Social Europe

Recommendation from the Scientific Committee for Occupational Exposure Limits for vanadium pentoxide

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8 hour TWA	: -
STEL (15 min)	: -
Additional classification	: -

Substance:

Vanadium pentoxide	:	V_2O_5
Classification	:	Muta Cat 3; R40 Repr Cat 3; R63 Toxic; R48/23 Harmful R20/22 Irritant; R37
Label	:	Toxic; R20/22-37-40-48/23-63 S1/2-36/37/38-45
Synonyms	:	vanadic anhydride; divanadium pentoxide
EINECS n	:	215-234-8
EEC n	:	023-001-00-8
C.A.S. number	:	1314-62-1
MWt	:	181.88

Relevant impurities: Vanadium (IV) oxide 0.2 % max

The commercial product is generally sold as solid crystals.

1. Occurrence/use

Vanadium (V) is an abundant element with a very wide distribution and is mined in South Africa, Russia, and China. Atmospheric emissions from natural sources have been estimated at 8.4 tonnes per annum globally (range 1.5-49.2 tonnes).

Industrial activities for the production of vanadium alloys are responsable for the presence of vanadium pentoxide in the environment and in working areas. During the smelting of iron ore, a vanadium slag is formed that contains vanadium pentoxide, which is used for the production of vanadium metal. Vanadium pentoxide is also produced by solvent extraction from uranium ores and by a salt roast process from boiler residues or residues from elemental phosphate plants. The use of vanadium pentoxide as such is limited to some catalytic process and the possible exposure is related to the catalyst recovery. However, by far the most important source of environmental contamination with vanadium is combustion of oil and coal; about 90% of the approximately 64,000 tonnes of vanadium that are emitted to the atmosphere each year from both natural and anthropogenic sources comes from oil combustion (CICAD, 2001).

Higher levels of V have been reported in the air close to industrial sources and oil fires. Representative deposition rates are 0.1-10 kg/ha per annum for urban sites affected by strong local sources, 0.010.1 kg/ha per annum for rural sites and urban ones with no strong local source, and < 0.001-0.01 kg/ha per annum for remote sites. Most surface fresh waters contain less than 3 μg V/litre; higher levels of up to about 70 μg/litre have been reported in areas with high geochemical sources. Data on levels of vanadium in surface water close to industrial activity are few; most reports suggest levels approximately the same as the highest natural ones. Seawater concentrations in the open ocean range from 1 to 3 μg/litre, and sediment concentrations range from 20 to 200 μg/g; the highest levels are in coastal sediments. There is no evidence of accumulation or biomagnification in food chains in marine organisms.

Estimates of total dietary intake of humans range from 11 to 30 μg/day. Levels in drinking-water range up to 100 μg/litre. Some groundwater sources supplying potable water show concentrations above 50 μg/litre. Levels in bottled spring water may be higher (CICAD, 2001).

Blood and urine levels (determined by NAA) in Italian non occupationally exposed subjects were reported as (mean +/- SD) 0.94 +/- 0.65 μg/l and 0.81 +/- 0.72 μg/l, respectively (Sabbioni & Maroni, 1983). A reference value of 1 μg/l for urinary V was also proposed by Lauwerys & Hoet (1993). More recently, a reference value ranging from "not detectable" to 2 μg/l for urinary V was reported in the 1st List of the Italian Society of Reference Value (Minoia & Apostoli, 2003).

2. Health Significance

2.1. Metabolism

Vanadium was found to be an essential element in chicks and rats, in which vanadium deficiency causes reduced growth, impairment of reproduction, and disturbance of the metabolism.

Vanadium is mainly absorbed via the lungs. Absorption via the digestive tract is limited, while cutaneous absorption seems to be of no significance in occupational exposure. Absorbed vanadium is transported mainly in the plasma.

The bone, kidney, liver, and lung were reported as the primary target of accumulation of vanadium in experimental animals exposed to VP (Conklin et al., 1982). No data are available concerning the distribution of absorbed vanadium in man after chronic experimental exposure. However, as shown in studies in occupationally exposed subjects (Maroni et al., 1983; Kiviluoto et al., 1981a), vanadium reality accumulates in the tissues and is slowly released by the organism.

Elimination of absorbed vanadium from the body occurs mainly via the kidneys. Detailed investigations of the urinary elimination rate confirmed that vanadium half-life in the human organism varies between 15-20 hours, and a long time is necessary for the complete elimination of vanadium.

