

Vanadium and its inorganic compounds

MAK Value Documentation – Translation of the German version from 2023

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Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) re-evaluated the data for vanadium [7440-62-2] and its inorganic compounds to derive an occupational exposure limit value (maximum concentration at the workplace, MAK value) considering all toxicological end points. Relevant studies were identified from a literature search and also unpublished study reports were used. The critical effects are irritation in the upper respiratory tract and carcinogenicity in the lungs of rats and mice. The available data do not provide sufficient evidence of carcinogenic effects in humans. Under physiological conditions, vanadium occurs as the tetravalent vanadyl cation or the pentavalent vanadate anion; these 2 forms readily convert from one to the other. As the cytotoxic, irritant and carcinogenic effects are induced by the vanadium ions, all inorganic vanadium compounds of varying solubility are included in the evaluation. Inorganic vanadium compounds cause (oxidative) DNA damage, clastogenicity and aneugenicity in mice and rats after administration by inhalation, intraperitoneal injection or with the drinking water. The induction of (oxidative) DNA damage is the most sensitive genotoxic effect. However, the primary carcinogenic mode of action is assumed to be initiated by inflammation leading to an increase in cell proliferation. Thus, it is possible to establish a concentration at which these effects do not occur and vanadium and its inorganic compounds have been classified in Carcinogen Category 4. The subacute NOAEC for the induction of inflammatory, histopathological and genotoxic effects in the lungs of mice was 0.14 mg vanadium/m³ (respirable fraction). On this basis, a concentration of 0.005 mg/m³ was derived for the respirable fraction at which no carcinogenic effects are to be expected. No NOAEC can be determined for effects on the upper respiratory tract from either animal data or data in humans. Therefore, the NOAEC of 0.14 mg vanadium/m³ for the induction of inflammatory, histopathological and genotoxic effects in the lungs of mice after subacute exposure is used to derive a limit value for the inhalable fraction to keep these effects from occurring in the upper respiratory tract. The concentration of 0.005 mg/m³ that was derived for the respirable fraction is set as the MAK value for the inhalable fraction. As the critical effect of vanadium and its inorganic compounds is systemic, the substances have been assigned to Peak Limitation Category II. Based on human data, an excursion factor of 2 has been set. Neurotoxic effects were observed in humans at mean concentrations of 0.216 mg/m³. As there are no studies suitable for deriving a NOAEC for developmental neurotoxic effects, vanadium and its inorganic compounds have been assigned to Pregnancy Group D. Germ cell mutagenicity is observed in animal studies

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only at very high doses. As no appreciable contribution to the genetic risk in humans is to be expected if the MAK value is observed, vanadium and its inorganic compounds have been classified in Category 5 for germ cell mutagens. Limited data show no sensitization. There are no data indicating that vanadium and its inorganic compounds are absorbed through the skin.

MAK value (2022)	0.005 mg/m³ I (inhalable fraction)
Peak limitation (2022)	Category II, excursion factor 2
Absorption through the skin	–
Sensitization	–
Carcinogenicity (2022)	Category 4
Prenatal toxicity (2022)	Pregnancy Group D
Germ cell mutagenicity (2022)	Category 5
BAR (2022)	0.15 µg vanadium/l urine

Tab. 1 Mean relative recoveries for the determination of CEMA and AMCC in urine (n = 8)

Substance	CAS No.	Formula	Oxidation state	Molar mass [g/mol]	pH in water	Solubility			
						in water [g/l]	in Gamble's solution (pH 7.4)	in artificial lysosomal fluid (pH 4.5)	in PBS (pH 7.2–7.4)
Vanadium	7440-62-2	V		50.94	5.8 ^{d)}	0.00015 ^(b),3) (sample weight 110 mg/l) max. 0.000039% (sample weight 1 mg/l at pH 6) ^{d)}	1.1% ^(b) 1.1 ± 0.22 mg/l ^(b)	1.2% ^(b) 1.2 ± 0.01 mg/l ^(b)	1.8% ^(b) 1.8 ± 0.07 mg/l ^(b)
Ammonium metavanadate	7803-55-6	NH ₄ VO ₃	V	116.98	6.0 ^(b) no data no data	7.81 ^(b) 58 ^(e) 48 ^(d)	no data	no data	no data
Ammonium trivanadium octaoxide	12207-63-5	NH ₄ V ₃ O ₈	V	298.9	3.9 ^(d)	0.18 ^(d)	no data	97% ^(e) 49.4 ± 0.6 mg/l	no data
Divanadium pentaoxide	1314-62-1	V ₂ O ₅	V	181.9	2.7 ^(d),f) no data	0.92 ^(b),f) 8 ^(c)	99% ^(f) 55.2 ± 0.7 mg/l ^(b) 8.6 ± 0.3 g/l ^(b) (sample weight 100 g/l)	96% ^(f) 54 ± 0.3 mg/l ^(b)	97% ^(f) 54 ± 0.4 mg/l ^(b)
Divanadium trioxide	1314-34-7	V ₂ O ₃	III	149.9	4.2 ^(h) no data	0.471 ^(b) 0.1 ^(f)	6% ^(k) 3.8 ± 0.3 mg/l ^(k) 20 ± 30 g/l ^(b) (sample weight 100 g/l)	16% ^(k) 10.7 ± 0.4 mg/l ^(k)	9% ^(k) 5.8 ± 0.1 mg/l ^(k)
Divanadium trisulfate	13701-70-7	V ₂ (SO ₄) ₃	III	390.07	0 ^(f)	660.2 ^(f)	no data	no data	no data
Potassium metavanadate	13769-43-2	KVO ₃	V	138.04	9	124 ^(b)	no data	no data	no data
Sodium metavanadate	13718-26-8	NaVO ₃	V	121.93	9.5 ^(d) no data	225 ^(b) 211 ^(e)	90% ^(f) 37.4 ± 0.2 mg/l ^(b)	93% ^(f) 38.9 ± 0.2 mg/l ^(b)	91% ^(f) 38.1 ± 0.3 mg/l ^(b)
Sodium orthovanadate	13721-39-6	Na ₃ VO ₄	V	183.91	no data	soluble ^(c)	no data	no data	no data
Vanadium carbide	12070-10-9	VC	metalloid	62.95	5.2 ^(p) 7.8 ^(d)	0.0021 ^(p) 13.95 ± 0.35 µg V/l ^(d)	no data	0.8% ^(f) 0.69 ± 0.009 mg/l ^(b)	no data
Vanadium carbide nitride	12069-91-9	VCN	metalloid	76.96	6.9 ^(p)	4.3 × 10 ⁻⁶ ⁽ⁿ⁾	no data	0.5% ^(s) 0.36 ± 0.001 mg/l ^(s)	no data
Vanadium dioxide (divanadium tetraoxide)	12036-21-4	VO ₂ (V ₂ O ₄)	IV	82.94	no data 4.2 ^(q)	< 1 ^(a) 0.039 ^(l)	1.7 ± 0.2 g/l ^(b)	12.1 ± 0.3 ^(u)	no data
Vanadyl dichloride	10213-09-9	VOCl ₂	IV	137.85	no data	decomposes ^(d)	no data	no data	no data
Divanadyl di(hydrogen phosphate) hydrate	93280-40-1	(VO) ₂ (HPO ₃) ₂ × H ₂ O	IV	180.93	no data	148 (sample weight 250 g/l)	no data	no data	no data
Vanadium oxalate complexes	98903-75-4	VO(C ₂ O ₄)	IV	154.96	1.9	145.1 ^(d)	no data	no data	no data

Tab. 1 (continued)

Substance	CAS No.	Formula	Oxidation state	Molar mass [g/mol]	pH in water	Solubility			
						in water [g/l]	in Gamble's solution (pH 7.4)	in artificial lysosomal fluid (pH 4.5)	in PBS (pH 7.2-7.4)
Vanadyl(IV) sulfate (vanadium(IV) oxide sulfate)	27774-13-6	VOSO ₄	IV	163	1.1 ^(f) no data ^(a)	467 ^(f) 100% (≈500 g/l) ^(a) 100% ^(b) (0.0002, sample weight 1 mg/l at pH 6 to 8)	95% ^(m) 19 ± 0.1 mg/l ^(m) 310 ± 20 g/l ^(a)	99% ^(m) 19.9 ± 0.2 mg/l ^(m)	97% ^(m) 19.6 ± 0.1 mg/l ^(m)
Vanadyl(IV) sulfate pentahydrate	12439-96-2	VOSO ₄ × 5 H ₂ O	IV	253.08	no data	no data	no data	no data	no data
Vanadyl trichloride	7727-18-6	VOCl ₃	V	173.3	no data	soluble, decomposes ^(g)	no data	no data	no data
Vanadium trichloride	7718-98-1	VCl ₃	III	157.3	no data	hydrolysis	no data	no data	no data
Divanadyl pyrophosphate	58834-75-6	(VO) ₂ P ₂ O ₇	IV	307.82	no data	no data	no data	no data	no data
Vanadium hydroxide oxide phosphate (vanadyl phosphate)	65232-89-5	H ₃ O ₃₀ P ₅ V ₆	V	945.54	no data	no data	no data	no data	no data

PBS: phosphate-buffered saline

a) Rajendran et al. 2016

b) This value is regarded as uncertain by the authors (Rajendran et al. 2016)

c) ATSDR 2018

d) ECHA 2019 b, 2020, 2021 b, c, d, 2022 a, g

e) WHO 2001

f) NCBI 2022

g) Greim 2009

h) AGS 2015 (The cited reference "EBRC (2013) Summary & discussion of bioaccessibility & genotoxicity of vanadium substances. Report prepared for the Vanadium Consortium for the REACH registration of vanadium substances. 2013-01-17" is not accessible.)

i) Fraunhofer IME 2010 a

j) Fraunhofer IME 2010 b

k) Fraunhofer IME 2011 a

l) Fraunhofer IME 2011 b

m) Fraunhofer IME 2012

n) Fraunhofer IME 2014 b

o) Fraunhofer IME 2022 a

p) Fraunhofer IME 2014 a

q) Fraunhofer IME 2013 b

r) Fraunhofer IME 2013 a

s) Fraunhofer IME 2022 b

t) Vanadium Konsortium 2023

u) Fraunhofer IME 2023

Documentation and addenda are available for divanadium pentaoxide (Henschler 1992; Greim 2002, available in German only). Documentation for vanadium and its inorganic compounds, including all data for divanadium pentaoxide, was published in 2006 (Greim 2009). A re-evaluation has become necessary because numerous studies of vanadium compounds have subsequently been published. Unpublished toxicological studies from companies were made available to the Commission.

Divanadium pentaoxide is the most stable and, from a technical point of view, most important vanadium oxide. Divanadium pentaoxide is produced either by burning the finely dispersed metal in oxygen or by heating one of a large number of vanadium compounds such as **ammonium metavanadate** in the presence of air. Divanadium pentaoxide crystallizes from the melt into orange-coloured rhombohedral crystals.

Divanadium pentaoxide is used as a catalyst for the production of sulfuric acid by the contact process. It is used as catalyst material also in flue-gas purification, for example in waste incineration plants, and for a wide range of organic syntheses such as maleic anhydride and phthalic anhydride synthesis. Additionally, divanadium pentaoxide is used in the production of ferrovanadium and vanadium metal. Vanadates are likewise used for textile dyeing, for UV absorption, for colouring glass with yellow and green tints and for reducing the melting point in enamel manufacturing (ECHA 2022 a).

Solubility: The solubility of various vanadium compounds was determined in water according to OECD Test Guideline 105 and in Gamble's solution (simulated lung fluid) at 37°C. The values are listed in Table 1. Vanadium from divanadium pentaoxide may be present in water or body fluids partly in ionized form as cations or anions.

Vanadium compounds that are relevant under physiological conditions: The vanadyl cation (VO^{2+} , tetravalent vanadium) and the vanadate anion (VO_4^{3-} , pentavalent vanadium) are the only forms that are relevant in human tissues and in the blood under physiological conditions at pH 7. These readily convert from one form to the other by redox reactions. Vanadium oxides with low oxidation states such as divanadium trioxide (V_2O_3) are known to undergo oxidation steps to form divanadium pentaoxide. However, divanadium trioxide has a much lower bioavailability (6% as opposed to 100%) due to its lower solubility in biological fluids. As a result, toxic and, in some cases, carcinogenic effects are expected to be induced only after exposure to much higher concentrations of trivalent vanadium compounds (AGS 2015).

Background levels: The following values were obtained for the background levels of vanadium in the urine: 0.26 to 0.8 µg/l (mean range) (Schaller 1996, available in German only), 0.24 µg/l (95th percentile, 24-hour urine, German Environmental Specimen Bank 2002–2009) (Dobler et al. 2011), 0.166 µg/l (95th percentile, spontaneous urine) (Heitland and Köster 2006) and 0.13 µg/l (95th percentile, spontaneous urine) (Heitland and Köster 2004). Vanadium is ingested with food in daily doses of 0.09 to 0.34 µg/kg body weight (ATSDR 2018) or 0.2 to 0.3 µg/kg body weight (EFSA 2004).

Vanadium concentrations in air of 0.02 to 5 mg/m³ were determined in factories with exposure to vanadium (Ehrlich et al. 2008; IARC 2006).

1 Toxic Effects and Mode of Action

Vanadium compounds cause irritation and carcinogenic effects. A 2-year study with exposure to divanadium pentaoxide found that the incidence of bronchoalveolar adenomas and carcinomas was increased with statistical significance in B6C3F1 mice after exposure to 0.56 mg vanadium/m³ and in male F344/N rats after exposure to 0.28 mg vanadium/m³. Other effects observed at these exposure concentrations were histiocytic hyperplasia and degeneration in the lungs in addition to chronic inflammation, hyperplasia and degeneration in the larynx. Exposure of mice to a vanadium concentration of 0.56 mg/m³ in the form of divanadium pentaoxide for 16 days caused oxidative DNA damage in the lungs. In vitro studies as well as in vivo studies with exposure of rats and mice to different vanadium compounds by inhalation, the drinking water and intraperitoneal injection reported the induction of (oxidative) DNA damage, clastogenicity and aneugenicity. The repair of DNA damage caused by UV light or bleomycin was inhibited by vanadium in vitro.

Neurotoxic effects were observed in workers at a mean vanadium concentration of 0.216 mg/m³ and in rodents at a vanadium concentration of 0.8 mg/m³.

Studies investigating developmental neurotoxicity in vitro and in rats found that oligodendrocyte progenitor cells are more sensitive to vanadium than mature oligodendrocytes. The impairment of oligodendrocytes was associated with effects on myelination and motor impairment. The effect dose of vanadium was 1.25 mg/kg body weight and day in rats.

The available sources do not provide clear evidence that vanadium compounds induce sensitizing effects on the skin. There are no findings available for sensitizing effects on the airways.

2 Mechanism of Action

Studies investigating the mechanism of action that were published up to 2005 are described in detail in Greim (2009). The intracellular mechanisms of action are described below.

2.1 Inflammation, genotoxicity

Vanadate anions pass into the cells via anion channels while **vanadyl cations**, bound to transferrin, enter the cells by passive diffusion. Inside the cells, vanadate anions can be reduced to vanadyl cations in the cytoplasm. Reactive oxygen species are released as a product of this reaction. High concentrations of vanadate anions thus cause oxidative stress within the cell. Furthermore, vanadyl cations are oxidized to metavanadate and orthovanadate anions in a Fenton reaction with hydrogen peroxide; these anions bind to the free cysteine residues of proteins. Free cysteine residues are found at the active site of many enzymes and are responsible for the catalytic function. In concentration ranges below 1 µM, for example, the oxidation of these cysteine residues leads to the inactivation of tyrosine phosphatases. Tyrosine phosphatases regulate various intracellular signaling pathways via the dephosphorylation of proteins. For example, the inactivation of tyrosine phosphatase triggers mitogen-activated protein kinase cascades. In addition, different vanadium compounds intervene to varying degrees in regulating the expression and activation of cyclooxygenases. Metavanadates and orthovanadates induce the flow of calcium into the cell. A number of vanadium compounds (mostly orthovanadates) activate the calcium-dependent phospholipase A₂ in the cytoplasm at concentrations of 7.5 µM and above. As a result, more arachidonic acid is released, leading, in turn, to increased prostaglandin synthesis. Vanadium compounds activate IκB-kinase via NFκB-inducing kinase either directly or by generating reactive oxygen species (ROS), leading to the release of the transcription factor NF-κB. This is important for the regulation of the immune response, cell proliferation and apoptosis (Korbecki et al. 2015 a, b).

In the workplace study described below under Section 4.2 that investigated 52 workers involved in vanadium production, the capacity for repairing bleomycin-induced DNA damage was impaired in lymphocytes isolated from the blood of the workers in comparison with the capacity found in control persons. The repair of UVC-induced DNA damage was likewise inhibited in lymphocytes in vitro. The authors suggest that **divanadium pentaoxide** inhibits repair processes that are responsible for the repair of bleomycin-induced damage, such as homologous recombination, non-homologous end joining or base excision repair. Nucleotide excision repair, which is necessary for the repair of UVC-induced damage, is inhibited to a lesser degree (Ehrlich et al. 2008).

In 2 of 3 mouse strains, the occurrence of inflammatory signs correlated with an increased incidence of tumours after oropharyngeal aspiration of **divanadium pentaoxide** and initiation with 3-methylcholanthrene. Increased binding activities of the transcription factors NFκB and c-fos to the DNA and increased ERK1/2 activation in the lung tissue were observed in the exposed animals (Rondini et al. 2010).

A study of the cytotoxic mechanisms of pentavalent vanadium in concentrations of 0, 50, 100 or 200 µM in isolated mitochondria from rat hepatocytes demonstrated an increase in lipid peroxidation and reactive oxygen species with a simultaneous decrease in glutathione (GSH). In addition, the cytotoxicity of vanadium is associated with the rupture

of lysosomal membranes, the collapse of mitochondrial membrane potential and the release of cytochrome c (Hosseini et al. 2012, 2013).

Summary: Vanadium compounds interfere with signaling cascades that are responsible for proliferation, cell growth and DNA repair by generating reactive oxygen species and by promoting the activation/inhibition of many different kinds of enzymes. This may ultimately lead to tumour formation.

2.2 Neurotoxicity

2.2.1 In vivo

The findings obtained after exposure of mice by intraperitoneal injection and by inhalation demonstrated that vanadium enters the brain via the blood–brain barrier and is distributed into various regions (Avila-Costa et al. 2005; Folarin et al. 2017).

