VO_4^{3-})]. On the one hand, vanadium as vanadate anion interacts competitively with phosphate in the metabolism; on the other hand, as vanadyl cation it forms complexes with biomolecules such as proteins. Toxicologically relevant are the reactions of pentavalent vanadium with thiols to form thiyl radicals

(Shi *et al*. 1990), of pentavalent vanadium with **NADH** to form the hydroxyl radical (Shi and Dalal 1992) and the production of reactive oxygen species by tetravalent vanadium (Shi *et al*. 1996).

"The genotoxicity of vanadate(V) can be attributed to an oxidative reaction mechanism. This was found in studies on cell-free systems, which were carried out at concentrations of 1 to 10mM vanadium. Using **ESR** spectroscopy, it was shown that vanadate(V) is reduced by rat liver microsomes with NADH to vanadium(IV), thereby generating hydroxyl radicals (Shi and Dalal 1992). The reaction of vanadate(V) with thiols generates thiyl radicals and vanadium(IV) (Shi *et al*. 1990). Vanadium(IV), in the form of vanadyl sulfate, caused molecular oxygen dependent 2'-deoxyguanosine hydroxylation to form 8-hydroxy-2'-deoxyguanosine. Vanadium(IV) produced strand breaks in the presence of molecular oxygen in isolated plasmid DNA (Shi *et al*. 1996). In human fibroblasts, repair of DNA strand breaks produced by **UV** radiation or bleomycin was inhibited *in vitro* by vanadate(V) at concentrations of 1**µM** and above (Ivancsits *et al*. 2002).

"Genotoxicity is furthermore based on an aneugenic effect of the vanadium compounds. Thus, vanadium pentoxide inhibited the formation of microtubules and induced a depolymerization of tubulin (Ramírez *et al*. 1997). The impairment of oocyte maturation produced in mice by sodium orthovanadate, the aneuploidy in bone marrow cells and the premature centromere separation were attributed to an inhibition of protein tyrosine phosphatases. Among other functions, protein tyrosine phosphatases regulate the activation of the maturation promoting factor during meiosis, the meiotic spindle assembly and the spindle checkpoint inactivation (Mailhes *et al*. 2003). Apart from the genotoxic effects, vanadium compounds possess marked inhibitory effects on the phosphate metabolizing enzymes, thus indicating the presence of a mechanism that stimulates cell proliferation. Vanadate(V) inhibits different **ATPases** to a relatively specific extent, in particular the protein tyrosine phosphatases (Stankiewicz *et al*. 1995).

"In **CHO** cells, vanadyl(IV) sulfate (0.1mM) activated mitogenic signal proteins such as phosphatidylinositol 3-kinase and the mitogen-activated protein kinases **ERK 1** and **ERK 2** (Pandey *et al*. 1999). In lung fibroblasts of rats, vanadium pentoxide (10µg/cm^2) also stimulated the mitogen-activated protein kinases ERK 1 and ERK 2 (Wang and Bonner 2000). In epidermis cells of mice, vanadate(V) (50µM) promoted activation of protein kinase B (Akt kinase) and stimulated transition into the **S phase** (Zhang *et al*. 2004). Additional mechanisms enhancing proliferation result from the activation of different transcription factors and genes by vanadium. In murine fibroblasts, vanadate(V) (10µM) activated the proliferin gene and induced morphological cell transformation. These reactions were attributed to oxidative stress, as they could be inhibited by *N*-acetylcysteine (Parfett and Pilon 1995). In a mouse macrophage cell line, vanadate(V) (40µM) induced the promoter of the gene for the tumour necrosis factor α (**TNF-α**), whereby this reaction could also be inhibited by *N*-acetylcysteine, and was thus also assigned to the formation of reactive oxygen species (Ye *et al*. 1999). In murine epidermis cells, vanadate(V) (40µM) activated activator protein-1 (**AP-1**), which also involved the participation of reactive oxygen species, as demonstrated by inhibition through catalases, superoxide dismutase and *N*-acetylcysteine (Ding *et al*. 1999).