Pistelli et al. (1991) studied 11 vanadium-exposed workers 40-60 h after they had removed ashes from boilers of an oil-fired power station. Urinary vanadium concentrations were determined by AAS and ranged between 1.4 and 27 µg/l in the exposed group. Four of the Controls had also measurable concentrations of vanadium in the urine (range, 0.5-1.0 µg/l).
Toya et al. (2001) showed that vanadium pentoxide powder (geometric mean diameter, 0.31 µm) was eight times more soluble in an artificial biological fluid (Gamble's solution) than in water. The study indicated that effects of vanadium pentoxide powder are not only produced by the particles per se but also by vanadium ions.
Therefore long-term vanadium accumulation may also occur during low-level chronic vanadium exposures (Sabbioni e Maroni, 1983; Maroni et al., 1983). A minor portion (about 10%) is excreted via the faeces.

2.2. Toxicity – Animal data

Vanadium is better tolerated by small animals (i.e rats, and mice) than by larger animals, including the rabbit and horse (Hudson, 1964).

A summary of experimental toxicity data of vanadium pentoxide is reported in table 1 and 2 (see below).

Acute toxicity data are summarized in table 1.1: the toxicity of vanadium is low when administered orally, moderated when inhaled, and high when injected. A LD50 of 23.4 mg/kg.bw was reported in mice administered with VP by gavage (Roshchin, 1967a). A 1-h LC50 of 70 mg/m^3 was reported in rats exposed to VP by inhalation, and the minimum concentration of VP that caused mild signs of acute poisoning was 10 mg/m^3 (Roshchin, 1967a). The exposure of rabbits to a VP concentration of 205 mg/m^3 resulted in conjuctivitis, and tracheitis, pulmonary oedema, bronchopneumonia, perivascular swelling and death within 7 hours (Sjoberg, 1950). A lethal-dose of 1-2 mg/kg.bw was reported in rabbits intravenously injected with VP (Hudson, 1964).

Neurophysiological effects have been reported following acute exposure (oral and subcutaneous injection) of dogs and rabbits to vanadium oxides and salts (V_2O_3, V_2O_5, VCl_3, NH_4VO_3). These include disturbances of the central nervous system, such as impaired conditioned reflexes and neuromuscular excitability (Roshchin, 1967a). The animals behaved passively, refusing to eat, and lost weight. In case of severe poisoning, diarrhoea, paralysis of the hind limbs and respiratory failure were followed by death (Roshchin, 1967, 1968).

In a study reported (WHO, 1988), solutions of vanadium pentoxide were administered orally to rats or mice at doses of 0.005-1 mg/kg bw per day for periods ranging from 21 days at the higher levels to 6 months at the lower levels. A dose of 0.05 mg/kg bw was found to be the threshold dose for functional disturbances in conditioned reflex activity in both mice and rats.

Repeated exposure to aqueous solutions (0.05-0.5 mg/kg bw per day, 80 days) of vanadium pentoxide impaired condition reflex mechanisms in rats (Lagerekvist et al. 1986).

The exposure by inhalation of rats for 2 h every other day for 3 months to 3-5 mg/m^3 VP condensation aerosol caused pathological changes in the lungs. Swelling of endothelium, capillary congestion, perivascular oedema, and altered vascular permeability were reported (Roshchin 1967b).

Moyer et al. (2002) evaluated the effect of particulate matter in B6C3F1 mice exposed by inhalation to 4.0 mg/m^3 vanadium pentoxide for 2 years or 16 mg/m^3 vanadium pentoxide for 90 days and found arteritis in the coronary and renal arteries of mice exposed for 2 years but not in mice exposed for 90 days.

In the evidences reported in the same table 1.1, the study performed by Leuschner et al. (1991) provided LD50 and LC50 values markedly lower than previous studies, suggesting that the vanadium-oxides acute toxicity may be overestimated in earlier investigations. The authors state that "the earlier results on vanadium-toxicities have introduced artefacts as a consequence of the administration techniques used leading (among other effects) to artificially increased toxicities by mobilisation of van date ions". As reported in the above mentioned table 1.1, in inhalation toxicity studies an LC50 value was reported of 0.07 mg/l for VP fumes (condensation aerosol), and of >5 mg/l for VP powder. Therefore, exposure to VP fumes appears more hazardous than exposure to VP powder; it seems reasonable to suppose that the lower granulometry of fume particles leads to a higher penetration via the respiratory tract.