The initial mechanism of action for the neurotoxic effects is the generation of reactive oxygen species by various vanadium ions in different neuronal cells. The brain is particularly susceptible to oxidative stress because of its high lipid content. **Sodium metavanadate** impaired oligodendrocyte maturation, activated astrocytes and led to demyelination in newborn and juvenile mice after exposure via the dam's milk and subsequent intraperitoneal treatment. Demyelinated areas were found in the brain in the regions of the neocortex and of the hippocampus. Demyelination was found also in the corpus callosum and in other areas. Microglial activation and signs of neuroinflammatory processes were additionally observed (Azeez et al. 2016; Mustapha et al. 2014). Sodium metavanadate impaired myelination also in newborn and juvenile rats (Soazo and Garcia 2007; Todorich et al. 2011). The myelin fibre density decreased in male rats in several regions of the brain after intraperitoneal injection of sodium metavanadate. A reduced GSH/GSH disulfide ratio, increased lipid peroxidation and the generation of free radicals mediated by vanadium were observed in the hippocampus and cerebellum (Cuesta et al. 2011; García et al. 2004, 2005).

The number of dendritic spines in the striatum decreased after whole-body exposure of male CD1 mice to **divanadium pentaoxide**. These structures play an important role in neuronal plasticity (Avila-Costa et al. 2006).

Sodium metavanadate administered to male BALB/c mice by intraperitoneal injection led to morphological changes in the prefrontal cortex in addition to cell degeneration and death in the hippocampus and cerebellum. At the same time, superoxide dismutase (SOD) and catalase activities were reduced and malondialdehyde and H₂O₂ levels were increased. Microglial cells were activated (Adebiyi et al. 2018; Folarin et al. 2017). These effects increased over time (Folarin et al. 2018).

Groups of 6 mice (strain not specified, age unclear) were given sterile water or **sodium metavanadate** in doses of 3 mg/kg body weight daily by intraperitoneal injection for 1 month. The study was carried out to investigate 3 new compounds for the treatment of neurotoxic effects. Vanadium was used to induce neurotoxicity. Exposure of the mice to vanadium led to cytotoxicity and various morphological changes in the Purkinje cells/dendrites of the CA1 region of the hippocampus and the cerebellum. These changes were characterized by cell clustering, loss of apical dendrites, loss of layering patterns and decreased vacuolation. These effects are signs of a deteriorating cell function that ultimately leads to the destruction of cell structures and cell death. Various immunohistochemical assays were used to identify these effects (Ladagu et al. 2020).

After intranasal application of 182 µg of **divanadium pentaoxide** in 50 µl of water in male C57BL/6 mice 3 times a week for 1 month, the findings revealed a statistically significant decrease in the olfactory bulb weights by 26%. In the glomerular layer of the olfactory bulb, tyrosine hydroxylase was decreased by 84%, dopamine by 82% and its metabolite by 88%. Marked proliferation of astrocytes in the glomerular layer was observed. Olfactory perception of female pheromones was impaired in the mice. According to the authors, these results suggest adverse effects on the olfactory bulb, which may lead to neurochemical interference and neurobehavioural disorders (see also Table 8) (Afeseh Ngwa et al. 2014).

2.2.2 In vitro

A number of different signalling pathways were activated in vitro in mesencephalic dopamine-producing neuronal cells by oxidative stress induced by exposure to **divanadium pentaoxide**. There was evidence for the increased release of cytochrome *c* from the mitochondria into the cytosol and increased activation of caspase-9, caspase-3 and protein kinase C delta. These processes may lead to DNA fragmentation and apoptosis (Afeseh Ngwa et al. 2009).

Vanadium was found to cause immunological effects by inhibiting cytokine-inducible functions and stimulating immune activity by increasing cytokine production, which may lead to inflammation. Vanadium induced cytotoxic effects in isolated neurons or glial cells (Zwolak 2014).

2.3 Gene expression

Treatment of immortalized human bronchial epithelial cells (BEAS-2B cells) with 10 µM **sodium metavanadate** for 8 weeks followed by a growth phase in soft agar without metals for 3 weeks altered gene expression patterns associated with the uncontrolled growth of transformed cells. These changes remained detectable in transformed cell clones for several generations even if there was no further exposure to vanadium. The changes included the downregulation of an important DNA repair gene (*BRCA1*), the upregulation of *SATB2* (also known as DNA-binding protein SATB2), a gene that activates the transcription of numerous genes by changing the chromatin structure and increases the activity of other transcription activators, and the upregulation of an enzyme responsible for demethylating histone (*H3K4*), resulting in the silencing of certain genes (Clancy et al. 2012). The same cell line was used to study gene expression changes induced by pentavalent vanadium. Incubation of the cells with 10 µM of **sodium metavanadate** for 5 weeks altered more than 460 genes, including genes for cell proliferation, differentiation, adhesion and DNA repair. Many of these changes remained detectable 11 weeks after treatment. The migration ability of the cells was likewise increased after incubation for 4 weeks and the number of transformed cells increased with the dose (Passantino et al. 2013).

Numerous genes that are responsible for inflammatory reactions and the immune response were induced in human lung fibroblasts after treatment with **divanadium pentaoxide**, whereas genes that control the cell cycle and cell adhesion were inhibited. In addition, changes were observed in the expression of genes that play a role in oxidative stress (Ingram et al. 2007).

Hyperplasia of the alveolar epithelium, inflammation and degeneration of the bronchial epithelium were observed in mice that were exposed to a **divanadium pentaoxide** concentration of 2 mg/m³ for 90 days. In a comparison with other substances that induce lung tumours, 1026 genes were differentially expressed, 483 of which were unique to divanadium pentaoxide. According to a functional ontology enrichment analysis, genes in the lungs were affected that are responsible for lipid metabolism, cAMP signalling and inflammatory pathways. However, no changes were observed in genes associated with the cell cycle, proliferation, DNA damage or oxidative stress (Black et al. 2015). Gene expression analysis provides data for a given moment in time. The results offer information about a non-genotoxic mechanism of action, specifically interaction with the phosphate balance and the damage to the membrane with which this is associated. The processes observed under the conditions of this study are not necessarily the same as those that occur at low concentrations at earlier time points, such as the effects reported by Schuler et al. (2011).

2.4 Other effects

The irritation induced by **vanadium trichloride** is probably caused by hydrolysis of the compound on moist skin (Bircher 2018).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

3.1.1 Humans

Workplace studies show that **divanadium pentaoxide** is absorbed after inhalation exposure (AGS 2015). In 60 workers of an iron ore mine who were exposed to vanadium concentrations of 0.002 to 0.42 mg/m³ (mean shift value 0.028 mg/m³), vanadium levels were determined in the serum directly after the shift and in the 18-hour urine. Mean vanadium concentrations of 220 nmol/l serum and 260 nmol/l urine were reported (Kiviluoto et al. 1979 a). No data were provided about the length of the shift.

In 8 workers of an iron ore mine who were exposed mainly to **divanadium pentaoxide**, vanadium levels in the blood were determined at the beginning and at the end of a holiday lasting 3 or 16 days. The urine samples were collected at the time points 0 to 8, 8 to 16, 16 to 24, 24 to 48 and 48 to 72 hours as well as 16 days after the last exposure. The vanadium concentrations in the workplace air were 0.03 to 0.77 mg/m³ (mean value 0.28 mg/m³) (no data for the length of the daily shift). The percentage of the respirable fraction (< 5 µm) was on average 58% (range 41%–71%). The findings reveal that the vanadium that was absorbed via the lungs was excreted with the urine in 2 stages, the first quite rapidly and the second more slowly. The vanadium concentrations in the urine were 73 ± 50 nmol/mmol creatinine after 8 hours, 46 ± 24 nmol/mmol creatinine after 3 days without exposure and 48 ± 26 nmol/mmol creatinine after 16 days. Significant correlations between the concentration in the factory air and the serum concentration or the creatinine-adjusted urine concentration were not established. The serum concentration correlated with the urine concentration at the beginning of the holidays. The vanadium concentration determined in the serum at the end of the work shift was 393 ± 223 nmol/l; this value was not increased with statistical significance relative to the value determined during the holidays (225 ± 83 nmol/l) (Kiviluoto et al. 1981 b).

In 20 workers who overhauled a large oil-fired boiler for 10 hours a day on 6 days a week and were exposed to vanadium in concentrations between 0.36 and 32.19 µg/m³ (mean 19.1 µg/m³), the urinary vanadium concentrations were 0.83 mg/g creatinine before the beginning of the shift and 1.52 mg/g creatinine after the shift (Hauser et al. 1998).

Various determinations taken at a workplace with exposure to a **divanadium pentaoxide** equivalent at a concentration level of 0.1 mg/m³ revealed urinary vanadium concentrations of about 200 to 400 µg/l urine. A vanadium concentration of 0.8 µg/l urine was determined in persons without noteworthy exposure to vanadium (Leuschner et al. 1994).

Workers found to have vanadium levels of 7.73 ± 7.86 µg/l serum (workers without exposure 3.43 ± 3.18 µg/l) excreted vanadium in amounts of 14.57 ± 13.31 µg/g creatinine (workers without exposure 1.13 ± 0.26 µg/g creatinine) (Ivancsits et al. 2002).

3.1.2 Animals

3.1.2.1 Oral administration

Groups of 12 female Sprague Dawley rats given a single gavage dose of 0 or 5 µmol [⁴⁸V] **sodium metavanadate** (= 610 µg/animal) excreted 17.5% of ⁴⁸V with the urine and 69% with the faeces over a period of 4 days (Wiegmann et al. 1982).

Sodium metavanadate was given orally for 7 days to female Wistar rats in concentrations of 100 mg/kg feed (41.49 mg vanadium/kg feed); this was equivalent to a daily vanadium dose of 7060 ± 574 µg/kg body weight. A total of 16.5% was absorbed, 0.86% of the dose was excreted with the urine and 83.5% with the faeces. As a result, 15.7% remained in the organism. The highest vanadium concentration of 1.84 µg/g was recovered in the tibia, followed by concentrations in the femur, spleen and kidneys. The lowest concentration of 0.13 µg/g was found in the brain (Adachi et al. 2000 b).

Sodium metavanadate (5 or 25 mg/kg feed, about 0.18 or 2.1 mg vanadium/kg body weight and day) given orally for 14 days to groups of 7 female Sprague Dawley rats was absorbed in amounts of $43\% \pm 13.7\%$ and $39\% \pm 20.3\%$, respectively (Bogden et al. 1982).

A total of 36 male Sprague Dawley rats were given vanadium in the form of **ammonium metavanadate** in a single gavage dose of 1.8 mg/kg body weight. Oral absorption was 4.2% after 24 hours (Al-Bayati et al. 1991).

About 16% of the **vanadyl sulfate** given to groups of 6 or 7 male Wistar rats for 21 days in daily gavage doses of 37.5 or 75 mg/kg body weight (7.6 or 15.1 mg vanadium/kg body weight and day) was absorbed (Azay et al. 2001).

Groups of 8 male Wistar rats were given **vanadyl sulfate** in the drinking water in concentrations of 0.5, 0.75 or 1.25 g/l over a period of 52 weeks. Vanadyl sulfate was administered to Group 1 in a concentration of 0.5 g/l for 52 weeks, to Group 2 in a concentration of 0.5 g/l in week 1 and 0.75 g/l for the remaining 51 weeks and to Group 3 in a concentration of 0.5 g/l in week 1, 0.75 g/l in week 2 and 1.25 g/l for the remaining 50 weeks. At the end of administration, the vanadium concentrations in the plasma had increased with the concentration (0.2 ± 0.04 , 0.33 ± 0.04 , 0.46 ± 0.11 µg vanadium/ml). After the 16-week observation period, however, the vanadium levels were below the limit of detection of 0.01 µg/ml. The highest vanadium levels were found in the bones (6.45, 11.0 and 11.8 µg vanadium/g), followed by the kidneys, testes, liver, pancreas and brain. Small amounts of vanadium were still detectable in all tissues after the observation period. However, the vanadium concentration in the bones was 5.32 µg/g (the pooled results from a total of 8 animals from all 3 dose groups) and thus had decreased only by about half (Dai et al. 1994).

A publication available only as an abstract and thus unsuitable for use in the evaluation reported that 2.5% of **vanadyl dichloride** was absorbed after gavage administration to male Sprague Dawley rats for 4 days (no other details; ECHA 2022 a).

In a publication that included only a very brief description of the method and the results and is thus not suitable for the evaluation, female rats (between 4 and 7 animals) given vanadium in the form of **divanadium pentaoxide** in gavage doses of 0.3 mg/kg body weight absorbed $2.6\% \pm 1.6\%$ over a period of 3 days (Conklin et al. 1982).

Twenty-four hours after 100 ng of tetravalent or pentavalent ⁴⁸**vanadium** (no other details) in 0.5 ml sodium chloride solution were given once orally to groups of 4 rats, 11% to 12% of the vanadium dose was recovered in the liver and 5% to 7% in the kidneys. No differences were found between tetravalent or pentavalent vanadium (Edel and Sabbioni 1988).

Groups of 5 male and 5 female SD rats were given **vanadyl sulfate** or **sodium metavanadate** via the drinking water. Vanadyl sulfate was given in concentrations of 0, 83.8, 167.5, 335, 670 or 1340 mg/l and sodium metavanadate in concentrations of 0, 125, 250, 500, 1000 or 2000 mg/l drinking water for 14 days. The relative concentrations of vanadium in the blood, plasma and liver (in ng vanadium/ml per mg of applied vanadium) were higher in the groups given pentavalent metavanadate than in those given tetravalent vanadyl sulfate, which the authors propose is the reason for the higher toxicity of pentavalent vanadium compounds (Harrington et al. 2021).

Vanadyl sulfate and **divanadium pentaoxide** (tetravalent and pentavalent vanadium compounds) are able to pass the placental barrier (Greim 2009). After vanadium was given to mice as vanadyl sulfate pentahydrate in gavage doses of 7.6, 15.1, 30.2 mg/kg body weight and day, the vanadium concentrations were increased in the placenta with statistical significance and, to a lesser degree, in the foetus (Paternain et al. 1990).

Summary of the findings for oral absorption: The studies carried out by Wiegmann et al. (1982), Adachi et al. (2000 b) and Azay et al. (2001) with repeated exposure to vanadium provide a detailed description of the method and the results. On the basis of the study findings and following the recommendations made in the REACH dossier (ECHA 2022 e), 16% of the dose of vanadium compounds is expected to be absorbed after oral administration.

3.1.2.2 Inhalation

There are no data for absorption after inhalation exposure or the elimination of vanadium metal dust (ECHA 2022 e).

Divanadium pentaoxide is able to pass the blood–brain barrier following inhalation exposure. Groups of 48 male CD1 mice were exposed whole-body to divanadium pentaoxide concentrations of 0 or 1.4 mg/m³ for 1 hour twice a

week over a period of 1 to 12 weeks. After only 1 week, the vanadium concentration in the brain was increased with statistical significance; however, the concentration did not increase any further over the following weeks. Damage to the ependymal cells was observed in a concentration-dependent manner (Avila-Costa et al. 2005).

Groups of 5 male F344 rats were exposed nose-only either to **divanadium pentaoxide** or **sodium metavanadate** (about 0.1 mg vanadium/m³) for 5 hours a day on 5 consecutive days. The exact concentrations of the vanadium compounds used for exposure and their mass median aerodynamic diameters (MMAD) are shown in Table 2. The vanadium levels determined in the lungs directly after the last exposure were considerably higher in the groups exposed to **divanadium pentaoxide** than in those exposed to **sodium metavanadate** (Cohen et al. 2007).

Groups of 60 female rats were exposed to **divanadium pentaoxide** concentrations of 0, 1 or 2 mg/m³ for 6 hours a day, on 5 days a week, for 16 days. The MMADs and vanadium levels in the lungs are given in Table 2 (NTP 2002).

Tab. 2 Vanadium levels in the lungs after 5-day exposure (male rats, Cohen et al. 2007) and after 16-day exposure (female rats, Greim 2009; NTP 2002)

Vanadium compound (exposure period)	Exposure concentration [µg V/m ³]	MMAD [µm]	Amount in lung tissue [ng V/g]
NaVO ₃ (5 days)	110.4	0.21	170
V ₂ O ₅ (5 days)	132.62	0.74	1157
V ₂ O ₅ (16 days)	560	1.2	5040
	1120	1.0/1.3	9890

MMAD: mass median aerodynamic diameter; V: vanadium

Groups of 6 female B6C3F1/Hsd mice were exposed nose-only to **divanadium pentaoxide** concentrations of 0, 0.25, 1 or 4 mg/m³ (about 0, 0.14, 0.56, 2.24 mg vanadium/m³) in aerosol form for 6 hours a day over a period of 16 days. Vanadium was not detected in the blood of the group exposed to a vanadium concentration of 0.14 mg/m³ (limit of detection for vanadium: 13 µg/l blood). Vanadium concentrations of 8.02 ± 0.84 µg/g tissue were found in the lungs. In the 2 high exposure groups, vanadium was detected in the blood in concentrations of 51.15 ± 6.02 and 160.13 ± 16.48 µg/l, respectively, and in the lungs in concentrations of 31.01 ± 2.22 and 64.35 ± 7.45 µg/g tissue, respectively (Schuler et al. 2011).

In the study described below, the animals were exposed for 6 hours a day on 5 days a week. After 14-day exposure of female F344 rats to **divanadium pentaoxide** concentrations of 0.5, 1 or 2 mg/m³ (0.28, 0.56 or 1.12 mg vanadium/m³), the lung burden was cleared with a half-life of 4.4 to 5.0 days. After exposure for 18 months, the half-life for lung clearance was 37, 59 and 61 days, respectively, and thus considerably higher than the values reported by the 14-day study. After 14-day exposure of female B6C3F1 mice to **divanadium pentaoxide** concentrations of 1, 2 or 4 mg/m³ (0.56, 1.12 or 2.24 mg vanadium/m³), the half-life for lung clearance was 2 to 3 days. In 3 groups of female mice that were exposed to **divanadium pentaoxide** concentrations of 1, 2 or 4 mg/m³, respectively, for 18 months, the half-lives were 6, 11 and 14 days, respectively. Vanadium was thus eliminated from the lungs of mice about 6 times faster than from those of rats. The exposure period of 18 months led to a slight, but statistically significant, increase in the vanadium concentrations in the blood and to a statistically significant increase in lung weights and in the vanadium concentrations in the lungs. In both species, this was dependent upon the external exposure levels. The increased occurrence of pathological changes in the lungs that was observed with an increase in the concentration and duration of exposure also affected deposition in the lungs (Dill et al. 2004; Greim 2009). Vanadium seems to be eliminated more rapidly from the lungs after short periods of exposure than after longer periods. There were marked species differences in lung clearance.