"These mechanisms suggest that vanadate is genotoxic via oxidative mechanisms and that it stimulates cell proliferation by activation of protein kinases and transcription factors." (References cited in DFG, 2009).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows vanadium exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

	VANADIUM, FUME OR RESPIRABLE DUST [as V_2O_5]		VANADIUM IV AND V COMPOUNDS, CALCULATED AS V [except CI pigment yellow 18410]	
JURISDICTION OR ADVISORY BODY	**8-HOUR LIMIT VALUE mg/m³**	**SHORT-TERM LIMIT VALUE mg/m³**	**8-HOUR LIMIT VALUE mg/m³**	**SHORT-TERM LIMIT VALUE mg/m³**
Australia	0.05			
Austria			0.05[1]	0.25[1]
Belgium	0.05[6,7]		0.05	
Canada – Ontario			0.05[2]	
Canada – Québec			0.05	
Denmark			0.03[2]	0.06[2]
Finland			0.02[3]	
France			0.05[2]	
Germany – AGS			0.005[1] 0.03[2]	0.005[1,4] 0.03[2,4]
Hungary			0.05[1]	0.2[1]
Ireland			0.05[2]	
Japan – MHLW			0.03	
Japan – JSOH			0.05	
Latvia	0.1[6]			
New Zealand	0.05			
People's Republic of China	0.05			
Romania	0.05[8] 0.1[9]	0.1[4,8]		
Singapore			0.05	
South Korea	0.05[6]		0.05	
Spain			0.05[1]	
Sweden			0.2[2]	0.05[1,4]
Switzerland			0.05[1]	0.05[1]
The Netherlands			0.01	0.03
USA – NIOSH			10[5] 5[1]	
USA – OSHA		0.1		0.5[1]
UK			0.05[2]	

TABLE 3: Exposure standards for vanadium, fume or respirable dust [as V_2O_5], and vanadium IV and V compounds, calculated as V [except **CI pigment yellow 184**] from around the world

[1] Respirable aerosol/ fraction.
[2] Inhalable aerosol/ fraction.
[3] Calculated as V.
[4] 15 minutes average value.
[5] Total dust.
[6] V_2O_5 fume.
[7] Respirable dust and smoke [as V_2O_5].
[8] Fume.
[9] Dust.

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on vanadium or vanadium pentoxide were DFG, ACGIH® and SCOEL.

5.2 DFG

The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) review of vanadium and its inorganic compounds concluded that no **MAK** value could be set; no Skin or Sensitisation notations; **Carcinogen Category**, 2; no Pregnancy Risk classification; and, **Germ cell mutation Category**, 2 (DFG, 2009).

The rationale for their conclusions included:

> "A NOAEL cannot be determined from the effects in humans and in animal studies.
>
> "Vanadium and its inorganic compounds are genotoxic *in vitro* and *in vivo*. Vanadium pentoxide caused DNA strand breaks in human lymphocytes. Vanadium(III) and vanadium(IV) compounds induced chromosome aberrations in CHO cells. Vanadium(IV) and vanadium(V) compounds caused micronucleus formation *in vitro* and *in vivo*. Vanadium compounds had an aneugenic effect in somatic cells and in germ cells *in vitro* and *in vivo*.
>
> "Vanadium pentoxide caused a significantly increased incidence of bronchioalveolar adenomas and carcinomas in B6C3F1 mice, and an incidence above the historical controls in male F344/N rats. More evidence of a carcinogenic effect was provided by the fact that vanadium acetylacetonate induced a dose-dependently increased incidence of lung tumours after intraperitoneal administration to strain A/Strong mice. The vanadate(V) ion or the vanadyl(IV) ion metabolically in balance with it is probably responsible for this carcinogenic effect. The mechanisms described in Section 2 suggest that vanadate ions are genotoxic via oxidative mechanisms and, additionally, activate mitogenic signal pathways as protein phosphatase inhibitors and stimulate cell proliferation. The aneugenic effect of the vanadium compounds is probably mediated by inhibition of the protein tyrosine phosphatases.
>
> "As a result of its carcinogenic and genotoxic effects, vanadium pentoxide is classified in Carcinogen category 2.
>
> "Conversion into the active vanadium ions most probably takes place in the other vanadium compounds as well. No data are available on vanadium metal dust. As it is known from other metals (for example, nickel) that they can be made bioavailable in the body and oxidized, oxidation and bioavailability are also assumed for vanadium metal, which is not stable in the presence of oxygen. On the basis of a common active agent and therefore the same mechanism of action and the demonstrated genotoxicity of various vanadium compounds, vanadium metal and its other inorganic compounds are also classified in Carcinogen category 2. As a result of its genotoxicity *in vitro* and *in vivo*, the accumulation of vanadium in the testes, the DNA damage caused in the testes and two positive dominant lethal tests in mice and rats, vanadium and its inorganic compounds are classified in Germ cell mutagen category 2.
>
> "As there are no data available on dermal penetration, it cannot be decided whether designation with an **"H"** is necessary or not.
>
> "There are no findings available in humans or from animal studies that would sufficiently demonstrate that vanadium or inorganic vanadium compounds have a contact sensitizing effect or a sensitizing effect on the respiratory tract. Therefore, the substance is not designated with **"Sa"** or **"Sh"**.
>
> "Complex chemical compounds, in which vanadium is present in inert form and cannot be made bioavailable in any form, are exempt from classification." (DFG, 2009).

5.3 ACGIH®

The American Conference of Governmental Industrial Hygienists [ACGIH®] review of vanadium pentoxide recommended a **TLV-TWA** of 0.05mg/m³ [inhalable particulate matter, measured as vanadium] for occupational exposure to vanadium pentoxide to minimise the potential risk of upper and lower respiratory tract irritation (ACGIH®, 2009).

The rationale for their conclusions included:

> "Vanadium pentoxide exposure produces upper respiratory symptoms in both man and animals (Kiviluoto, 1980; Knecht *et al*., 1985; Sjoberg, 1951; Zenz and Berg, 1967; Williams, 1952; Woodin *et al*., 2000; Lees, 1980; Lewis, 1959; Vintinner *et al*., 1955; Kiviluoto *et al*., 1979a). In the Lewis (1959) study, there was a statistically significant difference in eye, nose, and throat irritation, productive cough, and wheezing when vanadium pentoxide concentrations were, with one exception, between 0.1 and 0.3mg/m³. Objective confirmation of irritant effects at the 0.2 to 0.5mg/m³ level on chronic exposure is suggested by an increase in the number of neutrophils and lymphocytes in nasal swab and an infiltration of mononuclear cells and structural changes of the mucous membrane surfaces (Kiviluoto *et al*., 1979a). Eosinophils were not increased in nasal swab samples after exposure to vanadium pentoxide (Zenz and Berg, 1967; Kiviluoto *et al*., 1979a; Kiviluoto, 1980).
>
> "No studies suggesting an immune-mediated hypersensitivity to vanadium compounds were found. In subchronic inhalation studies of cynomolgus monkeys, Knecht *et al*. (1992) found that cytological, immunological and skin test results indicated the absence of allergic sensitization. However, plasma cells in nasal swabs were increased in a vanadium pentoxide exposed group compared to referents (Kiviluoto *et al*., 1979a). There is scant evidence to suggest that vanadium pentoxide exposure causes asthma. The evidence consists of *in vitro* data showing that sodium metavanadate applied to human bronchus *in vitro* resulted in smooth-muscle contraction (Cortijo *et al*., 1997). Case reports of asthma among exposed workers (Musk and Tees, 1982) and small-scale case-control and cross-sectional studies suggest that vanadium pentoxide exposure is associated with increased bronchial responsiveness (Pistelli *et al*., 1991; Irsigler *et al*., 1999).
>
> "No radiographic evidence of pneumoconiosis has been associated with vanadium pentoxide exposure (Vintinner *et al*., 1955; Sjoberg, 1950, Kiviluoto, 1980).
>
> "The critical effect upon which the TLV-TWA recommendation is made is chronic upper airway irritation. There are several epidemiologic studies linking upper respiratory symptoms to vanadium pentoxide exposure (Sjoberg, 1951; Woodin *et al*., 2000; Kiviluoto, 1980; Kiviluoto *et al*., 1979a; Vintinner *et al*., 1955; Lewis, 1959), and on controlled exposure (Zenz and Berg, 1967). The lowest mean exposure linked to respiratory symptoms was 0.0089mg V/m³ with some samples exceeding 0.05mg V/m³ (Woodin *et al*., 2000). However, in this study, in addition to V_2O_5 dust, exposures consisted of unspecified PM_{10} dust and ozone. Exposure concentrations were estimated using work-diaries and assumed respirator protection factors. For these reasons, the precision of exposure-response estimates should be questioned.
>
> "In the human study that provided the best lowest-observed-adverse-effect level (LOAEL) exposure-response information, subjects exposed at 0.2 to 0.5mg V/m³ measured as total dust for 11 years in the vanadium industry did not have an increased prevalence of upper respiratory symptoms.