In albino rats exposed by inhalation to condensation aerosol of VP at levels of 0.027 mg/m^3 continuously for 70 days, altered motor chronaxy in tibial muscles, degeneration with necrosis of epithelial cells of convoluted tubules in the kidneys, and metabolic changes were reported. No effects arised for an exposure to 0.002 mg/m^3 (Pazhynich, 1966). The results of this study should be considered not sufficiently reliable to derive conclusions for the proposal of limit values. In fact, it is difficult to understand why in exposed animals the motor chronaxy reduction is shown only in the extensor group of muscles and not in the flexor group, giving the mode of administration of the VP.

The nose and lungs were identified as target organs of direct toxic effect of subchronic inhalation of VP aerosol (Kirkpatrick et al., 1993). In both male and female F344/N rats – exposed to 0, 1, 2, 4, 8, 16 mg/m^3 VP aerosol for 6h/d, 5d/w for 13 weeks – hyperplasia and metaplasia of the respiratory ephitelium in the nose were found in ≥90% of male and female rats at ≥8 mg/m^3. A combination of airway and alveolar epithelial cell hyperplasia and lung fibrosis and inflammation, which were usually located near hyperplastic airways, was seen in nearly all rats at ≥ 4 mg/m^3. At 2 mg/m^3, no effects were reported as far as epithelial nasal lesions are concerned, but in the lung hyperplasia was found in all rats and fibrosis in 2 male rats. Bronchiolar exudation was also observed at ≥ 8 mg/m^3 for both sexes. No lung histopathological lesions were seen at 1 mg/m^3 for both sexes. From this study (F344/N rats, inhalation, 6h/day, 5d/w for 13 weeks), a NOEL could be concluded at an exposure level of 1 mg/m^3 (lung histopathology).

An oral daily dose of 0.05 mg vanadium/kg.bw for 6 months was found to be the threshold for functional disturbance in conditioned reflex activities in rats, and mice. A dose of 0.005 mg/kg.bw per day did not produce any adverse effect (Seljankina, 1961).

The reprotoxicity of VP, as well as to to other penta- and tetravalent compounds have been investigated in experimental fertility and developmental studies. No information is available from human studies.

Taking into account all the available data, it was concluded that fertility and development effects of VP, as well as other V compounds, have been poorly investigated (HSE, 2002). 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. Despite this, there are some uncertainties but not clear evidence that V compounds can express direct development toxicity of relevance to human health.

Mutagenicity effects of VP and vanadium pentoxide have been experimentally evaluated in both *in vitro* and *in vivo* studies; a summary of available data is reported in table 1.

Vanadium pentoxide was not mutagenic in Salmonella typhimurium, but conflicting results were obtained with E. coli. In vitro, in Chinese hamster lung fibroblasts vanadium pentoxide induces endoreduplication and micronuclei but no gene mutation or sister chromatid exchanges. In vitro in human lymphocytes, positive genotoxic effects were demonstrated for the induction of DNA damage with alkaline comet assay, sister chromatid exchange when the compound was given in combination with caffeine, aneuploidy with FISH staining and inhibition of microtubule polymerisation and polyploidy.

In vivo in CD-1 mice, induction of DNA damage was demonstrated with alkaline assay in several organs. In the same mice strain, lack of mutagenic effects was reported in bone marrow for sister chromatid exchange and chromosomal aberrations: however, dominant lethal effects were observed after i.p. injection of vanadium pentoxide. 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.

Ivancsist et al. (2002) studied the effect of occupational exposure to vanadium pentoxide by measuring DNA strand breaks using the single-cell gel electrophoresis assay (comet assay), 8-hydroxy-2'-deoxyguanosine (8-OHdG) formation and the frequency of sister chromatid exchange in whole blood or lymphocytes of 49 male workers employed in a vanadium factory. Workers showed a significant vanadium uptake (serum, 5.38 µg/mL), but no increase in cytogenetic end-points or oxidative DNA damage was observed in these workers.

The underlying mechanism for the observed aneugenicity and clastogenicity is uncertain.

Vanadium pentoxide is considered to induce oxidative damage leading to DNA alkali-labile sites and DNA strand breakage. Inhibition of microtubule polymerisation may explain the aneugenic effects of vanadium pentoxide. Whether these spindle disturbances are related to oxidative damage or to direct interaction with vanadium cations is unclear (Ramirez et al. 1997, Shi et al. 1992, Shi et al. 1996, Shi et al. 1997). Indirect effects of vanadium pentoxide through the inhibition of various enzymes involved in DNA synthesis and DNA repair also contribute to its mutagenicity. Induction of dominant lethal mutations in mice may result from either one or a combination of the modes of action .