3.1.2.3 Intratracheal instillation

Three hours after administering pentavalent or tetravalent ⁴⁸vanadium (no other details) (40 ng vanadium/kg body weight) to groups of 4 male Sprague Dawley rats by a single intratracheal instillation, 15% and 17%, respectively, of the applied dose was recovered in the lungs in addition to 2.8% in the liver and 2% in the kidneys. Therefore, about 80% to 85% of the vanadium was eliminated by clearance from the lungs within 3 hours. About 2% of the vanadium

remained in the lungs after 12 days. In the cytosol of the lung cells, vanadium was bound mainly to proteins with a molar mass > 100 000 daltons and to low-molecular components (< 5000 daltons). The authors suggest that interaction between vanadium and high-molecular components may lead to the accumulation of vanadium in the lungs after long-term exposure (Edel and Sabbioni 1988).

One day after intratracheal instillation of ⁴⁸**vanadyl trichloride** in male Wistar rats, more than 50% had been eliminated from the lungs (Oberg et al. 1978).

3.1.2.4 Dermal application

No experimental data are available for the absorption of vanadium and vanadium compounds through the skin. However, models cannot be used to estimate the levels of absorption through the skin because the skin absorption models have not been validated for metal compounds.

3.2 Metabolism

The element **vanadium** is not metabolised. However, vanadium is able to adopt multiple oxidation states and convert between them by redox reactions (ECHA 2022 e). Under physiological conditions in the tissues and in the blood of humans at a pH of 7, only the vanadyl cation (VO²⁺, tetravalent vanadium) and the vanadate anion (VO₄³⁻, pentavalent vanadium) are of significance. The cation and anion readily convert from one state to the other by redox reactions (Greim 2009). Vanadium undergoes reduction and reoxidation in the presence of reducing compounds such as GSH as well as NADPH, NADH and oxygen and is thus subject to redox cycling (ECHA 2022 a).

4 Effects in Humans

4.1 Single exposures

There are no new data available.

Two workers who shoveled **ammonium vanadate powder** for 2 to 3 or for 6 hours, respectively, and 2 other workers who worked for several hours in **divanadium pentaoxide** refineries developed the following symptoms after a delay of hours up to 3 days: a productive or non-productive cough, dyspnoea, wheezing, swollen nasal mucosa, a sore throat and hoarseness as well as nausea. The tongues of all 4 exposed persons exhibited green discoloration and additional green discoloration was found on the skin of 1 worker on the fingers, upper thighs and scrotum. Two of the exposed persons reported eye irritation. The irritation to the respiratory tract lasted several days to weeks and recurred with later exposure. No data for the level of exposure were provided (Greim 2009).

A concentration–effect relationship was detected in 11 volunteers after exposure to **divanadium pentaoxide** smoke and dust (particle size: 98% < 5 µm; no data for the length of exposure): the inhalation of divanadium pentaoxide smoke in a concentration of 0.4 mg/m³ (0.22 mg vanadium/m³) caused marked irritation in all volunteers, slight irritation was observed in only 5 persons at 0.16 mg/m³ (0.08 mg vanadium/m³) and no irritation was noticeable at 0.08 mg/m³ (0.04 mg vanadium/m³) (Greim 2009). Exposure to divanadium pentaoxide dust by inhalation in a concentration of 1 mg/m³ (particle size: 98% < 5 µm; 0.56 mg vanadium/m³) for 8 hours induced a sporadic cough after 5 hours that intensified after 7 hours. The volunteers who were exposed to a concentration of 0.25 mg/m³ (0.14 mg vanadium/m³) had a mild cough the following morning. The cough was more severe in the volunteers exposed to a concentration 0.1 mg/m³ (0.056 mg vanadium/m³) with increased production of phlegm. Subjective signs of irritation were not reported immediately during or directly after exposure (Greim 2009).

4.2 Repeated exposure

A study investigated the lung function of 63 workers at a **vanadium pentaoxide** factory who had worked at the factory for an average of 11 years, but at least for 4 months, and of 63 control persons matched for age and smoking habits. The cell count was determined in smears taken from the nasal and palatal mucosa. Respiratory symptoms were ascertained by questionnaire. The lung function tests were carried out in the summer of 1975 and X-rays were taken in April 1976. Vanadium concentrations in the breathing zone of the workers were determined from March to May 1976 by personal air monitoring over an entire shift. The values obtained for the total dust fraction of vanadium were in the range of 0.002 to 0.42 mg/m³. The mean shift value for vanadium was 0.028 mg/m³. About 20% of the particles were respirable (< 5 µm). Earlier data for vanadium exposure (total dust) that were collected from March 1970 to May 1975 revealed concentrations in the range of 0.01 to 1.9 mg/m³ in the work areas adjacent to the smelting furnaces and up to 10 mg/m³ during the grinding process. Vanadium concentrations of 0.22 ± 0.14 µmol/l in the serum and 0.26 ± 0.17 µmol/l in the urine (18-hour urine) were determined in 60 exposed persons. Vanadium was not detected in the urine of the 24 control persons (limit of quantification 0.04 µmol/l) and no data were provided for the serum concentrations (Kiviluoto et al. 1979 a). The haematological parameters did not differ with statistical significance between the exposed and control persons. In 16 to 18 exposed persons, the biochemical parameters serum albumin and bilirubin were increased with statistical significance and serum chloride, serum urea and conjugated bilirubin were decreased with statistical significance in comparison with the values determined in 16 to 18 control persons (Kiviluoto et al. 1981 a). The results of an anterior rhinoscopy did not show any significant differences between exposed persons and control persons when compared using McNemar's test. No effects on the mucous membrane of the palate, the posterior pharyngeal wall, the larynx and the vocal cords were observed. X-rays revealed fibrotic foci in the lungs of 4 control persons and of 2 exposed persons. In the group of 63 exposed persons, 25 reported wheezing on most days or during the night; this effect was increased with statistical significance in comparison with the findings in the control persons (11 of 63). In the nasal swabs, the number of neutrophils was increased in 16 exposed persons in comparison with the number found in control persons and differed with statistical significance. Biopsies of the nasal mucosa of 15 exposed persons revealed an increase in the number of plasma cells and lymphocytes ("round cells"); these results likewise differed with statistical significance from those determined in control persons. A second set of examinations was carried out with 31 employees after 7 to 11 months. The number of cells detected in biopsy specimens of the nasal mucosa did not differ with statistical significance across the age groups (19–29 (n = 18), 30–39 (n = 14), 40–56 years (n = 31)). The number of eosinophils remained unchanged in all groups. In the exposed group, no correlation was found between the number of cells and the duration of exposure to vanadium (4–109 months (n = 23), 110–169 (n = 20), 170–241 (n = 20)). The lung function values did not differ with statistical significance between the exposure and control groups, not even when the comparison was based on the duration of exposure. The authors assume that vanadium causes irritation in the nose (Kiviluoto 1980; Kiviluoto et al. 1979 b).

In the following studies, employees were exposed by inhalation to different vanadium compounds (Woodin et al. 2000; Zhou et al. 2007 in US EPA 2009). The compounds were not characterized further. There may have been additional exposure to other substances.

Eighteen boiler maintenance workers (aged 26 to 61 years, 7 smokers) were studied for 3 weeks to examine the frequency and severity of respiratory symptoms of the upper and lower airways. While working inside the boilers, the boilermakers were exposed to fuel oil ash that contained vanadium. The control group was made up of 11 workers (aged 30 to 55 years, 2 smokers) who worked only outside of the boilers. None of the workers exhibited asthma symptoms during the maintenance work. All participants answered questions about respiratory infections (such as the common cold) at the beginning of the study and immediately before and during work. Five times a day, the workers rated the severity of the symptoms in the upper and lower airways on a scale from 0 to 3. They were asked further questions about the duration of the work, the work area, welding work and the use of protective clothing. The exposure levels to respirable dust (PM₁₀), metals and ozone were determined by personal air monitoring and stationary determinations. The geometric mean of the vanadium levels found in the boilermakers was 1.2 µg/m³ before beginning with the maintenance work and 8.9 µg/m³ while carrying out the work. The geometric mean of the vanadium levels found in the control group was in the range of 1.1 to 1.4 µg/m³. The concentrations of cadmium, chromium, manganese, lead, arsenic and nickel

were very low at 1 to 3 orders of magnitude under the TLV (threshold limit values) valid in 1996. Four dose groups were formed based on the amount of vanadium estimated to be present in the lungs and nose and the PM₁₀ levels in the lungs and nose (Table 3).

Tab. 3 Dose groups based on the vanadium and PM₁₀ levels in the lungs and nose (Woodin et al. 2000)

Quartiles	Lungs (µg V)	Nose (µg V)	Lungs (mg PM ₁₀)	Nose (mg PM ₁₀)
Quartile 1	≤ 0.9	≤ 2.5	≤ 0.2	≤ 0.6
Quartile 2	> 0.9 ≤ 5.3	> 2.5 ≤ 23.2	> 0.2 ≤ 0.5	> 0.6 ≤ 1.6
Quartile 3	> 5.3 ≤ 22.3	> 23.2 ≤ 68.3	> 0.5 ≤ 1.5	> 1.6 ≤ 5.24
Quartile 4	> 22.3	> 68.3	> 1.5	> 5.24

PM₁₀: particulate matter < 10 µm; V: vanadium

During the overhaul, 72% of the boilermakers reported symptoms of the lower airways (27% in the control group) and 67% reported symptoms of the upper airways (36% in the control group). Symptoms of the upper and lower airways occurred more frequently and with greater severity in the workers carrying out the maintenance work than in the workers of the control group. These differences were most pronounced while carrying out work inside the boiler. A dose–response relationship for the frequency and severity of the symptoms in the lower and upper respiratory tract was established for the 3 lower dose groups that was statistically significant for vanadium and PM₁₀. The severity and frequency of the symptoms in the high dose group were of the same order of magnitude as those in the second-lowest dose group. The authors suggest that this is due to the healthy worker effect (Woodin et al. 2000).

More negative moods and lower performance in neuropsychological tests (Santa Ana dexterity, Benton visual retention and pursuit aiming) were observed in 106 workers who were exposed to mean vanadium concentrations (not further specified) of 0.034 to 0.805 mg/m³ compared with the findings in workers without exposure. The results are available only in the form of a secondary citation (Zhou et al. 2007 in US EPA 2009).

In a factory that manufactured products containing vanadium, 463 workers were exposed to **vanadium smoke** in a mean concentration of 0.216 mg/m³. No information was provided whether the determinations were taken by stationary or personal air monitoring. Control persons from a comparable factory were exposed to **vanadium smoke** in a mean concentration of 0.013 mg/m³. The levels of neurotoxic metals such as lead and manganese were not determined. The participants ranged in age between 20 and 60 years; the average age of the exposed persons was 39.5 and of the control persons 37.1 years. Both groups were made up of persons of a similar socioeconomic status. Exposure to other toxic substances was not reported. The groups did not differ in terms of smoking habits and alcohol consumption. The results of the neuropsychological tests were evaluated using a general linear model that took possible confounders into consideration; however, the confounders were not described in further detail. Overall, performance had declined with statistical significance in the exposed persons in 7 of the 13 evaluated parameters. Adverse effects on cognitive performance (number symbol test) and memory performance were observed. Reaction time parameters and manual dexterity did not decline. Normally, this motor skills parameter would be affected in groups exposed to varying concentrations of manganese. This indirectly confirms that the groups are suitable for comparison. The results shown in Table 4 suggest that longer periods of exposure have a greater effect on performance in several tests (number symbol test, memory test). The behavioural effects were promoted by longer P3 (P300) latencies, an electrophysiological indicator for auditory information processing. Overall, the results of the study are reliable. A medium-range effect size was determined for several tests based on a Cohen's *d* effect size of greater than 0.5. The results are shown in Table 4 (Li et al. 2013).

Tab. 4 Mood states and the results of neuropsychological tests (covariates: sex, age, cultural group) (Li et al. 2013)

Test items	< 10 years of employment		≥ 10 years of employment	
	Control persons (n = 32)	Exposed persons (n = 53)	Control persons (n = 219)	Exposed persons (n = 410)
Mood states				
anger/hostility	19.4 ± 6.2	21.5 ± 5.3	21.5 ± 6.1	23.1 ± 8.1*
confusion	12.9 ± 2.9	14.1 ± 3.5	14.2 ± 3.5	14.4 ± 4.2
depression	23.7 ± 6.8	26.7 ± 7.8*	25.9 ± 7.6	27.3 ± 11.0*
fatigue/inertia	12.9 ± 5.1	14.5 ± 3.7	13.4 ± 3.5	14.4 ± 4.4*
tension/anxiety	15.2 ± 4.1	16.8 ± 4.7	16.6 ± 4.1	17.1 ± 5.7
vigour/activity	22.2 ± 6.2	22.3 ± 6.0	19.6 ± 5.3	17.3 ± 6.1**
Neuropsychological tests				
simple reaction time				
fastest time	257.4 ± 49.2	256.6 ± 32.5	275.5 ± 53.7	278.2 ± 40.0
slowest time	613.6 ± 228.8	521.8 ± 198.4	603.1 ± 233.4	619.2 ± 284.4
average time	352.7 ± 68.8	329.4 ± 47.0	370.0 ± 81.9	369.0 ± 70.3
error dot score	0.5 ± 0.7	0.6 ± 0.8	0.4 ± 0.6	0.6 ± 0.8**
Digit spans				
digit span (forward)	12.6 ± 1.5	11.2 ± 1.5*	12.4 ± 1.5	11.5 ± 1.8**
digit span (backward)	7.5 ± 2.5	7.2 ± 2.4	7.0 ± 2.4	6.3 ± 2.2*
Dexterity tests				
preferred hand	15.7 ± 2.3	16.4 ± 2.6	16.1 ± 2.8	15.8 ± 2.6
non-preferred hand	15.2 ± 2.3	15.1 ± 2.3	14.8 ± 2.4	14.8 ± 2.5
digit symbol test	64.5 ± 11.9	65.9 ± 10.4	57.9 ± 8.8	53.5 ± 11.7**
Benton visual retention test	7.7 ± 1.4	7.8 ± 1.3	7.5 ± 1.6	7.0 ± 1.6
Pursuit aiming				
total pursuit aiming	117.1 ± 26.1	114.0 ± 35.9	108.1 ± 24.2	108.1 ± 28.4
correct pursuit aiming	84.8 ± 32.8	91.4 ± 28.0	90.1 ± 24.3	84.1 ± 25.7
error pursuit aiming	32.3 ± 34.5	28.6 ± 25.1	18.0 ± 22.0	24.1 ± 24.6*

*p < 0.05; **p < 0.01

A study of 49 workers (aged 41.4 ± 7.3 years) who had been occupationally exposed to vanadium on average for 12.2 years (± 7.9) (no other details) found that vanadium concentrations in the urine and blood correlated with cognitive performance in the following tests: block design test, digit span test, simple reaction time test, digit symbol substitution test and choice reaction test. The results were compared with those of a control group without exposure (aged 40.5 ± 7.7 years). Both groups were made up of persons with a similar socioeconomic status who had no pre-existing neurological and psychological conditions. The groups were adjusted for age and verbal intelligence. In the groups of exposed persons, mean vanadium concentrations of 14.4 ± 13.8 µg/l (2.1–95.3 µg/l) were determined in the urine and of 7.5 ± 7.7 µg/l (2.2–46.4 µg/l) in the serum. The concentrations in the groups without exposure were 0.4 ± 0.3 µg/l (0.07–1.35 µg/l) in the urine and 0.8 ± 0.6 µg/l (0.3–3.12 µg/l) in the serum. The performance of the exposed workers declined with statistical significance in the block design test and in the digit substitution test in comparison with the results of the workers in the control group. After taking the length of exposure into consideration and adjusting for age, the vanadium concentrations in the serum correlated with statistical significance with the results of the block design test, as did the concentrations in the urine and the results of the block design test and the digit substitution test. The authors concluded that effects on visuospatial abilities and attention first become noticeable at the middle vanadium concentrations of 14.4 µg/l urine and 7.5 µg/l serum (Barth et al. 2002).

The studies of Cavallari et al. (2008), Lagorio et al. (2006) and Kim et al. (2004) are not suitable for evaluating vanadium because of additional exposure to several metals such as aluminium, copper, iron, manganese, nickel, lead and zinc.

4.3 Local effects on skin and mucous membranes

Local irritation of the eyes and airways was observed after repeated exposure to different vanadium compounds in the form of dust or smoke. Irritation of the skin occurred only in isolated cases (Greim 2009).

Other, more recent findings are not available.

4.4 Allergenic effects

4.4.1 Sensitizing effects on the skin

There are several studies and case reports on the suspected sensitising effect of vanadium or vanadium compounds (see Table 5 and 6). However, the documentation for several findings does not include all aspects that are relevant for the evaluation. For example, information about the primary route of exposure was often not included. In many cases there was additional exposure to other substances and a clear exposure–effect relationship can thus not always be established. Some studies were conducted with very large amounts of substance, others did not provide information about the course of the reaction severity over time or about the time points of determination. Furthermore, important aspects of the methods used did not comply in some cases with the standards for conducting patch tests as described in the guidelines (Deutsche Dermatologische Gesellschaft e.V. 2019).

The German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe (DKG)) has not made a recommendation for formulations of vanadium or other inorganic vanadium compounds that are suitable for the diagnosis of type IV sensitization (Geier et al. 2008). An approved test formulation is not commercially available in Germany at present. None of the test series recommended by the DKG include vanadium or any of the vanadium compounds.

In analogy to chlorides of other transition metals such as manganese chloride and rhodium chloride, most of the reactions that are assumed to be positive should be assessed as irritation, particularly the weak “positive” decrescendo reactions to **vanadium trichloride**. The hydrolysis of vanadium trichloride on the moist skin is probably the primary cause of the irritation (Bircher 2018). As a result, reactions produced by vanadium (compounds) in patch tests that are interpreted as “positive”, particularly reactions to vanadium trichloride, should be reviewed critically (Geier et al. 2008; Geier and Schubert 2021).

In most of the clinical studies, patch tests were carried out with a 1% formulation of **vanadium trichloride** or a 5% formulation of **elemental vanadium** in petrolatum (Table 5 and 6). In the patch tests performed with 5% **vanadium**, 1 of 39 persons developed irritation and 1 person produced a questionable positive reaction. Of the 39 persons tested with 1% **vanadium trichloride**, 1 person developed irritation, 2 persons produced questionable positive reactions and 10 persons a 1+ reaction (Spiewak 2018).

4.4.1.1 Occupational exposure

A study examined 316 persons suspected of having occupational contact dermatitis. Irritant contact dermatitis was confirmed in 118 persons. According to the study report, 7 of the 118 were exposed to metals, 1 of them explicitly to vanadium (no other details). No positive reactions to **vanadium trichloride** were obtained (Friis et al. 2014). However, the number of persons tested with vanadium trichloride was not specified.