> These subjects did, however, have increased leukocytes on nasal biopsy and increased self-reported "wheezing" compared to a referent group (Kiviluoto, 1980; Kiviluoto *et al*., 1979a). Although the Kiviluoto *et al*. 1979a) description contains some ambiguities, it appears that the differences in nasal biopsy results between the exposed and referents resolved after exposure was reduced to the 0.01 to 0.04mg V/m³ range measured as total dust (Kiviluoto *et al*., 1979a). The human data of Kiviluoto *et al*. (1979a) support a TLV-TWA of 0.01 to 0.04mg/m³ measured by a "total dust" air sampler. In view of the upper airway location of the critical effect, upon which this TLV-TWA is recommended, an inhalable particulate matter designation is appropriate. Insufficient data on particle size distribution were available to determine a precise conversion factor. However, based on the fact that 80% of the particulate was >5µm and upon the work of Werner *et al*. (1996), a conversion factor of two may reflect the levels that would have been measured had an inhalable particulate matter sampler been used and would have been higher than those using a total dust sampler. The adjusted range of inhalable-equivalent concentrations not associated with nasal changes is 0.02-0.08mg V/m³. For these reasons, a TLV-TWA eight-hour inhalable particulate matter value of 0.05mg V/m³, the adjusted mean of the no effect range is recommended and is expected to protect workers exposed to vanadium pentoxide from airway inflammatory changes. The human exposure studies of Zenz and Berg (1967) showing positive effects at 0.1mg/m³ vanadium dust in which 98% of the particles were less than 5µ [sic] in diameter indicate that this TLV-TWA is not excessively conservative. It should be noted that although the TLV-TWA 0.05mg/m³ value for vanadium pentoxide is measured as elemental vanadium, this recommendation does not extend to other vanadium-containing compounds. With regard to carcinogenicity, our literature search found no human epidemiologic evidence of carcinogenic activity. However, epidemiological studies capable of discerning a carcinogenic effect have not been done. There is clear evidence of the carcinogenic activity of inhaled vanadium pentoxide in mice of both genders at exposures as low as 1mg/m³ with a no-observed-adverse-effect level (NOAEL) (NTP, 2002). However, the squamous carcinomas, lacking metastases or local invasivity, were felt to be uncharacteristic of malignant neoplasia. There is also some, or equivocal, evidence of carcinogenic activity in rats (NTP, 2002); the neoplastic response in male rats exposed to 1mg/m³ was just within the NTP-2000 diet or NIH07 diet (inhalation) historical control ranges, while there was equivocal evidence in female rats. Thus, the NTP study supports an A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans, notation.
>
> "Inadequate data exist upon which to base a **Skin** or sensitizer (**SEN**) notation or recommend a **TLV-STEL**." (References cited in ACGIH®, 2009).