It is also unclear how these findings can be generalized to more realistic routes of exposure or to other vanadium compounds. In conclusion, although aneugenicity is, in principle, a form of mutation which can have an identifiable threshold, the nature of the genotoxicity database on vanadium pentoxide 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 (CICAD, 2001; HSE, 2002).

Toxicology and carcinogenesis studies for VP were performed by National Toxicology Program (NTP, 2002). Male and female F344/N rats and $B6C3F_1$ mice were exposed to VP (99% pure) by inhalation for 16 days, 14 weeks, or 2 years. A summary of 2-years studies is reported in table 2. The observed evidences are discussed in the following paragraphs:

- 2-Year Study in Rats: Groups of rats (50 of each sex) were exposed to particulate aerosols of VP at concentrations of 0, 0.5, 1, or 2 mg/m^3 by inhalation, 6 hours per day, 5days per week for 105 weeks. Survival and body weights of males and females were generally similar to those of the chamber controls. Mean body weights of females exposed to 2 mg/m^3 were less than those of the chamber controls throughout the study. Alveolar/bronchiolar neoplasms were present in exposed groups of male rats, and the incidences often exceeded the historical control ranges. Alveolar/bronchiolar adenomas were present in 0.5 and 1 mg/m^3 females; one 2 mg/m^3 female also had an alveolar/bronchiolar carcinoma. The incidence of alveolar/bronchiolar adenoma in the 0.5 mg/m^3 group was at the upper end of the historical control ranges. Nonneoplastic lesions related to vanadium pentoxide exposure occurred in the respiratory system (lung, larynx, and nose) of male and female rats, and the severities of these lesions generally increased with increasing exposure concentration.
- 2-Year Study in Mice: Groups of mice (50 of each sex) were exposed to particulate aerosols of vanadium pentoxide at concentrations of 0, 1, 2, or 4 mg/m^3 by inhalation, 6 hours per day, 5 days per week for 105 weeks. Survival of 4 mg/m^3 males was significantly less than that of the chamber controls. Mean body weights of 4 mg/m^3 males and all exposed groups of females were generally less than those of the chamber controls throughout the study, and those of males exposed to 2 mg/m^3 were less from week 85 to the end of the study. Many mice exposed to vanadium pentoxide were thin, and abnormal breathing was observed in some mice, particularly those exposed to 2 or 4 mg/m^3. The incidences of alveolar/bronchiolar neoplasms were significantly increased in all groups of exposed males and females. Nonneoplastic lesions related to vanadium pentoxide exposure occurred in the respiratory system (lung, larynx, and nose) of male and female mice, and the severities of these lesions generally increased with increasing exposure concentration. Bronchial lymph node hyperplasia was present in many exposed females.

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 and **equivocal evidence** of carcinogenic activity of VP in female F344/Nrats 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 (NTP, 2002).

It was reported that alveolar/bronchiolar adenomas, and especially carcinomas and metastases from the site of origin are uncommon in rats (Hahn, 1993). Because of the increased incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) in the 0.5 and mg/m^3 groups and the rarity of these neoplasms in rats, this response was considered to be related to exposure to VP (NTP, 2002). To establish if the lung neoplasms induced in mice were unique to VP, genetic alterations in the K-*ras* oncogene and the *p53* tumor suppressor gene were investigated. K-*ras* codon 12 mutation and loss of heterozygosity on

chromosome 6 were detected in vanadium pentoxide-induced alveolar/bronchiolar carcinomas from mice, but there was not a clear exposure concentration-related response. It was concluded that the mechanism of lung carcinogenesis following VP exposure was different than that of spontaneously induced lung neoplasms. VP appears to be slightly soluble in the lung, and as such, may be cititoxic. The biological mechanism and the initiation and promotion of pulmonary disease and lung cancer induced by VP is not understood (NTP, 2002).

2.3. Toxicity – Human Data

Exposure to vanadium dusts and fumes in man causes irritant effects mainly in the respiratory tract (see below, table 5). Exposure to fumes appears to be more irritant than exposure to dust; it seems reasonable to suppose that the lower granulometry of fumes particles leads to a higher penetration in the respiratory mucosa. Even brief exposures cause rhinorrhea, epistaxis, dyspnea and acute asthmatic bronchitis with remission usually in a few days. Exposure to vanadium may also result in pneumonia (Kiviluoto et al., 1979b; Levy et al., 1984; Wyers, 1946).