Only in one case was occupational exposure to vanadium reported as the suspected cause of allergic contact dermatitis (see Table 6, “Possible occupational exposure”). The case involved a 39-year-old male patient who had worked at a steel factory for 8 years and had pruriginous eczema of the hands that had persisted for 6 months. The symptoms improved only slightly during treatment with corticosteroids; however, the symptoms improved markedly at the weekends and during his annual holidays. Patch tests yielded a 2+ reaction to 1% vanadium trichloride on days 2 and 4. A lymphocyte transformation test (LTT) carried out with a very high concentration (1 mg vanadium trichloride/ml, no data for other tested concentrations) produced positive results (no other details), while LTTs performed with potassium dichromate (0.5 mg/ml) and aluminium chloride (6.5 mg/ml) yielded negative results. Negative results for vanadium trichloride were

obtained with 5 control persons in the patch test and the LTT (Garcia-Nunez et al. 2019). The concentration tested in the LTT is highly questionable. Furthermore, the report does not clearly document the exposure conditions.

4.4.1.2 Non-occupational exposure

A patient who had eczema on her wrist, probably caused by her ceramic wristwatch, produced a positive reaction to **vanadium trichloride** (2+ reaction to 0.1% vanadium trichloride on days 2 and 4), but a negative reaction to elemental vanadium (Jordan et al. 2018). Again, the report does not clearly document the exposure conditions.

4.4.1.3 Implants

Most of the reactions observed in the patch tests are related to intolerance reactions to implants. Most of the studies are insufficiently documented and do not provide data for the severity of the reactions, the course of the reaction over time and for (other) irritant reactions. In many cases, the test formulation is not or is only incompletely characterized. However, the results suggest systemic availability and possible sensitization. These cases are not directly applicable to a workplace setting, but substantiate the mechanism of action of the materials and complete the overall picture.

Ti₆Al₄V, a titanium alloy that contains 4% vanadium, is commonly used for orthopaedic implants. However, also dental and cardiovascular implants may be made of alloys that contain vanadium. Positive results were obtained in patch tests carried out as part of the pre-operative assessment for planned orthopaedic implantations. In isolated studies, up to 9% of the patients tested produced positive reactions to **elemental vanadium** (5% in petrolatum) (Tam et al. 2020 a) or to **vanadium trichloride** (1% or 2% in petrolatum) (Granchi et al. 2006, 2008). However, positive reactions to vanadium (compounds) were a rare finding in most studies (Table 5).

Most of the tests were carried out because intolerances had developed after implantation. The post-operative complaints were pain, swelling and redness in the immediate area of the implant, but also in other parts of the body (for example the torso). In many of the cases, the implants were loose. These complications generally did not occur immediately after the operation, but several months later. If no other cause such as an infection was found and if the symptoms persisted, in most cases the implants were removed or replaced about 1 to 2 years later. The symptoms generally subsided immediately after the removal of the implant and improved up to complete recovery. However, the results of the patch tests demonstrate that positive reactions occurred as frequently in patients who showed symptoms of intolerance to an implant as in those without symptoms.

In a study with 223 patients, 6 of 66 patients who underwent a planned total hip arthroplasty produced positive reactions to **vanadium trichloride**. After the operation, positive reactions were detected in 9 of a total of 53 patients with stable implants, 51 of whom had implants made of an alloy containing vanadium. Positive reactions to vanadium trichloride were observed after the operation by 16 of a total of 104 patients with loose implants, 47 of whom had implants containing vanadium (Granchi et al. 2006).

The same research group carried out a similar study to determine how frequently sensitization developed in patients after total knee arthroplasty. Before the operation, 1 of 20 patients produced a positive reaction to **vanadium trichloride**. After the operation, positive reactions were obtained in 9 of 23 patients with stable implants that contained vanadium and in 7 of 27 persons with loose implants. The 27 patients with stable implants were divided further into cases with and those without clinical symptoms (moderate pain). Reactions to vanadium trichloride were found in 6 of 14 patients in the group who reported having pain and in 3 of 13 patients in the group without clinical symptoms. Overall, positive reactions were obtained with a higher incidence in patients tested after the operation than in those who underwent patch testing before the operation (Granchi et al. 2008).

In a study with 311 patients, pre-operative patch tests in 73 patients yielded no reactions to **vanadium** and only one positive reaction to **vanadium trichloride**. In patch tests carried out post-operatively in 238 patients suspected of having a metal allergy, 18 of whom had implants containing vanadium, 1 patient reacted to **vanadium** and 5 to **vanadium trichloride**. One of the 5 positive reactions to **vanadium trichloride** was detected in a patient who did not have an implant that contained vanadium (Furrer et al. 2018).

In another case, a 46-year-old female patient developed lichenoid lesions on the gums adjacent to a jaw implant 2 weeks after implantation. She reported having gastrointestinal complaints on the day of the examination that had emerged 10 weeks prior. The patient additionally had an intolerance to costume jewellery. She had had chronic gastritis several years before, which subsided after the removal of amalgam fillings. She reported experiencing gastrointestinal complaints after ingesting foods that may have contained nickel. In the patch test, the patient produced a 2+ reaction to 1% **vanadium trichloride** on day 2, which was still visible after 14 days. Positive reactions to other (metal) allergens were detected, including to nickel sulfate (Table 6). Of these reactions, the authors consider the reactions to gold sodium thiosulfate, palladium chloride and zirconium chloride as relevant for the clinical reactions (Pföhler et al. 2012). However, no data for exposure to vanadium were provided.

These studies, along with other studies and individual findings from patch tests carried out with vanadium or vanadium compounds on patients suspected of having metal allergies before or after implant surgery are shown in Table 5 and 6.

Tab. 5 Studies on skin reactions to vanadium and its inorganic compounds in patch tests on patients with suspected contact allergy from 2004 onwards.

Test persons	Test substance (concentration, vehicle)	Results: reactions ^{a)} in	Comments	References
Studies of persons with (possible) occupational exposure				
7 (questionable)	VCl ₃ (no other data)	0 of 7 (questionable)	Test period: 2010–2011, Collective: the diagnosis was confirmed in 228 persons from a total collective of 316 persons suspected of having occupational hand dermatitis. 118 persons (74 ♀, 44 ♂, average age 34 years) had occupational irritant contact dermatitis, 7 of them were exposed to metals (Cu, Cr, V, Ni), 1 of them explicitly to V, Time points and results: days 2, 3, or 4 and 7. The data do not show whether all 7 or fewer persons were tested with VCl ₃	Friis et al. 2014
150	V (5%, petrolatum) VCl ₃ (1%, petrolatum)	11 of 150 (7.5%) 4 of 150 (2.7%)	Test period: 01/2007–12/2016, Collective: 108 ♀, 42 ♂, average age 54 years, different indications (pre- and post-implantation, 4 of 150 patients with occupational exposure, 1 of them a welder), Time points and results: day 2 and on day 3 or 4. The authors confirmed the relevance of 6 positive reactions to V and 2 positive reactions to VCl ₃ . No other data for the course of the reactions over time and the severity of the reactions. Inexplicably large number of reactions to V; unclear how many patients reacted to both formulations, overlap of patient samples with that of Tam et al. 2020 a	Tam et al. 2020 b
1790	VCl ₃ (2%, petrolatum)	65 of 1790 (3.6%; 95% CI: 2.8–4.6)	Test period: 2007–2016, Collective: patients with occupational and non-occupational skin changes, Time points and results: days 2 or 3,	Geier and Schubert 2021
4156	V ₂ O ₅ (no other data)	15 of 4156 (0.4%; 95% CI: 0.2–0.6)	reactions in 8/430 patients (1.9%; 95% CI: 0.8–3.6) with occupational skin changes and in 51/1252 patients (4.1%; 95% CI: 3.0–5.3) with non-occupational skin changes. Reactions in 14/3751 patients (0.4%; 95% CI: 0.2–0.6) with non-occupational skin changes, no data for the course of the reactions over time and the severity of the reactions	
Implant studies				
14	VCl ₃ (1%, petrolatum)	3 of 14 (1+ in each case)	Test period: not specified, Collective: 9 ♀, 5 ♂, 27–76 years, average age 61 years, with complaints caused by orthopaedic implants, Time points and results: days 2 and 4. 3 women produced reactions, all 1+ reactions, with a strong (3+, 1×) or marked (2+, 2×) reaction to Ni ₂ SO ₄	Křecisz et al. 2006

Tab. 5 (continued)

Test persons	Test substance (concentration, vehicle)	Results: reactions ^{a)} in	Comments	References
223	VCl ₃ (2%, petrolatum)	6 of 66 pre-operative 25 of 157 post-operative	Test period: 2001–2004, Collective: 161 ♀, 57 ♂, 24–83 years, before or after total hip arthroplasty, Time points and results: days 2–3, pre-operative: 9.1% positive (n = 66) post-operative: – patients with stable implants, positive reactions in 17.0% (n = 53; 51 with an alloy containing vanadium), – patients with loose implants, positive reactions in 15.4% (n = 104; 47 with an alloy containing vanadium) no other data for the course of the reactions over time and the severity of the reactions; no clear distinction between irritation and allergic reactions	Granchi et al. 2006
94	VCl ₃ (2%, petrolatum)	1 of 20 pre-operative 18 of 74 post-operative	Test period: not specified, Collective of 94 patients (67 ♀, 27 ♂, 42–84 years), 10 with pre-existing sensitization to other allergens, patients tested for allergic reactions to vanadium before and after total knee arthroplasty, Time points and results: days 2 or 3 Post-operative: only patients with implants containing vanadium were evaluated – 27 patients with stable implants, 9 positive reactions – 47 patients with loose implants, 9 positive reactions no other data for the course of the reactions over time and the severity of the reactions; no clear distinction between irritation and allergic reactions; unclear how many patients were tested both before and after surgery	Granchi et al. 2008
239	“vanadium from an extended metal series” (no other data)	5 of 239	Test period: 2002–2007, Collective: 155 ♀, 84 ♂, average age 63 years. Patients suspected of having an intolerance to osteosynthesis and endoprosthesis materials, Time points and results: days 2, 3 and 7, no other data for the test formulation, the course of the reactions over time and the severity of the reactions	Eben et al. 2009
5	V (5%, petrolatum) VCl ₃ (1%, petrolatum)	0 of 5 0 of 5	Test period: not specified, Collective: 3 ♀, 2 ♂, 39–78 years, with previous implant surgery, Time points: days 2 and 3 or 4	Bircher et al. 2011
100	V (5%, petrolatum)	0 of 100 pre-operative 0 of 72 post-operative	Test period: 2007–2008, Collective: 73 ♀, 27 ♂, 51–84 years, tests performed before (n = 100) and after implant surgery (hip or knee; n = 72), 80 of the 100 test persons had implants containing V. 72 of them were tested after surgery, Time points: day 4 and in some cases day 7	Frigerio et al. 2011
60	V (5%, petrolatum) VCl ₃ (1%, petrolatum) V (5%, petrolatum) VCl ₃ (1%, petrolatum)	0 of 60 pre-operative 0 of 60 pre-operative 0 of 48 post-operative 1 (♀) of 48 post-operative	Test period: not specified, Collective: 43 ♀, 17 ♂, average age 62 years, before and after implant surgery 48 of 60 previously tested patients were tested again after surgery, Time points and results: days 2 and 4, no other data for the course of the reactions over time and the severity of the reactions; no clear distinction between irritation and allergic reactions	Kręcis et al. 2012

Tab. 5 (continued)

Test persons	Test substance (concentration, vehicle)	Results: reactions ^{a)} in	Comments	References
87	“vanadium” (no other data)	0 of 87	Test period: 2012–2013, Collective: 87 tested from a total collective of 96 (57 ♀, 39 ♂; 22–76 years), examination prior to total knee and hip arthroplasty, Time point: day 3	Zeng et al. 2014
311	V (5%, petrolatum) VCl ₃ (1%, petrolatum) V (5%, petrolatum) VCl ₃ (1%, petrolatum)	0 of 73 pre-operative 1 of 73 pre-operative 1 of 238 post-operative 5 of 238 post-operative	Test period: 2004–2017, Collective: 220 ♀, 91 ♂, average age 64 years, pre and post-operative testing (if complications arose or metal allergy suspected) of patients receiving (hip and knee) implants, osteosynthesis, 18 implants contained V; if and how many of the patients were tested both before and after surgery unclear, Time points and results: day 2 and once between days 3 and 6, no other data for the course of the reactions over time and the severity of the reactions; no clear distinction between irritation and allergic reactions	Furrer et al. 2018
100	“vanadium particles” (10%, no other data)	2 of 100	Test period: 2009–2017, Collective: 100 persons, 46 of them because of a (planned) implant, the others suspected of having a metal allergy (no other data), 2 groups: Group 1: 60 patients (32 ♀, 28 ♂, average age 53 years, with a history of dermatitis), 8 tested before, 13 after surgery, Group 2: 40 patients (26 ♀, 14 ♂, average age 39 years, without a history of dermatitis), 20 tested before, 5 after surgery, Time points and results: days 2 and 4. Overall, 1 person each from Group 1 and Group 2 yielded positive reactions; however, no data whether tests pre- or post-operative, no other data for the course of the reactions over time and the severity of the reactions	Haddad et al. 2019
101	V (5%, petrolatum) V (5%, petrolatum) VCl ₃ (1%, petrolatum)	3 of 33 pre-operative 3 of 68 post-operative 4 of 68 post-operative	Test period: 07/2006–09/2016, Collective: pre- and post-operative testing of persons from a collective of 127 persons, before surgery, 33 of a total of 40 patients (32 ♀, 8 ♂, 11–90 years, average age 49 years) were tested for an allergic reaction to V. The authors regarded 1 of the 3 positive reactions as relevant after surgery (if complications developed and a metal allergy was suspected), 68 of 87 patients (62 ♀, 25 ♂, 14–85 years, average age 58 years) with orthopaedic (49), cardiovascular (4), dental (28) and other (6) implants were tested for allergic reactions to V, Time points and results: day 2 and on day 3 or 4. The authors regarded all 3 positive reactions to V and 1 reaction to VCl ₃ as relevant. The data do not show how many patients reacted to both formulations, no other data for the course of the reactions over time and the severity of the reactions; no clear distinction between irritation and allergic reactions	Tam et al. 2020 a
364 (probably)	V (5%, petrolatum) VCl ₃ (1%, petrolatum)	2 of 364 (probably)	Test period: 2008–2017, Collective: 257 ♀, 107 ♂, average age 64 years; persons suspected of having a metal allergy (indium and iridium) to orthopaedic and other implants, Time points and results: day 2 and between days 4 and 7, 2 patients produced 2+ reactions, no data for the time point, in addition to 3+ reactions to nickel and palladium and 2+ reactions to IrCl ₃ as well as one 2+ reaction to RhCl ₃ . 23 of 364 patients produced a positive reaction to indium or iridium, 20 of them reacted also to another metal. It is unclear whether the positive reactions were caused by V or VCl ₃	Terrani et al. 2020

^{a)} Patch test results for vanadium (compounds) that are interpreted as positive, particularly those for vanadium trichloride, are to be assessed very critically because of the potential for irritation.

CI: confidence interval; V: vanadium; V₂O₅: divanadium pentaoxide; VCl₃: vanadium trichloride

In vitro findings were published by 2 sources; however, these are not suitable for the evaluation. In a study that investigated patients with post-operative pain after total knee or hip arthroplasty, 313 patients (289 ♀, 24 ♂) with a pre-existing

metal allergy and 34 control persons (17 ♀, 17 ♂) between 23 and 94 years of age were chosen from a total collective of 2081 persons and tested by LTT. Patients who exhibited a stimulation index (SI) > 8 for nickel were tested with 0.001, 0.01 and 0.1 mM **vanadium trichloride**. The only information included in the report was that 16% of the test persons produced a positive reaction (SI > 4) to vanadium or aluminium (Caicedo et al. 2014). However, the number of persons tested and the individual results were not specified.

A case report describes a female patient with a pre-existing intolerance to costume jewellery who had surgery to replace the screws of a foot implant and, at about the same time, metal braces applied to her teeth. The patient reacted to “vanadium” in a commercial modified LTT (Memory Lymphocyte Immuno Stimulation Assay, MELISA). The authors reported positive results also for “nickel” and titanium dioxide (FDA CDRH 2019). However, the test substance and the test concentrations were not characterized in more detail and no other data for the positive results were provided.

Tab. 6 Reported individual results from patch tests on persons suspected of having a metal allergy

Test persons	Test substance (concentration, vehicle)	Results: reactions ^{a)}	Comments	References
Possible occupational exposure				
39-year-old metal worker	VCl ₃ (1%, petrolatum)	2+ (days 2 and 4)		Garcia- Nunez et al. 2019
Non-occupational exposure				
female patient with eczema on her wrist caused by ceramic watch	VCl ₃ (0.1%, petrolatum) V (no other data)	2+ (days 2 and 4) –	days 2 and 4 also 2+ reactions to colophony, abietic acid and abitol, probably pre-existing sensitization to nickel	Jordan et al. 2018
Exposure from implants				
46-year-old female patient after a dental implant	VCl ₃ (1%, petrolatum)	– (day 1) 2+ (days 2, 3, 7 and 14)	patient developed pruritic lesions on the adjacent gums 2 weeks after an implant was placed in the jaw in addition to gastrointestinal complaints, also positive reactions to MnCl ₂ , palladium chloride, gold sodium thiosulfate, zirconium chloride, nickel sulfate and fragrance mixtures	Pföhler et al. 2012, 2016
35-year-old female patient with eczema after the implantation of a plate to fixate a tibial fracture	“vanadium” (extended DKG metal series)	– (days 2 and 3)	patient with a pre-existing nickel allergy	Thomas et al. 2006
46-year-old female patient with complaints 6 weeks after knee arthroplasty	“vanadium” (no other data)	–	alleviation of the complaints after replacement of the implant, no other data	Van Opstal and Verheyden 2011
52-year-old male patient with HVI (halo vest immobilization of the neck)	“vanadium” (no other data)	positive (no other data)	pins for fixation made of a titanium alloy containing vanadium, no other data	Coulter et al. 2012
50-year-old female patient with a suture anchor	“vanadium” (no other data)	–	all patch test results negative, but immediate improvement of the symptoms after removal of the suture anchor, no other data	Goto et al. 2013

Tab. 6 (continued)

Test persons	Test substance (concentration, vehicle)	Results: reactions ^{a)}	Comments	References
female patient after spinal fusion	V (concentration not specified, petrolatum)	1+ (no other data)	placement of an implant containing vanadium, 3 weeks later pruriginous eruptions around the surgical wound, on the torso and extremities, positive reactions also to V, Pd; no other data	Asemota et al. 2016
16-year-old female patient after spinal fusion	V (concentration not specified, petrolatum)	3+ (no other data)	patient with Ehlers-Danlos syndrome (disorder affecting the connective tissue) had back pain after placement of an implant containing vanadium, positive reaction to NiSO ₄ and “vanadium”	Asemota et al. 2016
	V ₂ O ₅ (10%, petrolatum)	positive (no other data)	of 90 patients suspected of having a vanadium allergy after implantation, none produced a positive reaction to V	
62-year-old female patient with a foot implant	VCl ₃ (1%, petrolatum)	1+ (days 3 and 4)	pre-existing metal allergy from jewellery, placement of an implant containing vanadium, 3 weeks later pruritic, nummular eczematous plaques on the arms, legs, back and buttocks	Engelhart and Segal 2017
	V (5%, petrolatum)	–		
68-year-old female patient with total knee arthroplasty	VCl ₃ (no other data)	1+ (no other data)		Peat et al. 2018
39-year-old male patient with a tattoo	V (5%, petrolatum)	– (days 2 and 4)	patient with a 20-year-old tattoo that suddenly became infected following osteosynthesis surgery; suspected of being caused by a contact allergy to metals in the black pigments, diagnosis was a titanium allergy, no complaints after removing the implant	de Cuyper et al. 2017
64-year-old male patient with a bone conduction hearing implant	VCl ₃ (1%, petrolatum)	1+ (days 3 and 7)	hearing aid made of titanium, partially covered with silicone, also reaction to titanium oxalate (1+)	Alves et al. 2020
	V ₂ O ₅ (10%, petrolatum)	–		
	V (5%, petrolatum)	–		
64-year-old female patient with knee arthroplasty	V (5%, petrolatum)	–	positive reaction to titanium oxalate	Dear et al. 2020
	V ₂ O ₅ (10%, petrolatum)	–		

^{a)} Patch test results for vanadium (compounds) that are interpreted as positive, particularly those for vanadium trichloride, are to be assessed very critically because of the potential for irritation.