5.4 SCOEL

The Scientific Committee on Occupational Exposure Limits [SCOEL] assessment of vanadium pentoxide concluded that a health-based OEL could not be derived (SCOEL, 2004).

The rationale for their conclusions included:

> "The toxicological end-points of concern for humans are genotoxicity and respiratory tract irritation.

"For respiratory tract irritation, and more generally speaking for upper and lower airways effects, dose-response relationships could be obtained in both experimental animals and humans (see below table 1 and 3, respectively). It can be assumed that 0.04mg/m^3 has to be considered as a **NOEL** in occupationally exposed subjects (10 months), while in rodents a NOEL could be concluded at an exposure level of 2mg/m^3 (B6C3F1 mice, m. f., inhalation, 6h/day, 5d/w for 16 days) and of 1mg/m^3 (F344/N rats, m. f., inhalation, 6h/day, 5d/w for 14 weeks).

"Pentavalent and tetravalent forms of vanadium have produced aneugenic effects *in vitro* in the presence and absence of metabolic activation. There is evidence that these forms of vanadium as well as trivalent vanadium can also produce DNA/chromosome damage *in vitro*, both positive and negative results having emerged from the available studies. The weight of evidence from the available data suggests that vanadium compounds do not produce gene mutations in standard *in vitro* tests in bacterial or mammalian cells. *In vivo*, both pentavalent and tetravalent vanadium compounds have produced clear evidence of aneuploidy in somatic cells following exposure by several different routes. The evidence for vanadium compounds also being able to express clastogenic effects is, as with *in vitro* studies, mixed, and the overall position on clastogenicity in somatic cells is uncertain. A positive result was obtained *in vivo* in germ cells of mice receiving vanadium pentoxide by intraperitoneal injection: this finding suggests that **VP** can act as a germ cell mutagen. It is also unclear how these findings can be generalized to more realistic routes of exposure or to other vanadium compounds. In conclusion, altough [sic] aneugenicity is, in principle, a form of mutation which can have an identifiable threshold, the nature of the genotoxicity database on vanadium pentoxide and other vanadium compounds is such that it is not possible to clearly identify the threshold level, for any route of exposure relevant to humans, below which there would be no concern for potential genotoxic activity.

"No reprotoxicity information is available from human studies. Fertility and development effects of VP, as well as other V compounds, have been poorly investigated in experimental animals. It is worth stressing that due to the administration route of V (orally, or intraperitoneally), the findings of the available studies cannot be extrapolated to predict human toxicological hazard because of the unrealistic exposure route used; moreover, it was often difficult to assess the contribution of maternal toxicity to the reported effects. In any case, in the only study conducted with VP by intraperitoneal administration (Altamirano-Lozano *et al*., 1993; 1996), a single dose was used, demonstrating some effects. In conclusion, there are some uncertainties but not clear evidence that V compounds can express direct development toxicity of relevance of human health.

"The key reference appears to be represented from toxicology and carcinogenicity studies performed by NTP (2002). As discussed above, it was concluded that under the conditions of this 2-year inhalation study, there was *some evidence* of carcinogenic activity of VP in male F344/N rats (starting at the exposure level of 0.5mg/m^3) and *equivocal evidence* of carcinogenic activity of VP in female F344/N rats based on the occurrence of alveolar/bronchiolar neoplasms. There was *clear evidence* of carcinogenic activity of VP in male and female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms (starting at the exposure level of 1mg/m^3). Lung neoplasms occurrence was considered to be related to exposure to VP. (NTP, 2002). In essence, vanadium pentoxide was found to be carcinogenic in rats and mice. However, the biological mechanism underlying the initiation

and promotion of pulmonary disease and lung cancer induced by vanadium pentoxide is not understood. *In vivo* and *in vitro* studies suggest that VP is genotoxic and reprotoxic. In consequence, a health-based Occupational Exposure Limit cannot be derived for vanadium pentoxide.

"It appears that exposure to concentrations <0.1mg/m^3 do not induce irritating effects on the respiratory tract.

"In 2003 the IARC overall evaluation concluded that vanadium pentoxide is possibly carcinogenic to humans (Group 2B)." (Reference cited in SCOEL, 2004).