The exposure of 2 volunteers to 1 mg/m^3 for 8h resulted, 5h later, in coughing that lasted for 8 days. Following inhalation of 0.2 mg/m^3 VP by 5 volunteers, similar symptoms were reported, i.e. coughing that started a little later (20h after exposure) and lasted for 7-10 days. Similar irritating effects were also observed in 2 volunteers exposed to 0.1 mg/m^3 VP for 8h (Zenz & Berg, 1967).
Zenz et al. (1962) reported on 18 workers exposed to varying degrees to vanadium pentoxide dust (mean particle size, < 5 µm) in excess of 0.5 mg/m^3 (apparently measured over a 24-h period) during a pelletizing process. Three of the most heavily exposed men developed symptoms, including sore throat and dry cough. Examination of each on the third day revealed markedly inflamed throats and signs of intense persistent coughing, but no evidence of wheezing. The three men also reported "burning eyes" and physical examination revealed slight conjunctivitis. Upon resumption of work after a 3-day exposure-free period, the symptoms returned within 0.5-4 h, with greater int

A dose-response relationship was observed when 11 volunteers were exposed to 0.4 mg VP/m^3 condensation aerosol. A tickling and itching sensation and a feeling of dryness of the mucous membranes of the mouth were reported in all exposed subjects. A concentration of 0.16 mg/ m^3 caused mild signs of irritation in only 5 of the 11 volunteers, and a concentration of 0.08 was not noticed by any volunteer. The duration of the exposure was not specified (Pazhynic, 1967).

In workers exposed to dust containg vanadium (as VP) 0.2-0.5 mg/m^3 for about 11 years, irritants effects on the mucous membranes of the upper respiratory tract were reported. After hygienic improvements, the same workers were exposed to VP concentrations in the range of 0.01-0.04 mg/ m^3 for about 10 months. No worsening of the irritant effects observed as a consequence of the previous exposure was reported for this low-level exposure. In these workers, the exposure did not cause any pathological effects on the blood picture, the cystein level in the hair, or the respiratory function (Kiviluoto et al., 1979a,b, 1980, 1981a,b; Kiviluoto, 1980).

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

The data on allergenic properties of Vanadium pentoxide is meagre. Exposure to VP has been reported to cause allergic eczema. A dry eczematous dermatitis developed in 9 out of 36 workers exposed to VP concentrations of 6.5 mg/m^3 ; however, on patch testing only one worker showed a positive reaction (Sjöberg 1950). An allergic mechanism for the

frequently occurring rhinitic symptoms, asthma and pneumonitis have been suspected (Sjöberg 1950, Zenz et al 1962). However, Musk & Tees (1982) reported on asthma in four workers exposed to VP dust in a newly established VP refinery. One of the workers experienced irritation of the upper respiratory tract after a single exposure with dyspnoe and wheezing developing two weeks later. All workers developed similar irritant symptoms. Two workers showed an increased bronchial reactivity when challenged with histamine; these two workers had the most recent exposure to VP. No indication of an immunological aetiology was found. On these grounds the auhtors concluded thet the effect was likely to be a direct chemical one. Kiviluoto et al (1979a,b, 1980, 1981 a, b) in there studies on 63 males exposed in a vanadium factory for 11 years at concentrations in the range of 0.1-3.9 mg/m3 (estimated average concentrations 0.2-0.5 mg/m3) and after a further 7-11 month later when concentrations had been reduced to 0.01-0.04 mg/m3 studied nasal smears and biopsies. The findings were consistent with irritant effects. Eosinophils did not differ between exposed and non-exposed, nor did IgE-antibody levels. Although exposed workers complained significantly more often of wheezing, pulmonary function tests did not differ. There is, thus, little evidence indicating sensitizing effects on the respiratory tract. The known irritant effects of VP can well explain effects on the respiratory tract including rhinitis, bronchial hyperreactivity, wheeze, asthma as well as bronchitis.

Human data on the effects of vanadium on reproduction and embryotoxicity, or possible teratogenic effects, are lacking.

Recommendation

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 0.04 mg/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 2 mg/m^3 (B6C3F$_1$ mice, m. f., inhalation, 6h/day, 5d/w for 16 days) and of 1 mg/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 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 0.5 mg/m^3) and **equivocal evidence** of carcinogenic activity of VP in female F344/Nrats 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 1 mg/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 <0.1 mg/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).