DKG: German Contact Dermatitis Research Group; V: vanadium; V₂O₅: divanadium pentaoxide; VCl₃: vanadium trichloride

4.4.1.4 Conclusions

Overall, neither clinico-epidemiological findings nor case reports provide sufficient evidence that vanadium causes contact sensitization. In particular, there are no findings that vanadium or inorganic vanadium compounds have skin sensitizing potential after topical application that are relevant for occupational medicine.

4.4.2 Sensitizing effects on the airways

No new findings have become available to supplement the individual case reports involving occupational exposure to **vanadyl pyrophosphate** (divanadyl pyrophosphate) and ores containing vanadium that were described in the documentation from 2006 (Greim 2009). Isolated reports of acute toxicity after inhalation of **divanadium pentaoxide** (Henschler 1992) suggest irritation, but not sensitization of the airways.

More recently published findings are not available.

4.5 Reproductive and developmental toxicity

4.5.1 Studies with determination of the vanadium concentration in urine

Studies investigated prenatal and postnatal effects in a cohort of mother–infant pairs from 3 maternity wards located in Wuhan, Ezhou and Macheng in the Chinese province of Hubei. The study data were collected from September 2012 to October 2014. The concentrations of various metals in the urine were correlated with different end points by multi-variable regression analysis. Women who did not provide urine samples, who had consumed alcohol during pregnancy or whose newborn babies had birth defects were excluded from the study. Preterm delivery was defined as giving birth before the 36th week of pregnancy and early-term delivery was defined as giving birth between the 37th and 38th weeks of pregnancy. Birth weights under 2500 g were considered low birth weights. The results were evaluated taking into consideration the age of the mothers at delivery, their level of education, primiparity or multiparity, BMI (body mass index) before pregnancy, smoking habits, passive smoking, blood pressure disorders, gestational diabetes and sex of the newborn baby. Additionally, the data were adjusted for concentrations of other metals in the urine, such as chromium, manganese, nickel, arsenic, cadmium, thallium and lead. The following studies were largely based on these datasets: Jin et al. (2018), Hu et al (2017, 2018) and Jiang et al. (2016). If other confounders were taken into consideration, these are included in the description of the study.

A nested case–control study was carried out with a total of 816 mother–infant pairs from the cohort described above to investigate the effects of vanadium on low birth weights. The control group was made up of 612 mother–infant pairs who matched in terms of hospital delivery, sex of the baby and age of the mother at conception. A total of 204 children had low birth weights under 2500 g. The birth weight was determined 1 hour after delivery. In addition to information about the confounders described above, the mothers were interviewed after delivery about household income, occupation, menstruation (for example, age at menarche), prenatal care and health care (for example, the use of multivitamins during pregnancy) as well as physical activity. The mother's gestational history (for example, number of pregnancies and births) and information about the delivery were taken from the patient's medical records. The gestational age was calculated based on the self-reported last menstrual period. An additional adjustment for the following variables changed the parameter estimates of the main effect by no more than 10%, so they were not included in the subsequent model calculations: household income, occupational status, use of multivitamin supplements during pregnancy, and weight gain during pregnancy. The mean urinary concentration of vanadium was 2.11 µg/g creatinine (1.22 µg/l urine). The vanadium concentrations in the urine were increased with statistical significance in mothers who delivered babies with birth weights under 2500 g (median: 3.04 µg/g creatinine, 1.27 µg/l) in comparison with the levels determined in control group mothers (median: 1.93 µg/g creatinine, 1.22 µg/l). Three groups were formed based on the vanadium levels: ≤ 1.42, 1.42 to 2.91, ≥ 2.91 µg/g creatinine (as specified by the authors). After taking all deliveries including preterm deliveries into account, the risk for low birth weights was increased with statistical significance in the high concentration group (odds ratio (OR): 2.95, 95% CI: 1.93–4.51) and remained increased even after adjusting for gestational age at delivery, education, primiparity, BMI prior to pregnancy and passive smoking (OR: 2.23, 95% CI: 1.23–4.05). A statistically significant trend for low birth weights was derived that was dependent on the vanadium concentration. No effect on the OR was observed after adjusting for lead, nickel, arsenic and cadmium. If the babies who were born before gestation week 37 were not included in the analysis, the adjusted OR was increased with statistical significance also in the middle concentration group (Jiang et al. 2016). Unlike the creatinine-based concentrations, the volume-based vanadium concentrations in the urine were of the same order of magnitude in the control group and in the exposure group. In women, the volume-based and creatinine-based concentrations in the urine are generally of the same order of magnitude. The authors do not explain why the creatinine-based vanadium concentrations diverge considerably from the volume-based levels in the exposure group. The authors likewise do not provide data for the creatinine levels in the urine. The probable explanation for this discrepancy is that the urine was highly diluted, which results in disproportionately high creatinine-based metal concentrations. The metal concentrations in the urine were therefore over-estimated.

A group of 7297 women, all recruited from Wuhan, were divided into quartiles based on the vanadium concentrations: < 0.84 µg vanadium/g creatinine (n = 1825), 0.84 to 1.4 µg vanadium/g creatinine (n = 1824), 1.4 to 2.96 µg vanadium/g creatinine (n = 1824) (as specified by the authors) and > 2.96 µg/g creatinine (n = 1824). In all groups, 10–13% of women

were diagnosed with gestational diabetes, and in the entire cohort, only 7 women (0.1%) smoked during pregnancy, but 23% were exposed to passive smoking. After adjusting for the above-mentioned confounders, the risk of low birth weight (< 2500 g) was statistically significantly increased for all mothers with increasing vanadium concentration (per unit increase in the natural logarithm-transformed maternal urinary vanadium concentration ($\mu\text{g/g}$ creatinine)) (OR 1.22; 95% CI: 1.04–1.43) as well as for mothers with full-term births (OR 1.41; 95% CI: 1.18–1.7). For women who had urinary vanadium concentrations of above 2.96 $\mu\text{g/g}$ creatinine, the statistically significantly increased OR for both end points was 3.56 (95% CI: 1.79–7.1) and 4.62 (95% CI: 2.04–10.47), respectively. In the women in the highest quartile, the risk of a preterm delivery (OR 8.86; 95% CI: 5.66–13.86) and of an early-term delivery (OR 1.53; 95% CI: 1.32–1.77) was increased with statistical significance in comparison with the risk determined for women in the lowest quartile. The risk was decreased after adjusting for concentrations of other metals, but remained elevated for all end points with statistical significance in the highest concentration group (Hu et al. 2017). Additionally, a possible association between vanadium concentrations in the urine and the birth weight, body length, abdominal circumference, femur length and head circumference of the newborn babies was investigated in 3025 mother–infant pairs from this cohort. The sex ratio, gestational age, birth weights, body length and ponderal index (a measure used to evaluate body weight) were in the normal range in the whole collective. In addition to the confounders above, the mothers answered questions about folic acid supplementation as well as the height and weight of the fathers. Medical records were consulted for parity, hypertensive disorders during pregnancy, gestational diabetes and the sex of the baby. The vanadium concentrations were determined in weeks 13, 23.3 and 37.8. Three urine samples were available from 864 participants (28.6%), 2 urine samples from 1344 (44%) and 1 urine sample from 817 (27%). The concentrations of arsenic, cadmium and lead were determined. Only 2 urine samples were below the limit of detection of 0.0077 μg vanadium/l. Four groups were formed based on vanadium concentrations: ≤ 0.6 $\mu\text{g/l}$ urine (controls), 0.6 to 0.83 $\mu\text{g/l}$, 0.83 to 1.18 $\mu\text{g/l}$, > 1.18 $\mu\text{g/l}$ (as specified by the authors). Multivariate models were used to calculate decreases in biparietal diameter, head circumference and occipitofrontal diameter when vanadium concentration in urine doubled. The trend was statistically significant for most of the parameters mentioned above (Hu et al. 2018). The relevance and significance of the changes calculated by the multivariate models that were dependent on the vanadium concentrations are unclear.

A group of 7290 mothers was used to study the association between metal concentrations in the urine and premature membrane rupture (spontaneous membrane rupture before the onset of labour) as well as membrane rupture prior to week 37 of pregnancy. Urine samples were collected within 3 days of the calculated day of delivery. No urine samples were taken from pregnant women who had delivered vaginally and who had an accumulation of amniotic fluid or blood. Urine samples were taken by catheter from pregnant women who had delivered by Caesarean section. No other data were provided for the time point of urine collection. The median concentrations of all metals (aluminium, vanadium, chromium, manganese, cobalt, nickel, copper, selenium, cadmium, thallium, lead) were increased with statistical significance in the mothers who had membrane rupture before the onset of labour or membrane rupture prior to gestational week 37 in comparison with the levels found in the mothers who did not have premature membrane rupture. The unadjusted and adjusted OR for premature membrane rupture were increased with statistical significance for vanadium and chromium (Jin et al. 2018). As the concentrations of all metals were increased with statistical significance in the mothers with premature membrane rupture, no conclusion concerning the effects of vanadium can be drawn.

A study was carried out from January 2014 to October 2016 in a total of 1865 mother–infant pairs recruited from Wuhan. The vanadium concentrations in the urine of the pregnant women were determined in weeks 13, 24 and 34 of pregnancy. The mean vanadium concentrations were 0.84, 0.74, and 0.68 $\mu\text{g/l}$, respectively, at the different time points. The mean concentration over the entire pregnancy was 0.77 $\mu\text{g/l}$. The newborn babies were examined at birth and 6, 12 and 24 months after birth. A linear regression model did not establish an association between the mean vanadium concentration during pregnancy and the body weight, body length, the weight-to-length ratio and the BMI of the newborn babies and all infants up to 2 years of age. A separate analysis carried out with only boys found a statistically significant association for these end points (Li et al. 2021), but did not provide a plausible explanation for why the association was statistically significant only in boys.

In 675 mother–infant pairs, the thyroid hormone and vanadium levels were determined in the urine of pregnant women prior to week 18 of pregnancy. More information was not given for the time point when the determination was per-

formed. All but one of the mothers were non-smokers. The mean birth weights of 3361.4 ± 422.1 g, mean body length of 50.5 ± 1.7 cm and mean gestational age at birth of 39.3 ± 1.1 weeks were in the normal range. After adjusting for the age of the mother, education, parity, BMI prior to pregnancy, exposure to cigarette smoke via passive smoking and sex of the newborn baby, a statistically significant association was found between the vanadium concentrations and decreased birth weights and body length. The concentrations of arsenic, cadmium, chromium, lead and thallium were determined in the urine; a significant association was not found between decreased birth weights and body length and the concentrations of these metals. No association was established between the urinary concentrations of vanadium, or those of other metals, and the levels of the thyroid hormones TSH and free T₄ (fT₄). An inverse association was found for the urinary concentrations of vanadium, arsenic and lead and the serum concentrations of the thyroid hormone free T₃ (fT₃). Another was established only for vanadium with the fT₃/fT₄ ratio. A positive association between the serum concentrations of fT₃ and fT₃/fT₄ and the birth weights was observed. According to the authors, mediation analyses demonstrate that 5.33% to 30.57% of the associations between the vanadium, arsenic and lead concentrations in the urine and birth size are mediated by changes in maternal fT₃ or the fT₃/fT₄ ratio (Sun et al. 2019).

4.5.2 Studies with determination of the vanadium concentration in umbilical blood and serum

In a study with a total of 227 mother–infant pairs (116 male / 111 female newborn babies), the vanadium concentrations in the serum of the mothers were determined at 3 intervals (weeks 15 to 19, 24 to 28, 31 to 35) during pregnancy and in the umbilical blood of 55 male and 60 female newborn babies. The median vanadium concentrations in the serum of the mothers were between 2.17 µg/l and 2.47 µg/l. In the second trimester, the vanadium concentrations in the mothers of boys were increased with statistical significance compared with the levels found in the mothers of girls. The cytokines brain-derived neurotrophic factor (BDNF), insulin-like growth factor-binding protein 3 (IGFBP-3) and growth hormone (GH) were determined in the plasma of the mothers and in the umbilical blood. Multivariate regression models were used to identify associations. The mothers answered questions relating to education, income, smoking status, alcohol consumption, physical activity, high blood pressure during pregnancy, gestational diabetes and parity. Medical records were consulted to obtain the age of the mothers at the birth and the BMI prior to pregnancy. An increase in the vanadium concentration by 1 µg/l was associated with a calculated decrease in the body size of newborn boys by 0.1 cm and a calculated decrease in the body weights of newborn girls by 64.73 g. The calculations additionally revealed that an increase in the vanadium concentration by 1 µg/l led to a statistically significant decrease in the biparietal diameter by 0.87 mm, in the head circumference by 3.00 mm, in the femur length by 0.71 mm and in the humerus length by 0.62 mm. An increase in the vanadium concentration by 1 µg/l was significantly associated with a decrease in GH in the umbilical blood in the boys and with a decrease in BDNF in the girls. Vanadium concentrations in the maternal serum revealed a statistically significant negative association with GH in the boys and a positive association with IGFBP-3 in the girls. According to the authors, the study had the following limitations: the levels of other heavy metals were not determined and a small collective was used, leading to low statistical power. The authors suggest that the effects may have been underestimated and that additional studies need to be carried out to clarify the results (Zhou et al. 2019).

In 81 mother–infant pairs, the serum concentrations of the following metals were determined in the umbilical blood and post-partum in the mothers: vanadium, lead, thallium, cadmium, selenium, arsenic, nickel, cobalt and mercury. Multiple linear regression analyses, adjusted for the age and BMI of the mothers, the week of gestation, and the sex of the newborn baby, were carried out to establish an association between metal concentrations and birth weights. None of the women consumed alcohol or smoked during pregnancy; nine were exposed to cigarette smoke via passive smoking. Eight newborn babies weighed less than 2500 g. The median vanadium concentration was below the limit of detection and the 75th percentile was equivalent to a vanadium concentration of 0.2 ng/g blood in the mothers and 1.3 ng/g in the umbilical blood. No association was found between the vanadium concentrations and the birth weights (Hu et al. 2015).

The study of Basu et al. (2014) does not provide any information for the exposure concentrations or biomonitoring data for the mothers. As a result, the study has not been taken into consideration for the evaluation of the effects on reproductive toxicity.

4.5.3 Conclusions

It remains unclear to what extent the results from the pure multivariate regression analyses are to be regarded as adverse. The minor effects that lie within the biological range of variation are not regarded as adverse. However, the described effects are not plausible because there were no great variations in the vanadium concentrations in the urine. Moreover, no information was provided about other chemicals that the women were exposed to due to the environmental pollution in China. It is therefore uncertain whether the effects can be attributed only to vanadium. Jiang et al. (2016) determined that the body weight gains of the mothers during pregnancy did not change the estimated value of the parameters for the main effect by more than 10%. As a result, this factor was not included in the evaluation. This is assumed to be the reason why none of the other studies that were based on this birth cohort provided information about the body weight gains of the mothers during pregnancy. However, there are studies that show that the body weight gains of mothers during pregnancy have a considerable influence on birth weight (Marshall et al. 2022).

The above studies are not included in the evaluation of reproductive toxicity due to the described limitations.

4.6 Genotoxicity

A study that was included in Greim (2009) investigated the induction of DNA damage and sister chromatid exchange (SCE) in the leukocytes of the peripheral blood of 49 male workers involved in vanadium production. There are no data for the exposure concentrations of the workers; the average period of exposure was 12.4 years. The vanadium concentrations determined in the serum samples of the exposed persons were on average $7.73 \pm 7.86 \mu\text{g/l}$ with a median of $5.38 \mu\text{g/l}$ (range 2.18–46.35); the corresponding values in the control persons were $3.43 \pm 3.13 \mu\text{g/l}$ and $2.54 \mu\text{g/l}$ (range 1.01–12.5), respectively. The exposed persons had mean urinary concentrations of vanadium of $14.57 \pm 13.81 \mu\text{g/g}$ creatinine with a median value of $11.25 \mu\text{g/g}$ creatinine (range 2.11–95.2); the control persons had mean values of $1.13 \pm 0.26 \mu\text{g/g}$ creatinine with a median of $0.74 \mu\text{g/g}$ creatinine (0.41–3.37). The vanadium concentrations in the serum and urine of the exposed persons were increased with statistical significance in comparison with the levels found in the control persons. The incidence of DNA damage (DNA strand breaks in the comet assay, oxidative DNA damage (8-oxo-2'-deoxyguanosine)) in the leukocytes and of SCE in the lymphocytes was not increased, not even after taking smoking habits into account. The serum and urine levels of vanadium were not increased with statistical significance and DNA damage was not increased in workers who had reported green or black discoloration of the tongue over the levels found in exposed persons who did not report having this symptom (Ivancsits et al. 2002).