6.0
Analytical methods for the assessment of airborne vanadium

A common method to measure vanadium exposure is using a modification of NIOSH Method 7303, Issue 1 (NIOSH, 2003).

Using this method, an air sample is collected onto a cellulose ester filter membrane using a sampling train set at a flow rate of 2L of air per minute. The sample is analysed by inductively coupled plasma – atomic emission spectroscopy (ICP-AES). The limit of quantitation of this modified method has been quoted as 0.25µg (or 0.00025mg) of vanadium per sample.

Collecting an air sample for 8 hours at a flow rate of 2**L/min** would allow a minimum concentration of 0.0003mg of vanadium per cubic metre of air to be measured based on the quoted limit of quantitation.

7.0
Discussion

WorkSafe's WES for vanadium as V_2O_5 has been unchanged since adoption in 1994.

The toxicological database reviewed above indicates vanadium pentoxide and other vanadium compounds are locally and systemically toxic to humans, causing eye and respiratory tract irritation/corrosion, liver, kidney, cardiovascular and neurological effects; and locally and systemically toxic to laboratory species.

Based on the aforementioned documentation, informed by the conclusions of the DFG, ACGIH® and SCOEL reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 0.05mg/m³ for vanadium as V_2O_5, respirable dust and fume to be inadequate to manage health risks from possible workplace exposure:

- Vanadium pentoxide has the potential to induce eye and respiratory tract irritation/corrosion in exposed workers and experimental animals (ASTDR, 2012; DFG, 2009; ACGIH®, 2009).
- Vanadium pentoxide has the potential to induce liver, kidney, cardiovascular and neurological effects in exposed humans and/or experimental animals by inhalation exposure (ASTDR, 2012; DFG, 2009; ACGIH®, 2009).
- Vanadium pentoxide has the potential to induce lung tumours in mice, with some evidence of lung tumour induction in male and equivocal evidence in female rats (NTP, 2002; DFG, 2009; ACGIH®, 2009; SCOEL, 2004; Environment Canada, 2010).
- The mutagenic potential of vanadium pentoxide appears to be due to the generation of reactive oxygen species, mimicking phosphate, and aneugenicity (ASTDR, 2012; DFG, 2009).
- The mechanism(s) by which vanadium pentoxide induces toxicity has not been fully elucidated, but it has been suggested includes oxidative damage, stimulation of cell proliferation, inhibition of phosphate metabolising enzymes, and forming complexes with biomolecules (ASTDR, 2012; DFG, 2009).
- The DFG and SCOEL recommended that MAK values or **HBR-OEL** could not be set due to the evidence that vanadium pentoxide was carcinogenic in test species, mutagenic and exhibited reproductive toxicity (DFG, 2009; SCOEL, 2004).
- The ACGIH® adopted a TLV-TWA for vanadium pentoxide at 0.05mg/m³, inhalable particulate matter, measured as vanadium, based on a NOAEL of 0.01 to 0.04mg V/m³, measured as total dust, for upper respiratory tract symptoms in exposed workers; and, assuming a factor of 2 if an inhalable particulate matter sampler had been used instead of a total dust sampler (ACGIH®, 2009).
- The DFG noted the correlation between external exposures, air concentrations of vanadium and internal exposures, urinary concentrations of vanadium, and that air concentrations of 0.05mgV/m³ correlated with 70µgV/g creatinine at the end of shift(s) (DFG, 2016).