Table 1. Genetic and related effects of Vanadium Pentoxide

Teest system	Result[a]		Dose[b] (LED/HID)	Reference
	Witout Exogenous Metablic system	With exogenous metabolic system		
Escherichia coli, sot test	-	NT	0.5 M	Kanematsu et al. (1980)
Escherichia coli, WP_2, WP_2vrA, CM_{891}, ND_{160} and MR_{102}, reversion assay		-	NT	1200 µg/plate Sun (1996)
Bacillus subtilis, recombination-repair-deficient (rec^-)	+	NT	0.5 M	Kanematsu & Kada, (1978)
Bacillus subtilis, H17 and M45 recombination-repair deficent	+	NT	0.5 M	Kada et al., 1980 Kanematsu & Kada, (1980)
Bacillus subtilis, H17 (rec+) and M45 (rec^-) recombination-repair deficent		+	NT	100 mg/ml Sun (1996)
Salmonella typhimurium, TA100, TA1535, TA1537, TA1538, (his^-)	-	NT	0.5 M	Kanematsu et al. (1980)
Salmonella typhimurium, TA100, TA98, TA100, TA1535, reverse mutation		-	-	333 µg7plate NTP2002
Salmonella typhimurium, TA97, TA98, TA100, TA102, reverse mutation		-	NT	200 µg/plate Sun (1996)
Sister chromatid exchanges, human lymphocytes *in vitro*	-	NT	47 M	Sun (1996)
Sister chromatid exchanges, human lymphocytes *in vitro*	-	NT	6 µg/ml	Roldán & Altamirano(1990)
Sister chromatid exchanges, human lymphocytes *in vitro*	-	NT	4 µg/ml	Roldán-Reyes et al.(1997)
Structural chromosomal aberrations, human lymphocytes *in vitro*		-	NT	6 µg/mlRoldán & Altamirano(1990)
Numerical chromosomal aberrations, polyploidy, human lymphocytes *in vitro*	+	NT	2 µg/ml	Roldán & Altamirano(1990)
Aneuploidy, FISH centromeric probes, human lymphocytes *in vitro*		+	NT	0.001 µM Ramírez et al.(1967)

Inhibition of microtubule polymerisatiohn, immunostaining, human lymphocytes *in vitro*	+	NT	0.1 µM	Ramírez et al.(1967)
Chromosome and satellite associations, human lymphocytes *in vitro*	+	NT	4 µg/mlRoldán & Altamirano(1990)	

Table 1 (contd)

Teest system	Result[a]		Dose[b] (LED/HID)	Reference
	Witout Exogenous Metablic system	With exogenous metabolic system		
DNA strand breaks, alkaline comet assay, human lymphocytes *in vitro*	+		NT	0.3 µM Rojas et al. (1996a, b)
DNA Synthesis, inhibition assay, human lymphocytes *in vitro*	-		NT	58.4 mg/kg po Sun (1996)
Micronucleus formation in binucleated cells, cytochalasin-B assay, Chinese hamster lung fibroblast cell line (V79) *in vitro*	+		NT	1 µm/ml Zhong et al. (1994)
Gene mutation, 6-thioguanine resistant mutation, Chinese hamster lung fibroblast cell line (V79) *in vitro*	-			4 µg/ml Zhong et al. (1994)
Sister chromatic exchanges, Chinese hamster lung fibroblast cell line (V79) *in vitro*	-			4 µg/ml Zhong et al. (1994)
Numerical chromosomal aberrations, endoreduplicaton, Chinese hamster lung fibroblast cell line (V79) *in vitro*	+			1 µg/ml Zhong et al. (1994)
Numerical chromosomal aberrations, aneuploidy, Kinetochore staining of micronuclei in binucleated cells, Chinese hamster lung fibroblast cell line (V79) *in vitro*	+			1 µg/ml Zhong et al. (1994)
Structural chromosomal aberrations, albino rat, bone marrow cells *in vitro*	*?*			4 mg/kg Giri et al. (1979)
Dominant lethal mutations, CD-1 mice *in vivo*	+			*8.5* mg/kg, i.p. Altamirano-Lozano et al. (1996)
Dominant lethal mutations, CD-1 mice *in vivo*	-		NT	4.0 mg/kg sc Sun (1996)
Structural chromosomal aberrations, CD-1 mice, bone morrow, *in vivo*	-			*23* mg/kg, i.p. Altamirano-Lozano & Alvarez-Barrera (1996)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Witout Exogenous Metablic system	With exogenous metabolic system		
Sister chomatid exchanges, CD-1 mice, bone marrow, *in vivo*	-		23 mg/kg, ip	Altamirano-Lozano et al. (1993 Altamirano-Lozano & Alvarez-Barrera (1996)
Micronucleous formation, 615 and Kunming albino mice, bone marrow, *in vivo*	+	NT	0.17 mg/kg ip	Sun (1996)
Micronucleous formation, 615 and Kunming albino mice, bone marrow, *in vivo*	+	NT	0.25 mg/kg sc	Sun (1996)
Micronucleous formation, 615 and Kunming albino mice, bone marrow, *in vivo*	+	NT	0.5 mg/m3, inhal.	Sun (1996)
Micronucleous formation, 615 and Kunming albino mice, bone marrow, *in vivo*	-	NT	11.3 mg/kg po	Sun (1996)
Micronucleous formation, Kunming albino mice, fetal liver, maternal bone marrow, maternal spleen, *in vivo*	+	NT	5 mg/kg ip	Sun (1996)
Micronucleous formation, B6C3Ftmice, peripheral blood, *in vivo*		-	NT	16 mg/m', inhal. NTP (2002)
DNA strand breaks, alkaline comet assay, in several organs of mice *in vivo*	+		5.75 mg/kg, i.p.	Altamirano-Lozano *et al.* (1996, 1999)
Inhibition of double-strand DNA breaks repair, alkaline and neutral comet assay, human fibroblast *in vitro*		+	$+V_2O_5$0.5µM	UV (4.8 KJ/m^2) Ivancist et al. (2002)