The blood leukocytes of 52 workers in vanadium production with exposure to **divanadium pentaoxide dust** were analysed for DNA damage by alkaline comet assay. Oxidative DNA damage was detected by comet assay by adding formamidopyrimidine glycosylase (FPG) and endonuclease III. The leukocytes were additionally treated with bleomycin and the capacity to repair the DNA damage caused by the substance was assessed in the comet assay. The control group consisted of 52 prison wardens without exposure. In addition, the lymphocytes of 24 workers were examined for the induction of micronuclei by cytokinesis block assay and the results compared with those of a corresponding control group of 23 persons. A total of 2000 lymphocytes per person were evaluated. Information about the age, height, weight and smoking status of the persons was obtained by questionnaire. The workers were exposed for 8 hours per shift. They were required to wear masks and gloves. The exposed persons were on average 43 years old, 12 of them were smokers (7 cigarettes/day). The control persons were 38 years old, 11 of them were smokers (5 cigarettes/day). The vanadium levels in the blood plasma were $2.2 \mu\text{g/l}$ (1.54–3.89; 25th–75th percentile) in the exposed persons and $0.3 \mu\text{g/l}$ (0.24–0.39; 25th–75th percentile) in the control persons. No differences between exposed and control persons were determined based on the results for DNA strand breaks obtained by standard comet assay. After adding FPG or endonuclease III, oxidized purine bases were increased by 7% and oxidized pyrimidine bases by 33%. The sensitivity to bleomycin-induced DNA damage of the leukocytes of exposed persons was 25% greater than in the control persons, and, at the same time, the damage was repaired to a lesser degree. The lymphocytes of the exposed workers exhibited an increase in micronuclei and in micronuclei-containing cells (2.5-fold in each case), in nucleoplasmic bridges (NPB; 7-fold) and in nuclear buds (Nbuds; 3-fold) in addition to an increased fraction of apoptotic cells (+50%, not statistically significant) and necrotic cells (+55%, statistically significant). The rate of cell division was the same in both exposed

persons and control persons. Exposed smokers had a lower micronucleus frequency than exposed non-smokers and the incidence of NPBs and Nbuds was of the same order of magnitude. Therefore, smoking habits did not have any effect on these parameters. The induction of oxidized purine and pyrimidine did not correlate with the induction of micronuclei, which suggests that several mechanisms are involved in the genotoxic effects. No correlation was found between the vanadium concentration in the plasma and the induction of oxidized bases and micronuclei. In this context, the authors refer to polymorphisms in repair genes that have a strong impact on micronuclei formation in other metals (Ehrlich et al. 2008). The publication does not include data for additional exposure to other substances or metals. In response to a request for more information about the exposure conditions, the authors explained that the workers included in the study had worked exclusively in the production of vanadium salts 3 to 4 weeks prior to sample collection. However, the company manufactured other metal compounds as well. The authors had not been able to verify this information (Knasmüller 2021). It is therefore uncertain whether the DNA damage that was observed can be attributed solely to vanadium. The vanadium concentration in the whole blood is an indicator of vanadium exposure; however, the increase in the vanadium concentration is less pronounced in this medium than in the urine after occupational exposure (Schaller 1996). For this reason, it is not possible to calculate the exposure concentrations based on the levels of vanadium determined in the blood.

A positive association was found between the concentrations of 8-oxo-2'-deoxyguanosine in the lymphocytes of 49 students from Copenhagen and the vanadium and chromium concentrations in samples of respirable dust (PM_{2.5}) (9.4–27.7 µg/m³, 25th–75th percentile). The aqueous PM_{2.5} suspensions contained vanadium in concentrations of 0.3 to 5.7 µg/l and chromium in concentrations of 2.3 to 5.8 µg/l. No relationship was determined between the concentrations of platinum, nickel, copper and iron and the findings of DNA damage. No correlation was established between the concentration of 8-oxo-2'-deoxyguanosine in the urine and the concentrations of vanadium or chromium in the respirable dust or between the concentrations of 8-oxo-2'-deoxyguanosine in the urine and in the lymphocytes (Sørensen et al. 2005).

Summary: Workers in vanadium production who had higher vanadium concentrations in the urine than the control persons did not have an increased incidence of DNA damage in the lymphocytes (SCE) or leukocytes (DNA strand breaks in the comet assay, oxidative DNA damage) (Ivancsits et al. 2002). A second study that was carried out in workers involved in vanadium production (Ehrlich et al. 2008) reported oxidative DNA damage in the leukocytes and micronuclei and an increased incidence of apoptotic (not statistically significant) and necrotic cells in the lymphocytes. In this study, vanadium levels were determined only in the serum, but not in the urine. Serum levels are considered an indicator of vanadium exposure, but do not allow any conclusions to be drawn about the exposure concentration. The exposure concentrations were not determined and no information was provided about exposure to other substances. For this reason, the observed effects could not be attributed to vanadium.

4.7 Carcinogenicity

A nested case–control study with 440 lung cancer cases and 1320 healthy, matched control persons from the Dongfeng-Tongji cohort assessed the lung cancer risk based on the plasma concentrations of 11 metals (cobalt, copper, iron, manganese, molybdenum, rubidium, selenium, strontium, tin, vanadium and zinc). The central aim of the study was to investigate the reduced risk of lung cancer that was observed with increasing concentrations of zinc in the plasma and the associated molecular mechanisms of action. The median vanadium concentration in the plasma was 1.38 µg/l (1.03–2.26; 25th–75th percentile) in persons with lung cancer and 1.51 µg/l (1.07–2.33; 25th–75th percentile) in the control persons and thus did not differ with statistical significance. The vanadium concentrations in the plasma were not associated with a statistically significant increase in the lung cancer risk either in men (OR 0.78; 95% CI: 0.59–1.05) or in women (OR 0.93; 95% CI: 0.63–1.36) or in both groups together (OR 0.89; 95% CI: 0.79–0.99) compared with the level of risk determined in the control group (Bai et al. 2019). The vanadium concentrations in the plasma correlated only insufficiently with external exposure. As data for external sources of exposure were not provided, the level of exposure to vanadium is unclear and the study is not suitable for evaluating the carcinogenic effects.

A hospital-based case–control study investigated a possible association between the breast cancer risk and the concentrations of titanium and vanadium in the urine of 240 women with breast cancer and of 246 women without breast

cancer. The following information was obtained by interview: menstrual and reproductive history, lifestyle, family history of cancer, height, weight and demographic factors. Urine samples were collected from the breast cancer patients immediately after admission to the hospital. Samples were collected from the healthy women directly after the interview (health screening assessment). Breast cancer patients had a median urinary concentration of vanadium of 1.7 µg/g creatinine (1.08–2.75; 25th–75th percentile), healthy women had a concentration of 2.01 µg/g creatinine (1.36–3.03; 25th–75th percentile). After adjusting for possible confounders for breast cancer such as age, weight, onset of puberty, marital status, education, ethnicity, menopause and family history of cancer, the risk was decreased by 64% in the group with the highest exposure to vanadium (OR 0.36; 95% CI: 0.21–0.60) and by 40% in the group with moderate exposure (OR 0.6; 95% CI: 0.43–1.01) compared with the risk found in the tertile of women with the lowest level of exposure. The authors propose that vanadium and its compounds may be suitable for chemoprevention and thus for the development of new anti-cancer drugs (Tang et al. 2012). However, the aim of the present evaluation is not to assess evidence for the anti-tumour effects of vanadium compounds.

A retrospective case–control study was published in the form of a dissertation. The study data were collected by questionnaire. Workers (n = 196) of a **divanadium pentaoxide** factory who had been employed there for at least 5 years were exposed to divanadium pentaoxide concentrations of 20 to 30 µg/m³. The cumulative exposure was given as 0.17 ± 0.46 mg × years/m³. There was no evidence of an increased risk of cancer (AGS 2015).

Summary: The findings of the available studies do not demonstrate that vanadium and its inorganic compounds induce carcinogenic effects in humans.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

A number of studies reported LC₅₀ values for **vanadium** of 0.68 to 7.5 g/m³ in rats (Greim 2009).

After groups of 5 female and 5 male rats and mice were exposed nose-only to a **divanadium pentaoxide** concentration of 2 g/m³ for 4 hours, all animals died. **Divanadium trioxide** was less toxic under the same exposure conditions and caused mortality only in 2/5 female rats and 3/5 female mice (Vanadium Producer & Reclaimers Association 2010 c).

Nose-only exposure of groups of 6 female and 6 male rats and mice to a **divanadium trioxide** concentration of 1 g/m³ for 4 hours led to mortality in 1/6 female rats and 3/6 female mice. Mottled lungs were observed and 1 animal had foci in the lungs (Vanadium Producer & Reclaimers Association 2010 a).

Nose-only exposure of 6 female mice to a **divanadium trioxide** concentration of 0.5 g/m³ for 4 hours caused mortality in 2/6 mice. The authors derived a LC₅₀ for **divanadium trioxide** of 0.5 to 1 g/m³ from the study data (Vanadium Producer & Reclaimers Association 2010 b).

Using a method that was in compliance with OECD Test Guideline 436, groups of 5 male and 5 female B6C3F1 mice and groups of 5 male and 5 female F344/N rats were exposed nose-only to **divanadium pentaoxide** or **vanadyl sulfate** in concentrations of 0.05, 0.5, 1.0 or 2 g/m³ and to **divanadium tetraoxide** or **divanadium trioxide** in concentrations of 1.0 or 2.0 g/m³. The purity of the granular substances that were tested was 99.9% for **divanadium pentaoxide** with an MMAD of 2.71 µm, 95.7% for **divanadium tetraoxide** with an MMAD of 2.46 µm, 97.1% for **divanadium trioxide** with an MMAD of 2.49 µm and 97.4% for **vanadyl sulfate** with an MMAD of 1.92 µm. The LC₅₀ values are given in Table 7. Hypoactivity was evident in the female mice of all exposure groups; this effect was observed in male mice only in the high exposure group. In the rats, hypoactivity was observed in all groups and increased in severity with the concentration. The histopathological examination revealed discoloured, mottled lungs with dark-red foci in all animals

at concentrations of 0.5 g/m³ and above regardless of which vanadium compound was being tested. Only the mice exposed to vanadyl sulfate had laboured breathing (Rajendran et al. 2016).

Tab. 7 LC₅₀ values (g/m³) after nose-only exposure for 4 hours (Rajendran et al. 2016)

Species	Sex	V ₂ O ₅	V ₂ O ₄	V ₂ O ₃	VOSO ₄
B6C3F1 mice	male	0.25	1.5	2.0	0.125
	female	0.25	1.5	1.0	0.125
F344/N rats	male	0.25	1.5	2.0	1.5
	female	0.25	1.5	1.0	1.5

V₂O₅: divanadium pentaoxide; V₂O₄: divanadium tetraoxide; V₂O₃: divanadium trioxide; VOSO₄: vanadyl sulfate

LC₅₀ values > 5.05 g/m³ were determined for **vanadium carbide**, **vanadium carbide nitride** and **vanadium dioxide**. The LC₅₀ for **divanadyl di(hydrogen phosphate) hydrate** was between 1.078 g/m³ and 4.27 g/m³. The LC₅₀ values for **ammonium trivanadium octaoxide** were 0.67 g/m³ in male rats and 1.08 g/m³ in female rats (ECHA 2019 c, 2021 a, 2022 c, d, f). After nose-only exposure of Sprague Dawley rats for 4 hours, the LC₅₀ for **potassium metavanadate** was 1.85 g/m³ in the males and 4.16 g/m³ in the females; the combined value for males and females was 2.89 g/m³ (ECHA 2019 b).

5.1.2 Oral administration

The oral LD₅₀ values for various vanadium oxides were between 5.6 and 470 mg vanadium/kg body weight in rats. The LD₅₀ values in mice were 13 to 93 mg vanadium/kg body weight (Greim 2009).

The LD₅₀ values for **vanadium metal**, **vanadium carbide nitride** and **divanadium trioxide** were > 2000 mg/kg body weight in rats. An LD₅₀ of 911 mg/kg body weight was derived for **divanadyl pyrophosphate**. The LD₅₀ for **divanadyl di(hydrogen phosphate) hydrate** was between 50 and 300 mg/kg body weight (ECHA 2019 a, c, 2021 b, 2022 d, e). An LD₅₀ of 448 mg/kg body weight was obtained for **vanadyl sulfate pentahydrate** in male rats and an LD₅₀ of 288.5 mg/kg body weight was derived from this value for **vanadyl sulfate** (Llobet and Domingo 1984). The LD₅₀ for **potassium metavanadate** was 322.8 mg/kg body weight in rats (ECHA 2019 b).

5.1.3 Dermal application

The dermal LD₅₀ for **divanadium pentaoxide** and for **potassium metavanadate** and **ammonium metavanadate** was above 2500 mg/kg body weight in male and female Sprague Dawley rats (ECHA 2019 b; Leuschner et al. 1994). In male and female rabbits, the dermal LD₅₀ for **divanadium pentaoxide** was > 200 and < 1000 mg/kg body weight (> 112 and < 560 mg vanadium/kg body weight). In this study, the substance was applied occlusively for 24 hours. All 4 rabbits died at 1000 mg/kg body weight, but none of the 10 exposed animals died at 200 mg/kg body weight. Oedema was noticeable in all animals as early as on the first day after application. In the animals that died, erythema persisted up to the day of death (3 to 6 days after application). In the animals that survived, erythema was observed only on the first day after application (BRRC and UCC 1994). **Vanadyl pyrophosphate (divanadyl pyrophosphate)** applied to the skin of rats in a dose of 2000 mg/kg body weight did not cause mortality (ECHA 2014). No mortality was observed in rabbits after occlusive dermal application of 5000 mg/kg body weight (ECHA 2019 a).

5.1.4 Intraperitoneal injection

Groups of 6 male Wistar rats were injected intraperitoneally with a single dose of vanadium of 0, 10, 20 or 40 mg/kg body weight in the form of **sodium metavanadate**. In the exposed animals, a statistically significant increase in the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities in the serum was observed. In isolated rat liver mitochondria, a statistically significant increase in ROS and in the mitochondrial membrane potential (MMP) and a decrease in GSH were observed ex vivo at vanadium doses of 20 mg/kg body weight and above in addition to a statistically significant increase in lipid peroxidation at doses of 40 mg/kg body weight and above (Hosseini et al. 2013).

After intraperitoneal injection, the LD₅₀ values for **sodium metavanadate** were 18.4 mg/kg body weight (rat) and 35.9 mg/kg body weight (mouse) and the values for **vanadyl sulfate pentahydrate** were 74.1 mg/kg body weight (rat) and 113.0 mg/kg body weight (mouse) (Llobet and Domingo 1984).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Table 8 provides a detailed overview of the data from the studies described below.

Groups of 10 male F344 rats were exposed nose-only to vanadium concentrations of 0 or 2 mg/m³ in the form of **ammonium metavanadate** for 8 hours a day on 4 consecutive days. The lung burden of vanadium increased over time. The vanadium levels determined in the lungs on the first day after the last exposure were about 40% lower than those determined on the last day of exposure. The percentage of macrophages in the bronchoalveolar lavage fluid (BALF) was decreased with statistical significance 24 hours after the end of a 4-day exposure period; however, the percentage of macrophages < 15 µm in diameter was increased and the percentage of larger macrophages was decreased. The polymorphonuclear neutrophils (PMN), protein levels and lactate dehydrogenase activity were increased (Cohen et al. 1996 b).

Groups of 5 male F344 rats were exposed nose-only to a vanadium concentration of about 0.1 mg/m³ for 5 hours a day on 5 consecutive days. Table 2 lists the exact concentrations of the vanadium compounds used for exposure and their MMAD. The iron and ferritin levels in the BALF were increased with statistical significance after exposure to **divanadium pentaoxide** or **sodium metavanadate**. The transferrin levels were increased only after exposure to **divanadium pentaoxide**. Tumour necrosis factor alpha (TNF-α) and MIP-2 (macrophage inflammatory protein) were likewise increased with statistical significance; the concentrations of the interleukins IL-6, IL-10 and IL-12 remained unchanged. MCP-1 (monocyte chemoattractant protein) was increased, but not with statistical significance. Fewer PMN were detected in the animals with exposure to vanadium than in the controls. An infection of the lungs with bacteria (*Listeria monocytogenes*, 4 × 10⁶/rat) 24 hours after the last exposure led to a marked increase in *Listeria* in the groups exposed to soluble **sodium metavanadate** after 72 hours and thus to reduced clearance of the bacteria. **Divanadium pentaoxide**, by contrast, induced a slight, but not significant, reduction in the bacterial load of 24% compared with the findings in the infected control group. Due to the effects induced by **sodium metavanadate**, exposure to 0.01 and 0.001 mg vanadium/m³ as **sodium metavanadate** was also assessed. The number of bacteria were not increased 72 hours after exposure to a vanadium concentration of 0.01 mg/m³ as **sodium metavanadate** (Section 3.1.2.2; Cohen et al. 2007, 2010).

In a 14-day inhalation study, groups of 6 male and 6 female Sprague Dawley rats were exposed to vanadium concentrations of 0, 1.5, 15 or 170 mg/m³ as **divanadium trioxide** for 6 hours a day on 5 days a week. Divanadium trioxide was tested as an aerosolized powder with an MMAD of 1.92, 2.02 and 2.25 µm, respectively. The body weight gains and feed consumption were reduced in the male animals at vanadium concentrations of 15 mg/m³ and above; these effects were statistically significant in all animals of the high concentration group. The increased lung weights and the increased number of partly pigmented macrophages are considered adaptive because these are processes that occur as a part of clearance. Inflammatory markers (total cell count, number of neutrophils, protein levels) were increased in the BALF of the males at vanadium concentrations of 21.5 mg/m³ and above. Some of the markers were found to have decreased in the high concentration group; this was attributed to the small amount of BALF that was recovered due to the poor condition of the animals. The authors described the study as a non-GLP study. The filters were analysed for vanadium in compliance with OECD ENV/MC/CHEM(98)17 (ECHA 2021 b; IITRI 2011). None of the animals were observed after the end of the exposure period; whether complete lung clearance occurred is therefore not known. The effect that correlates histologically with increased neutrophil levels was not examined in the males of the low concentration group. The validity of the study is limited due to the small number of animals.