- Vanadium pentoxide is the most prevalent vanadium compound encountered in the workplace and has the most completely studied toxicological profile but is not the only vanadium compound in industrial use. On the basis of a common active agent, vanadium ions, the same mechanism of action and the demonstrated genotoxicity of various vanadium compounds, vanadium metal and its other inorganic compounds, including vanadium pentoxide could form a wider WES [as designated by DFG].
- The proposed WES-TWA of 0.05mg/m^3 for vanadium and its inorganic compounds, except CI pigment yellow 184, inhalable particulate matter, measured as V, is set to be protective against all non-carcinogenic and non-genotoxic endpoints, based on a NOAEL of 0.01 to 0.04mg V/m^3 from exposed workers, and the expectation that all inorganic vanadium compounds can convert to active vanadium ions in biological matrices (DFG, 2009; ACGIH®, 2009).
- The proposed WES-TWA retains the same value but for the inhalable dust fraction rather than the respirable dust fraction.
- A ***skin*** *notation* is not justified for vanadium, based on the expected low dermal exposure contribution, and reported low systemic toxicity after dermal administration to experimental animals (NICNAS, 2016; ATSDR, 2012).
- Available information indicates that there is insufficient evidence about dermal and respiratory sensitisation in humans exposed to vanadium, so a ***dsen*** or ***rsen*** *notation* is not warranted (DFG, 2009; ACGIH®, 2009).

8.0
Recommendations

WorkSafe considers its current WES-TWA of 0.05mg/m^3 for vanadium as V_2O_5, respirable dust and fume to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. adopt a WES-TWA for vanadium and its inorganic compounds, except CI pigment yellow 184 of 0.05mg/m^3 inhalable particulate matter, measured as V.

Noting that the recommended WES-TWA of 0.05mg/m^3 inhalable particulate matter for vanadium and its inorganic compounds, measured as V, may not eliminate all risk, due to the potential for genotoxicity, so exposures should be minimised.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
8-OHdG	8-hydroxy-2' -deoxyguanosine.
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
ADME	Absorption, Distribution, Metabolism and Excretion.
AGS	Ausschuss für Gefahrstoffe [Committee for Hazardous Substances] is a consultative body of the German Federal Ministry of Labour and Social Affairs on issues of the Ordinance on Hazardous Substances. Administered by the BAuA.
AP-1	Activator protein-1.
ATPase	Adenosine 5'-triphosphatase.
ATSDR	Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services.
BAL	Bronchoalveolar lavage.
BAT	Biologische Arbeitsstoff-Toleranzwerte [Biological Tolerance Value], a DFG term.
Carcinogen category 2	DFG MAK designation: Substances that are considered to be carcinogenic for man because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can contribute to cancer risk. Limited data from animal studies can be supported by evidence that the substance causes cancer by a mode of action that is relevant to man and by results of *in vitro* tests and short-term animal studies.
CHO	Chinese hamster ovary.
CI ; C.I.	Colour Index.
CI pigment yellow 184	Bismuth vanadate yellow; CAS No.: 14059-33-7; $BiVO_4$.
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
DNA	Deoxyribonucleic acid.
dsen	A substance that can 'sensitise' the skin, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
EC	Environment Canada. Canadian Federal Agency.
EKA	Expositionsaquivalente fur krebserzeugende Arbeitsstoffe [Exposure equivalents for carcinogenic substances]. DFG term.
EPA	The New Zealand Environmental Protection Authority.
ERK-1	Extracellular signal–regulated kinase 1, also called mitogen-activated protein kinase 3 (MAPK3).
ERK-2	Extracellular signal–regulated kinase 2, also called mitogen-activated protein kinase 1 (MAPK1).
ESR	Electron spin resonance or electron paramagnetic resonance (EPR).
FEV1	Forced expiratory volume in 1 second.
Fume	Fumes are very small airborne solid particulates with diameters generally less than 1μm. They may be formed by both thermal mechanisms (for example, condensation of volatilised solids, or incomplete combustion) and chemical processes (for example, vapour phase reactions). Agglomeration of fume particles may occur, resulting in the formation of much larger particles.