		+	Bleomycin (1 µg/ml)+ +$V_2O_5$0.5µ

[a]+, positive; -, negative; (+), weak positive; NT, not tested; ND, not described, ?, inconclusive
[b]LED, lowest effective dose; HID, highest ineffective dose; in-vitro ests, µg/ml; in-vivo tests, mg.kg bw per day; NR, not reported
[c]Combined with 20 µg of caffeine

Table 2 Summary of 2-y studies – VP ihl exp, 6 h/day, 5 d/week (NTP, 2002)

	Male F344/N Rats	Female F344/N Rats	Male B6C3F1 Mice	Female B6C3F1 Mice
Exp. levels	0, 0.5, 1, or 2 mg/m3	0, 0.5, 1, or 2 mg/m3	0, 1, 2 or 4 mg/m3	0, 1, 2 or 4 mg/m3
Body weights	Exposed groups similar to controls	2 mg/m3 group less than controls	2 and 4 mg/m3 group less than controls	Exposed groups less than controls
Survival Rates	20/50, 29/50, 26/50, 27/50	33/50, 24/50, 29/50, 30/50	39/50, 33/50, 36/50, 27/50	38/50, 32/50, 30/50, 32/50
Nonneoplastic effects	Lung: alveolar epithelium, hyperplasia (7/50, 24/49, 34/48, 49/50); bronchiole, epithelium hyperplasia (3/50, 17/49, 31/48,49/50); alveolar epithelium, metaplasia, squamous (1/50, 0/49, 0/48, 21/50); bronchiole, metaplasia, squamous (0/50, 0/49, 0/48, 7/50); inflammation, chronic active (5/50, 8/49, 24/48, 42/50); interstitial, fibrosis (7/50, 7/49, 16/48, 38/50); alveolus, infiltration cellular, histiocyte (22/50, 40/49, 45/48, 50/50)	Lung: alveolar epithelium, hyperplasia (4/49, 8/49, 21/50, 50/50); bronchiole, epithelium hyperplasia (6/49, 5/49, 14/50, 48/50); alveolar epithelium, metaplasia, squamous (0/49, 0/49, 0/50, 6/50); inflammation, chronic active (10/49, 10/49, 14/50, 40/50); interstitial, fibrosis (19/49, 7/49, 12/50, 32/50); alveolus, infiltration cellular, histiocyte (26/49, 35/49, 44/50, 50/50)	Lung: alveolar epithelium, hyperplasia (3/50, 41/50, 49/50, 50/50); bronchiole, epithelium, hyperplasia (0/50, 15/50, 37/50, 46/50); inflammation chronic (6/50, 42/50, 45/50, 47/50); alveolus, infiltration cellular, histiocyte (10/50, 36/50, 45/50, 49/50); interstitial fibrosis (1/50, 6/50, 9/50, 12/50)	Lung: alveolar epithelium, hyperplasia (0/50, 31/50, 38/50, 50/50); bronchiole, epithelium, hyperplasia (0/50, 12/50, 34/50, 48/50); inflammation chronic (4/50, 37/50, 39/50, 49/50); alveolus, infiltration cellular, histiocyte (0/50, 34/50, 35/50, 45/50); interstitial fibrosis (0/50, 1/50, 4/50, 8/50)
	Larynx: inflammation, chronic (3/49, 20/50, 17/50, 28/49); respiratory epithelium, epiglottis degeneration (0/49, 22/50, 23/50, 33/49); respiratory epithelium, epiglottis, hyperplasia (0/49, 18/50, 34/50, 32/49); respiratory epithelium, epiglottis,	Larynx: inflammation, chronic (8/50, 26/49, 27/49, 37/50); respiratory epithelium, epiglottis degeneration (2/50, 33/49, 26/49, 40/50); respiratory epithelium, epiglottis, hyperplasia (0/50, 25/49, 26/49, 33/50); respiratory epithelium,	Larynx: respiratory epithelium, epiglottis, metaplasia, squamous (2/49, 45/50, 41/48, 41/50)	Larynx: respiratory epithelium, epiglottis, metaplasia, squamous (0/50, 39/50, 45/49, 44/50) Bronchial lymph node: hyperplasia (3/39, 13/40, 14/45, 41/20)