Groups of 5 male and 5 female F344/N rats and B6C3F1 mice were exposed to **divanadium pentaoxide** concentrations of 0, 2, 4, 8, 16 or 32 mg/m³ (0, 1.12, 2.24, 4.48, 8.96, 17.92 mg vanadium/m³) in aerosol form for 5 hours a day, on 5 days a week, over a period of 16 days. Three male rats and all male mice in the high concentration group died. The body weight gains were decreased with statistical significance in rats of both sexes and in male mice at concentrations of 8 mg/m³ and above. In comparison with the values determined in the controls, the relative lung weights were increased with statistical significance in the male rats and in the mice at concentrations of 4 mg/m³ and above and in the female rats at concentrations of 2 mg/m³ and above. The immune system was tested by exposing groups of 10 male rats and 10 female mice to **divanadium pentaoxide** concentrations of 0, 4, 8 or 16 mg/m³ (0, 2.24, 4.48 or 8.96 mg vanadium/m³). Inflammatory markers in the BALF (total cell count, protein levels, lymphocyte count) were elevated at vanadium concentrations of 2.24 mg/m³ and above. The immune function of the treated animals was not impaired by viral or bacterial infections. The tests were performed by the IITRI laboratory; this laboratory did not carry out the 2-year carcinogenicity study (NTP 2002).

According to MacGregor et al. (2020), the rats and mice in the NTP (2002) study began to show signs of inflammation at the same concentration; the tumour incidence, however, was increased only in mice in this concentration range.

The Batelle Toxicology Northwest laboratory, the same laboratory that was contracted by the NTP to carry out its 2-year carcinogenicity study, conducted a 16-day study with **divanadium pentaoxide**. In this study, the animals were exposed to divanadium pentaoxide in the following concentrations: groups of 60 female rats were administered 0, 1 or 2 mg/m³ and 40 rats received 4 mg/m³; groups of 60 female B6C3F1 mice were administered 0, 2 or 4 mg/m³ and 40 mice received 8 mg/m³. Hyperplasia and inflammation were observed in the lungs of rats at the low concentration and above. Minimal hyperplasia was found in the lungs of all exposed mice after only 6 days. Cell proliferation was increased in the lungs of both species after subcutaneous injection of bromodeoxyuridine (Section 3.1.2.2, NTP 2002).

The NTP studies with exposure of F344 rats and B6C3F1 mice to **divanadium pentaoxide** for 13 weeks (IITRI laboratory) and 104 weeks (Batelle Toxicology Northwest laboratory) (NTP 2002) are described in detail by Greim (2009). The main findings are listed in Table 8. A LOAEC (lowest observed adverse effect concentration) for divanadium pentaoxide of 0.5 mg/m³ (0.28 mg vanadium/m³) was derived based on the findings of these studies. The carcinogenic effects are described in Section 5.7.2.

Female B6C3F1/Hsd mice, 48 animals per concentration group, were exposed nose-only to **divanadium pentaoxide** concentrations of 0, 0.25, 1 or 4 mg/m³ (0, 0.14, 0.56, 2.24 mg vanadium/m³) in aerosol form for 6 hours a day over a period of 7 to 16 days. The divanadium pentaoxide had a purity of 99.8% with 0.13% impurities from divanadium tetroxide. The MMAD of the aerosol particles was between 1.22 and 1.43 µm. The markers for oxidative stress revealed slight changes only in the low concentration group. GSH and α-tocopherol were decreased, but not at higher concentrations. F2-isoprostane levels were not increased. GSSG levels increased to 159%, 223% and 215%, respectively, of the values determined in the controls; the increases were weakly dependent on the concentration. The GSH/(2 × GSSG) ratio was decreased to 53%, 55% and 53% of the control values, respectively, without concentration dependency. The lung weights and inflammatory changes in the lungs such as histiocytosis and alveolitis increased with the concentration at divanadium pentaoxide concentrations of 1 mg/m³ and above. The increased lung weights cannot be attributed to an accumulation of divanadium pentaoxide even though the vanadium levels in the blood and lungs increased with the dose. Instead, the increase was caused by the inflammatory response and the subsequent accumulation of fluids as well as the immune response (Schuler et al. 2011). The increase in GSSG is considered adaptive. Isoprostane and 8-oxo-2'-deoxyguanosine are more stable parameters for oxidative stress. These parameters did not increase or, in the case of 8-oxo-2'-deoxyguanosine, increased only from the middle concentration. As a result, a NOAEC (no observed adverse effect concentration) of 0.14 mg vanadium/m³ was derived from this study for oxidative DNA damage (see Section 5.6.2) and for inflammatory and histopathological effects in the lungs caused by vanadium.

In the studies below, mice were exposed whole-body twice a week for 1 hour a day. These exposure conditions were chosen because vanadium has a half-life of 48 hours. No changes were observed in studies with exposure of CD1 mice to 0.005 or 0.01 M suspensions of nebulized **divanadium pentaoxide** (examination with a light microscope, no other details). As a result, a divanadium pentaoxide concentration of 0.02 M (Avila-Costa et al. 2004) (about 3.6 g/l, 1.4 mg

divanadium pentaoxide/m³ (Avila-Costa et al. 2005) was chosen as the exposure concentration. In the studies described below that used these exposure conditions, the **divanadium pentaoxide** had a purity of 99.99% (Ustarroz-Cano et al. 2012) and 80% of the aerosol particles had an MMAD of 0.5 to 5.0 µm (as specified by the authors; this probably refers to the diameter) (Colín-Barenque et al. 2015).

Groups of 20 male CD1 mice were exposed whole-body to an aerosol generated from a suspension of 0 or 0.02 M **divanadium pentaoxide** (about 0 or 1.4 mg **divanadium pentaoxide**/m³) in Tween buffer twice a week for 1 hour, over a period of 4 weeks. The number of thymic dendritic cells was reduced in the exposed animals; this was demonstrated by a decrease in CD11c surface markers. This effect induces a negative selection of T-cells, ultimately leading to the development of autoreactive T-cells and thus to autoimmune reactions (Ustarroz-Cano et al. 2012).

The olfactory function (buried food test (chocolate)) of male CD1 mice (n = 10) was decreased after whole-body exposure to vanadium twice a week for 1 hour over a period of 4 weeks in the form of an aerosol generated from a suspension of 0 or 0.02 M **divanadium pentaoxide** in saline (about 0 or 1.4 mg **divanadium pentaoxide**/m³). The olfactory bulbs of 5 animals from each group were examined histopathologically. The results revealed smaller granule cells, a decrease in dendritic spine density and changes to the ultrastructure. In addition, vanadium increased lipid peroxidation in the olfactory bulb. An analysis of the matrix metalloproteinases 2 (MMP-2) and 9 (MMP-9) revealed marked increases in MMP-9 in the brain. MMP-9 was increased in the hippocampus as early as after a week, while the increases in MMP-2 were hardly noticeable and occurred only in the hippocampus and striatum (only in week 2) (Colín-Barenque et al. 2008, 2015).

After whole-body exposure of groups of 48 male CD1 mice to 0 or 0.02 M **divanadium pentaoxide** (about 0 or 1.4 mg **divanadium pentaoxide**/m³) twice a week for 1 hour, over a period of 8 weeks, the mice that were exposed to vanadium had fewer dendritic spines in the striatum (part of the basal ganglia of the brain). A decrease in immunoreactive cells was detected in the substantia nigra starting in week 3 (Avila-Costa et al. 2004).

Groups of 48 male CD1 mice were exposed whole-body to **divanadium pentaoxide** in concentrations of 0 or 1.4 mg/m³ twice a week for 1 hour, over a period of 1 to 12 weeks. The vanadium concentrations in the brain were increased with statistical significance as early as after a week, but the concentrations did not continue to increase over the following weeks. The damage to the ependymal cells was dependent on the concentration (Avila-Costa et al. 2005).

After whole-body exposure of groups of 24 male CD1 mice to 0 or 0.02 M **divanadium pentaoxide** (about 0 or 1.4 mg **divanadium pentaoxide**/m³) twice a week for 1 hour, over a period of 4 weeks, the mice that were exposed to vanadium had fewer dendritic spines in the hippocampus. In addition, necrosis and ultrastructural changes were observed in the hippocampus. The mice with exposure to vanadium had limited spatial memory (Avila-Costa et al. 2006).

After exposure of groups of 10 male CD1 mice whole-body to **divanadium pentaoxide** concentrations of 0 or 0.02 M (about 0 or 1.4 mg **divanadium pentaoxide**/m³) twice a week for 1 hour, over a period of 6 weeks, a statistically significant increase in inflammatory infiltration (eosinophils, neutrophils, mononuclear cells), increased lipid peroxidation and an increased number of meganuclei were observed in the liver of the exposed animals. Increases in the ALT and AST values in the serum that reach statistical significance also suggested cell damage in the liver (Cano-Gutiérrez et al. 2012).

After exposure of groups of 10 male CD1 mice whole-body to 0 or 0.02 M **divanadium pentaoxide** (about 0 or 1.4 mg **divanadium pentaoxide**/m³) twice a week for 1 hour, over a period of 4 or 8 weeks, inflammatory effects in the kidneys were observed with increased protein and erythrocyte levels in the urine (Espinosa-Zurutuza et al. 2018).

Groups of 10 male CD1 mice were exposed whole-body to 0 or 0.02 M **divanadium pentaoxide** (about 0 or 1.4 mg **divanadium pentaoxide**/m³) twice a week for 1 hour, over a period of 4, 8 or 12 weeks. Thrombocyte aggregation in the plasma was inhibited in the exposed mice after 4 weeks, but had returned to normal levels after 8 weeks. Vanadium concentrations in the serum and bone marrow were increased with statistical significance. Thrombocyte levels were increased markedly after exposure for 12 weeks; this effect was statistically significant as from week 3. The authors suggest that thrombocyte function is impaired by exposure to divanadium pentaoxide (González-Villalva et al. 2006, 2011).

Male CD1 mice were exposed whole-body to **divanadium pentaoxide** concentrations of 0 or 1.4 mg/m³ twice a week for 1 hour, over a period of 12 weeks. Divanadium pentaoxide led to an increase in the number and size of megakaryocytes in the spleen and bone marrow of male CD1 mice. Modifications in the cytoplasm, granule content and nuclear ultrastructure were evident. The authors suggest that this may lead to increased production of thrombocytes accompanied by an increased risk of thromboembolic disorders (Fortoul et al. 2008).

Male CD1 mice were exposed whole-body to **divanadium pentaoxide** in concentrations of 0 or 1.4 mg/m³ for 1 hour a week over two 12-week periods. Spermatogenesis was investigated by determining the connexion 43 levels in the seminiferous tubules of the mice. Connexin 43 had been redistributed and was present in the membranes in lower amounts. In addition, the histological examination revealed severe damage to the epithelial cells (Bizarro-Nevares et al. 2016).

Groups of 12 male and 12 female CD1 mice were exposed whole-body to **divanadium pentaoxide** in concentrations of 0 or 1.4 mg/m³ twice a week for 1 hour, over a period of 12 weeks. Ki-67 positive lymphocytes (in the nucleus and cytoplasm) were increased with statistical significance in the spleen of the exposed male mice after only 1 week of exposure; this effect became more pronounced over the course of the exposure period. In the males of the control group, the Ki-67 signal was of lower intensity and was found only in the nucleus. In the females, including those exposed to divanadium pentaoxide, a low signal was observed only in the nucleus (Rodríguez-Lara et al. 2016 b).

Groups of 112 male CD-1 mice were exposed to **divanadium pentaoxide** concentrations of 0 or 0.02 M (about 0 or 1.4 mg **divanadium pentaoxide**/m³ (mean concentration 1436 ± 273 µg/m³)) twice a week for 1 hour, over a period of 12 weeks. An increase in spleen weights was observed, with a peak in week 9. The weights then decreased, until they reached values in week 12 that were about equal to the weights of the control animals. Not only the number of germinal centres was increased in the spleen in the animals that were exposed to divanadium pentaoxide, but also the number of very large and not clearly delimited germinal centres that contained more lymphocytes and megakaryocytes. The red pulp was poorly delimited and had an increase in CD19+ cells within hyperplastic germinal nodes. According to the authors, the immune response was severely impaired by the functional and histopathological changes in the spleen (Piñon-Zarate et al. 2008).

Groups of 5 female AKR mice were exposed 2 times (on days 1 and 7) by **laryngeal aspiration** to 50 µl phosphate-buffered saline (PBS) containing a **divanadium pentaoxide** dose of 0 or 4 mg/kg body weight. The lungs of the mice were removed 24 hours later. The animals that were exposed to vanadium exhibited clear signs of inflammation and increased mucous production in the lungs (Yu et al. 2011).

Male C57BL/6J or DBA/2J mice were exposed 2 times (on days 1 and 8) by **oropharyngeal aspiration** to **divanadium pentaoxide** doses of 0, 0.1, 0.5, 1, 2 or 4 mg/kg body weight (groups of 4–8 animals/dose and strain). The total cell count in the BALF was increased with statistical significance even in the low dose group; this effect was most pronounced in the DBA/2J mice (Walters et al. 2014).

Groups of 3 to 8 male mice of the A/J, BALB/cJ and C57BL/6J strains were given **divanadium pentaoxide** doses of 0 or 4 mg/kg body weight by **oropharyngeal aspiration** once a week for 4 weeks. The divanadium pentaoxide was suspended in PBS. The controls were exposed only to PBS. The inflammatory markers detected in the BALF after the last aspiration and on days 1, 3, 6 or 21 after the last aspiration were markedly stronger in the strains A/J and BALB/cJ than in the C57BL/6J strain. The protein level, total cell count and numbers of macrophages, PMN and lymphocytes were determined. After 21 days, signs of inflammation were no longer found in the BALF of C57BL/6J mice, but in that of both other strains. Increased proliferation of the bronchiolar and alveolar epithelium was found in A/J mice. Increased chemokine levels were found in the lung homogenate of the strains A/J and BALB/cJ; these levels were hardly increased in the C57BL/6J strain (Rondini et al. 2010).

Groups of 5 male C57BL/6 mice were given 0 or 182 µg of **divanadium pentaoxide** in 50 µl of water by **intranasal administration** 3 times a week over the course of a month. The olfactory bulb weights, the tyrosine hydroxylase levels and the levels of dopamine and its metabolites in the glomerular layer of the olfactory bulb were decreased with statistical significance. Neurochemical changes in the form of impaired olfactory perception of female pheromones and

impaired locomotion using activity monitors were determined. According to the authors, the results suggest adverse effects on the olfactory bulb that may lead to neurochemical impairments and impairment of neurological behaviour (Afeseh Ngwa et al. 2014).

Tab. 8 Effects induced by vanadium compounds after repeated inhalation exposure

Species, strain, number per group	Exposure	Findings	References
rat, F344, 2 ♂ per exposure duration (V level), 10 ♂ (BALF)	1 to 4 days (V level), 4 days (BALF), 0, 2 mg V/m ³ (NH ₄ VO ₃ , MMD = 0.32 µm), 8 hours/day, examination: directly after the end of exposure, nose-only	2 mg V/m³: lungs: V ↑ (dependent on time), BALF: percentage of macrophages ↓* (small ↑, large ↓) and PMN ↑*, LDH ↑*, protein levels ↑*	Cohen et al. 1996 b
rat, F344, 5–10 ♂	5 days, 0, 0.1 mg V/m ³ (V ₂ O ₅ and NaVO ₃ , MMAD = 0.74 and 0.21 µm, respectively, GSD 2.1 and 2.8, respectively), 5 hours/day, 24 hours after last exposure = day 0, infected with bacteria 24 hours after last exposure, examination 72 hours later = day 3, nose-only	0.1 mg V/m³: day 0: lungs: V ↑* (V ₂ O ₅ 7 times as high as NaVO ₃), BALF: Fe ↑* (V ₂ O ₅ by 72%, NaVO ₃ by 82%), ferritin ↑* (V ₂ O ₅ by 75%, NaVO ₃ by 133%), transferritin ↑* (by 47%, only V ₂ O ₅), TNF-α ↑*, MIP-2 ↑*, day 3: bacterial load: NaVO ₃ : +435%, pathogen clearance ↓*, V ₂ O ₅ : -24%	Cohen et al. 2007, 2010
rat, F344, 5–10 ♂	5 days, 0, 0.01 mg V/m ³ (NaVO ₃), 5 hours/day, infected with bacteria 24 hours after last exposure, examination 72 hours later = day 3, nose-only	0.01 mg V/m³: day 3: bacterial load: NaVO ₃ : +1.73% (not significant)	Cohen et al. 2007
rat, Sprague Dawley, 6 ♂, 6 ♀	14 days, 0, 1.5, 15, 170 mg V/m ³ (0, 2.2, 22, 250 mg V ₂ O ₃ /m ³), 6 hours/day, 5 days/week, nose-only	1.5 mg V/m³ and above: BALF: macrophages ↑*, lymphocytes ↓*, ♀: total cell count ↑*, ♂: neutrophils ↑*, LDH ↑*, protein levels ↑*, lungs: pigmented macrophages in the alveoli, alveolar histiocytosis (only this concentration), ♀: pigmentation, lymph nodes, bronchial: enlarged, ♂: hyperplasia of the paracortical zone; 15 mg V/m³ and above: body weights ↓, feed consumption ↓ (not significant), BALF: ♂: total cell count ↑*, ♀: LDH ↑*, protein levels ↑*, lungs: relative weights ↑**, pigmentation, lymph nodes, bronchial and mediastinal: enlarged, hyperplasia of the paracortical zone of the mediastinal lymph nodes, ♀: hyperplasia of the paracortical zone of the bronchial lymph nodes; 170 mg V/m³: body weights ↓*, feed consumption ↓*, BALF: ♀: neutrophils ↑*, lungs: alveolar and interstitial infiltrates, spleen: ♂: relative weights ↓*, brain: relative weights ↑**, testes: ♂: relative weights ↑**, liver: ♀: relative weights ↑*, thymus: ♂: atrophy	IITRI 2011