TERM	MEANING
FVC	Forced vital capacity: the volume of air that can be forcibly blown out after full inspiration (litres).
GD	Gestation Day.
Germ cell mutagen category 2	DFG MAK designation: Germ cell mutagens which have been shown to increase the mutant frequency in the progeny of exposed mammals.
g/m³	Gram substance per cubic metre of matrix.
g/mol	Gram substance per mole of matrix.
"H"	DFG MAK designation: *danger of percutaneous absorption*. Equivalent to the *skin notation* in the WorkSafe WES special guide.
HBR-OEL	Health-based recommended exposure limit. European Union term.
HSDB	Hazardous Substances Data Bank, administered by the US National Library of Medicine.
HSE	Health and Safety Executive, UK.
HSNO	Hazardous Substances and New Organisms Act, New Zealand.
IARC	International Agency for Research on Cancer, World Health Organization.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
IgE	Immunoglobulin E.
Inhalable fraction	Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly < 100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009b). (*cf.* Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter)
i.p.	Intraperitoneal.
IPCS	International Programme on Chemical Safety – a World Health Organisation Programme.
JSOH	Japan Society for Occupational Health.
LC_{50}	Lethal Concentration for 50% of the test population.
LD_{50}	Lethal Dose for 50% of the test population.
L/min	Litres per minute.
LOAEL	Lowest Observed Adverse Effect Level.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
µm	Micrometre or one millionth of a metre.
µM	Micromole.
mg	Milligram or one thousandth of a gram.
mg/kg b.w./ mg/kg bw	Milligram of substance per kilogram body weight.
mg/kg b.w./ day/ mg/kg bw/d	Milligram of substance per kilogram body weight per day.

TERM	MEANING
mg/L	Milligram of substance per litre.
mg/m³	Milligrams of substance per cubic metre of air.
MHLW	Japanese Ministry of Health, Labour and Welfare.
MMAD	Mass Median Aerodynamic Diameter (MMAD) is the diameter at which 50% of the particles by mass are larger and 50% smaller.
mmHg	Millimetres of mercury [unit of pressure].
mRNA	Messenger ribonucleic acid.
NADH	Nicotinamide adenine dinucleotide, reduced.
NCTB	Neurobehavioural core test battery.
NICNAS	National Industrial Chemicals Notification and Assessment Scheme is the Australian government's regulatory body for industrial chemicals.
NIOSH	The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.
NLM	National Library of Medicine, administered by the US National Institutes of Health.
NOAEL	No Observed Adverse Effect Level.
NOEL	No Observed Effect Level.
NPB	Nucleoplasmic bridge.
NTP	National Toxicology Program, US Department of Health and Human Services.
OECD	Organisation for Economic Co-operation and Development.
OEL	Occupational Exposure Limit (equivalent to a WES).
OSHA	Occupational Safety and Health Administration, US Department of Labor.
P300	Event-related auditory evoked potentials test.
$PC_{20(histamine)}$	Histamine provocative concentration causing a 20% drop in FEV1.
PMN	Polymorphonuclear.
ppm	Parts of vapour or gas per million parts of air.
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals. An EU program and regulation.
Respirable dust/ Respirable fraction	Respirable particulate fraction is that fraction of inhaled airborne particles that can penetrate beyond the terminal bronchioles into the gas-exchange region of the lungs (alveoli). Particulate size: mostly <4µm, 50% cut point. For sampling purposes the respirable dust samples are to be collected according to the method set out in the Standards Australia publication AS 2985-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Respirable Dust (Standards Australia, 2009). (*cf.* Inhalable fraction) (Also referred to as: respirable aerosol; respirable particulate matter)
RoC/ROC	Report on Carcinogens.
rsen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
S phase	Synthesis Phase is the phase of the cell cycle in which DNA is replicated.
"Sa"	Sensitising to airways. A DFG MAK notation.
s.c.	Subcutaneous.
SCE	Sister Chromatid Exchange.

TERM	MEANING
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
SD	Sprague Dawley.
SEN	A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
"Sh"	DFG MAK designation: *danger of sensitisation of the skin*
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
TG	Test Guidelines. An OECD term.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-STEL	TLV-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term.
TLV-TWA	TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
TNF-α	Tumour necrosis factor alpha.
UV	Ultraviolet.
V	Vanadium.
V_2O_5	Vanadium pentoxide.
VP	Vanadium pentoxide.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-STEL	The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.
WHO	World Health Organisation, Geneva.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

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