	metaplasia, squamous (0/49, 9/50, 16/50, 19/49)	epiglottis, metaplasia, squamous (2/50, 7/49, 7/49, 16/50)		
	Nose: goblet cell, respiratory epithelium, hyperplasia (4/49, 15/50, 12/49, 17/48)	Nose: goblet cell, respiratory epithelium, hyperplasia (13/50, 18/50, 16/50, 30/50)	Nose: inflammation suppurative (16/50, 11/50, 32/50, 23/50); olfactory epithelium, degeneration, hyaline (1/50, 7/50, 23/50, 30/50); respiratory epithelium, degeneration, hyaline (8/50, 22/50, 38/50, 41/50); respiratory epithelium, metaplasia, squamous (0/50, 6/50, 6/50, 2/50)	Nose: inflammation suppurative (19/50, 14/50, 32/50, 30/50); olfactory epithelium, atrophy (2/50, 8/50, 5/50, 14/50); olfactory epithelium, degeneration, hyaline (11/50, 23/50, 32/50, 48/50); respiratory epithelium, degeneration, hyaline (35/50, 39/50, 46/50, 50/50); respiratory epithelium, metaplasia, squamous (0/50, 3/50, 7/50, 8/50); respiratory epithelium, necrosis (0/50, 0/50, 1/50, 7/50)

Table 2 Toxicology and Carcinogenesis Studies by National Toxicology Program (NTP, 2002) [cont.]

	Male F344/N Rats	Female F344/N Rats	Male B6C3F1 Mice	Female B6C3F1 Mice
Exp. levels	0, 0.5, 1, or 2 mg/m^3	0, 0.5, 1, or 2 mg/m^3	0, 1, 2 or 4 mg/m^3	0, 1, 2 or 4 mg/m^3
Neoplastic effects	Lung: alveolar/ bronchiolar adenoma (4/50, 8/49, 5/48, 6/50); alveolar/bronchiolar carcinoma (0/50, 3/49, 1/48, 3/50); alveolar/ bronchiolar adenoma or carcinoma 4/50, 10/49, 6/48, 9/50)	None	Lung: alveolar/ bronchiolar adenoma (13/50, 16/50, 26/50, 15/50); alveolar/ bronchiolar carcinoma (12/50, 29/50, 30/50, 35/50); alveolar/ bronchiolar adenoma or carcinoma (22/50, 42/50, 43/50, 43/50)	Lung: alveolar/ bronchiolar adenoma (1/50, 17/50, 23/50, 19/50); alveolar/ bronchiolar carcinoma (0/50, 23/50, 18/50, 22/50); alveolar/ bronchiolar adenoma or carcinoma (1/50, 32/50, 35/50, 32/50)
Equivocal findings	None	Lung: alveolar/ bronchiolar adenoma (0/49, 3/49, 1/50, 0/50); alveolar/bronchiolar adenoma or carcinoma (0/49, 3/49, 1/50, 1/50)	None	None
Levels of evidence of carcinogenic activity	Some Evidence	Equivocal Evidence	Clear Evidence	Clear Evidence

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