Tab. 8 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 5 ♂, 5 ♀, BAL: groups of 10 ♂	16 days, 0, 2, 4, 8, 16, 32 mg V ₂ O ₅ /m ³ (0, 1.12, 2.24, 4.48, 8.96, 17.92 mg V/m ³), BALF: ♂: 0, 4, 8, 16 mg V ₂ O ₅ /m ³ (0, 2.24, 4.48, 8.96 mg V/m ³), 6 hours/day, 5 days/week, whole-body, IITRI laboratory	1.12 mg V/m³ and above: ♀: relative lung weights ↑*; 2.24 mg V/m³ and above: ♂: relative lung weights ↑*, BALF: ♂: lysozymes ↑*, protein levels ↑*, total cell count ↑*; 4.48 mg V/m³ and above: body weights ↓*, BALF: ♂: macrophages ↓*, neutrophils ↑*; 8.96 mg V/m³ and above: rapid breathing, nasal and ocular discharge; 17.92 mg V/m³: hypoactivity, hunched posture, diarrhoea, salivation ↑, discoloured urine, ♂: mortality (3/5)	NTP 2002
rat, F344, 60 ♀, 4 mg/m ³ 40 ♀, BrdU incorporation: 10 ♀: subcutaneous injection of BrdU on the day before and on day 7 of exposure	16 days, 0, 1, 2, 4 mg V ₂ O ₅ /m ³ (0, 0.56, 1.12, 2.24 mg V/m ³), 6 hours/day, 5 days/week, whole-body, Batelle Toxicology Northwest laboratory	0.56 mg V/m³ and above: lungs: hyperplasia (3/10), macrophages ↑ (10/10), inflammation (8/10), cell proliferation in the bronchioles and in the alveolar tissue (BrdU incorporation); 1.12 mg V/m³ and above: lungs: hyperplasia (10/10), inflammation (10/10); 2.24 mg V/m³ and above: lungs: fibrosis (6/10)	NTP 2002
rat, F344, 10 ♂, 10 ♀	13 weeks, 0, 1, 2, 4, 8, 16 mg V ₂ O ₅ /m ³ (0, 0.56, 1.12, 2.24, 4.48, 8.96 mg V/m ³), 6 hours/day, 5 days/week, whole-body, IITRI laboratory	0.56 mg V/m³: NOAEC; 1.12 mg V/m³: lungs: hyperplasia** (10/10), ♂: inflammation** (9/10), fibrosis (2/10), microcytosis †; 2.24 mg V/m³ and above: ♂: body weights ↓*, lungs: fibrosis (10/10), ♀: inflammation** (10/10), relative weights ↑, nose: ♀: hyperplasia** (10/10), metaplasia** (8/10); 4.48 mg V/m³ and above: nose: ♂: hyperplasia** (10/10), metaplasia** (10/10)	Greim 2009; NTP 2002
rat, F344, 50 ♂, 50 ♀	104 weeks, 0, 0.5, 1, 2, 4 mg V ₂ O ₅ /m ³ (0, 0.28, 0.56, 1.12, 2.24 mg V/m ³), 6 hours/day, 5 days/week, whole-body, Batelle Toxicology Northwest laboratory	0 mg V/m³: lungs: ♂: hyperplasia (7/50 alveolar, 3/50 bronchiolar), chronic inflammation (5/50), fibrosis (7/50), larynx: chronic inflammation (3/49, 8/50), hyperplasia (0/49, 0/50), degeneration (0/49, 2/50), squamous cell metaplasia (0/49, 2/50), nose: ♂: goblet cell hyperplasia (4/49); 0.28 mg V/m³ and above: LOAEC, lungs: alveolar histiocytic infiltration**, ♂: hyperplasia**** (24/49 alveolar, 17/49 bronchiolar), larynx: chronic inflammation** (20/50, 26/49), hyperplasia** (18/50, 25/49), degeneration** (22/50, 33/49), squamous cell metaplasia (9/50, 7/49), nose: ♂: goblet cell hyperplasia (15/50); 0.56 mg V/m³ and above: lungs: ♂: chronic inflammation** (24/48), interstitial fibrosis* (16/48), ♀: alveolar pigmentation*, hyperplasia** (14/50); 1.12 mg V/m³ and above: lungs: alveolar metaplasia, ♀: chronic inflammation**, interstitial fibrosis**, ♂: alveolar pigmentation, nose: ♀: goblet cell hyperplasia	Greim 2009; NTP 2002

Tab. 8 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1/Hsd, 48 ♀ per concentration group, 6 ♀ from each concentration group per end point	7 and 16 days, 0, 0.25, 1, 4 mg V ₂ O ₅ /m ³ (0, 0.14, 0.56, 2.24 mg V/m ³), 6 hours/day, nose-only	0.14 mg V/m³: NOAEC; 0.56 mg V/m³ and above: body weights ↓ (only 7 days), lungs: (16 days): relative weights ↑*, multifocal, diffuse alveolar histiocytosis (6/6), subacute multifocal alveolitis (5/6), multifocal infiltration of granulocytes (4/6), cell proliferation ↑ (Ki-67 and PCNA); 2.24 mg V/m³: lungs (7 days): weights ↑*, increase in severity of subacute multifocal alveolitis (no other data), multifocal infiltration of granulocytes (5/6)	Schuler et al. 2011
mouse, B6C3F1, 5 ♂, 5 ♀, BAL: groups of 10 ♀	16 days, 0, 2, 4, 8, 16, 32 mg V ₂ O ₅ /m ³ (0, 1.12, 2.24, 4.48, 8.96, 17.92 mg V/m ³), 6 hours/day, 5 days/week, whole-body, IITRI laboratory	1.12 mg V/m³ and above: ♀: hyperplasia of the mediastinal lymph nodes; 2.24 mg V/m³ and above: relative lung weights ↑*, ♂: hyperplasia of the mediastinal lymph nodes, ♀: BALF: lysozymes ↑*, protein ↑*; 4.48 mg V/m³ and above: ♀: body weights ↓*, ♀: BALF: macrophages ↓*, total cell count ↑*; 8.96 mg V/m³ and above: ♂: body weights ↓*, relative liver weights ↑*, ♀: BALF: neutrophils ↑*; 17.92 mg V/m³: hypoactivity, ♂: mortality (5/5)	NTP 2002
mouse, B6C3F1, 60 ♀, 8 mg/m ³ 40 ♀, BrdU incorporation: 10 ♀: subcutaneous injection of BrdU on the day before and on day 7 of exposure	16 days, 0, 2, 4, 8 mg V ₂ O ₅ /m ³ (0, 1.12, 2.24, 4.48 mg V/m ³), 6 hours/day, 5 days/week, whole-body, 10 animals each examined on days 6 and 13, Batelle Toxicology Northwest laboratory	1.12 mg V/m³ and above: lungs: minimal hyperplasia (from day 5), cell proliferation in the bronchioles and the alveolar tissue (BrdU incorporation); 2.24 mg V/m³ and above: lungs: low-grade hyperplasia	NTP 2002
mouse, B6C3F1, 10 ♂, 10 ♀	13 weeks, 0, 1, 2, 4, 8, 16 mg V ₂ O ₅ /m ³ (0, 0.56, 1.12, 2.24, 4.48, 8.96 mg V/m ³), 6 hours/day, 5 days/week, whole-body	0.56 mg V/m³: NOAEC; 1.12 mg V/m³ and above: lungs: hyperplasia (♂: 4/10*, ♀: 6/10**), ♀: inflammation** (7/10); 2.24 mg V/m³ and above: ♀: body weights ↓**, lungs: relative weights ↑*, ♂: inflammation* (4/10); 4.48 mg V/m³ and above: ♂: body weights ↓**, sperm motility ↓, lungs: hyperplasia** (10/10), inflammation** (10/10), foci, discoloration	Greim 2009; NTP 2002
mouse, B6C3F1, 50 ♂, 50 ♀	104 weeks, 0, 1, 2, 4 mg V ₂ O ₅ /m ³ (0, 0.56, 1.12, 2.24 mg V/m ³), 6 hours/day, 5 days/week, whole-body	0 mg V/m³: lungs: hyperplasia (alveolar: 3/50, 0/50, bronchiolar: 0/50, 0/50), chronic inflammation (6/50, 4/50), interstitial fibrosis (1/50, 0/50), alveolar histiocytic infiltration (10/50, 0/50), larynx: squamous cell metaplasia (2/49, 0/50), nasal respiratory epithelium: ♂: degeneration (8/50); 0.56 mg V/m³ and above: LOAEC lungs: hyperplasia* (alveolar: 41/50, 31/50, bronchiolar: 15/50, 12/50), chronic inflammation** (42/50, 12/50), interstitial fibrosis (6/50, 1/50), alveolar histiocytic infiltration** (36/50, 34/50), larynx: squamous cell metaplasia** (45/50, 39/50), nasal respiratory epithelium: respiratory metaplasia; ♂: degeneration** (22/50), lymph nodes, bronchial: ♀: hyperplasia**	Greim 2009; NTP 2002

Tab. 8 (continued)

Species, strain, number per group	Exposure	Findings	References
Studies with whole-body exposure for 1 hour/day, 2 × per week, V₂O₅ (purity 99.99%), 80% with 0.5–5.0 µm			
mouse, CD1, 20 ♂	4 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: thymus: dendritic cells: CD11c ↓*	Ustarroz-Cano et al. 2012
mouse, CD1, 10 ♂	4 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: olfactory bulb: olfactory function ↓, cell changes, brain (prefrontal cortex, olfactory bulb, striatum, hippocampus): MMP9 ↑*	Colín-Barenque et al. 2008, 2015
mouse, CD1, 24 ♂	4 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: spatial memory ↓* (as early as after 24 hours), brain (hippocampus): number of dendritic spines ↓* (as early as after 24 hours), necrosis ↑*, ultrastructural changes ↑	Avila-Costa et al. 2006
mouse, CD1, 10 ♂	6 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: ALT ↑*, AST ↑*, liver: eosinophils, neutrophils, mononuclear cells ↑*	Cano-Gutiérrez et al. 2012
mouse, CD1, 10 ♂	1–8 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: brain: number of dendritic spines ↓ (striatum), TH-immunoreactive neurons ↓* (substantia nigra, from week 3)	Avila-Costa et al. 2004
mouse, CD1, 10 ♂	4 or 8 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	4 weeks: no effects 1.4 mg/m³ (8 weeks): urine: protein ↑*, erythrocytes ↑*, kidneys: oxidative damage	Espinosa-Zurutuza et al. 2018
mouse, CD1, 10 ♂	1–12 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 per week	1.4 mg/m³: blood: V concentration ↑*, thrombocytes ↑* (from week 3), thrombocyte aggregation ↓* (from week 8), bone marrow: V concentration ↑*	González-Villalva et al. 2006, 2011
mouse, CD1, 5 ♂, controls 24 ♂	1–12 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: seminiferous tubules: connexin 43 ↓* (membrane localization, from week 8), epithelial cells ↓	Bizarro-Nevares et al. 2016
mouse, CD1, 10 ♂	1–12 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: brain: V concentration ↑*, changes to the ependymal layer (cilia ↓, detachment)	Avila-Costa et al. 2005
mouse, CD1, ♂ (no other data)	12 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: spleen: megakaryocytes ↑, bone marrow: megakaryocytes ↑	Fortoul et al. 2008
mouse, CD1, 12 ♂, ♀	12 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: spleen: ♂: proliferation ↑ (Ki-67 labelling)	Rodríguez-Lara et al. 2016 b
mouse, CD1, 112 ♂	12 weeks, 0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.78 mg V/m ³), 1 hour/day, 2 × per week	1.4 mg/m³: spleen: weights ↑ (peak week 9, no data for body weights), number and size of germinal centres ↑, CD19+ ↑, red pulp poorly delimited	Piñon-Zarate et al. 2008

Tab. 8 (continued)

Species, strain, number per group	Exposure	Findings	References
Aspiration assays			
mouse, C57BL/6J, DBA/2J, 49 BXD recombinant inbred, 4–8 ♂	days 1 and 7, 0, 0.1, 0.5, 1, 2, 4 mg V ₂ O ₅ /kg body weight, oropharyngeal aspiration, observation period 7 days	0.1 mg/kg body weight: DBA/2J: LOAEC, BALF: cell count ↑*; 0.5 mg/kg: C57BL/6J: BALF: cell count ↑*; 1 mg/kg: DBA/2J: lungs: function ↓*; 2 mg/kg: C57BL/6J: lungs: function ↓*	Walters et al. 2014
mouse, AKR, 5 ♀	days 1 and 7, 0, 4 mg V ₂ O ₅ /kg body weight, laryngeal aspiration, observation period 24 hours	4 mg/kg body weight: lungs: inflammation, mucous production ↑	Yu et al. 2011
mouse, A/J, BALB/cJ, C57BL/6J (B6), 3–8 ♂	4 weeks, 0, 4 mg V ₂ O ₅ /kg body weight, 1 × per week oropharyngeal aspiration, observation period 1–21 days	4 mg/kg body weight: BALF: A/J, BALB/cJ: signs of inflammation ↑* (protein levels, total cell count, number of macrophages, PMN and lymphocytes), lung tissues: A/J, BALB/cJ: chemokines ↑*, A/J: proliferation ↑*, BALF: C57BL/6J (only after days 1–6 of the observation period): signs of inflammation ↑*	Rondini et al. 2010
mouse, C57BL/6, 5 ♂	4 weeks, 0, 182 µg V ₂ O ₅ in 50 µl H ₂ O, 3 × per week, intranasal administration	182 µg: activity ↓*, olfactory perception of pheromones ↓***, olfactory bulb: weights ↓*, tyrosine hydroxylase levels ↓***, dopamine ↓***, DOPAC ↓***, astrocyte proliferation ↑	Afeseh Ngwa et al. 2014

*p < 0.05, **p < 0.01, ***p < 0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BAL: bronchoalveolar lavage; BALF: bronchoalveolar lavage fluid; BrdU: 5-bromo-2'-deoxyuridine; CD11c: cell surface marker for dendritic cells; CD19: B-cell-specific surface molecule; DOPAC: 3,4 dihydroxyphenylacetic acid; LDH: lactate dehydrogenase; MMAD: mass median aerodynamic diameter; MMD: mass median diameter; MMP-9: matrix metalloproteinase 9; PMN: polymorphonuclear neutrophils; TH: tyrosine hydroxylase; V: vanadium

Monkeys

In groups of 8 cynomolgus monkeys exposed whole-body to **divanadium pentaoxide** concentrations of 0.5 or 5.0 mg/m³ (0.28 or 2.8 mg V/m³) for 6 hours a day over a period of 7 days, air-flow limitation and impaired lung function were observed at the vanadium concentration of 2.8 mg/m³. The lung function values determined in the monkeys prior to exposure were used as the control values. The total cell count in the BALF was increased significantly at this concentration; this was attributed to a marked increase in PMN and thus to an inflammatory response (Knecht et al. 1985).

Groups of 9 cynomolgus monkeys were exposed to **divanadium pentaoxide** concentrations of 0 or 0.5 mg/m³ (0 or 0.28 mg vanadium/m³) for 26 weeks (6 hours/day, 5 days/week) and subsequently to a divanadium pentaoxide concentration of 3.0 mg/m³ (1.7 mg vanadium/m³) for 2 weeks. The lung function values that were determined did not reveal any impairment in lung function. The lungs were slightly less responsive in the methacholine challenge test, but without statistical significance. The analysis of the BALF found that only the number of eosinophils was decreased with statistical significance (Greim 2009; Knecht et al. 1992).

5.2.2 Oral administration

Groups of 5 male and 5 female SD rats or B6C3F1/N mice were given **vanadyl sulfate** (VOSO₄) or **sodium metavanadate** (NaVO₃) for 14 days with the drinking water in concentrations of 0, 125, 250, 500, 1000 or 2000 mg/l (for data given in mg/kg body weight and day, see Table 9). The water containing vanadyl sulfate had a pH of 3.5 and that containing sodium metavanadate had a pH of 7. Water consumption was decreased in all animals by 26% to 80% at concentrations of 500 mg/l and above. The two high concentration groups were exposed for only 8 days because of high mortality and

clinical symptoms. The clinical symptoms and changes in the organ and body weights are given in Table 9. Sodium metavanadate was more toxic than vanadyl sulfate, even though the amount of vanadium absorbed was similar in both cases (Roberts et al. 2016).

Tab. 9 Findings in Sprague Dawley rats and B6C3F1/N mice after administration of sodium metavanadate and vanadyl sulfate with the drinking water (Roberts et al. 2016)

Species, strain, number per group	Exposure, 14 or 8 ^{b)} days [mg V/kg body weight and day]	Findings ^{a)}
Sodium metavanadate		
rat, SD		
5 ♂	0, 5.4, 10.4, 16.3, 18.1, 20.1	5.4 mg V/kg body weight and above: liver weights ↑; 10.4 mg V/kg body weight and above: body weights ↓, not dose-dependent: kidney weights ↑, lung weights ↓; 16.3 mg V/kg body weight: NOAEL for clinical symptoms; 18.1 mg V/kg body weight and above: ruffled fur, hunched posture, shallow breathing, lethargy, abnormal gait, discoloration of the eyes and nose, mortality: 1/5
5 ♀	0, 6.0, 10.5, 17.7, 24.8, 18.3	17.7 mg V/kg body weight: NOAEL for clinical symptoms, body weights ↓; 24.8 mg V/kg body weight and above: lethargy; 18.3 mg V/kg body weight: ruffled fur, hunched posture, lethargy, abnormal gait, discoloration of the nose, mortality: 1/5
mouse, B6C3F1/N		
5 ♂	0, 7.7, 17.1, 24.3, 25.1, 46.9	7.7 mg V/kg body weight and above: lung weights ↓; 17.1 mg V/kg body weight: NOAEL for clinical symptoms; 24.3 mg V/kg body weight and above: ruffled fur, hunched posture, shallow breathing, lethargy, abnormal gait, mortality 1/5, body weights ↓; 25.1 mg V/kg body weight: mortality 3/5
5 ♀	0, 6.4, 11.0, 16.1, 20.3, 19.5	6.4 mg V/kg body weight and above: lung weights ↓; 11.0 mg V/kg body weight: NOAEL for clinical symptoms; 16.1 mg V/kg body weight and above: ruffled fur, hunched posture, rapid and shallow breathing, abnormal gait, discoloration of the eyes and nose, body weights ↓; 20.3 mg V/kg body weight: mortality 1/5
Vanadyl sulfate		
rat, SD		
5 ♂	0, 4.1, 8.1, 14.3, 23.6, 24.0	4.1 mg V/kg body weight and above: liver weights ↑; 23.6 mg V/kg body weight: NOAEL for clinical symptoms, body weights ↓, kidney weights ↑, lung weights ↓; 24.0 mg V/kg body weight: liver weights ↓, kidney weights ↓
5 ♀	0, 4.7, 9.0, 16.0, 23.5, 24.8	9.0 mg V/kg body weight: NOAEL for clinical symptoms; 16.0 mg V/kg body weight: 4/5 thin; 23.5 mg V/kg body weight and above: body weights ↓; 24.8 mg V/kg body weight: 2/5 hunched posture
mouse, B6C3F1/N		
5 ♂	0, 5.4, 10.7, 16.5, 25.2, 35.7	16.5 mg V/kg body weight: NOAEL for clinical symptoms; 25.2 mg V/kg body weight: 2/5 thin, body weights ↓; 35.7 mg V/kg body weight: ruffled fur, hunched posture, thymus weights ↓
5 ♀	0, 4.6, 7.8, 13.1, 18.8, 25.9	13.1 mg V/kg body weight: NOAEL for clinical symptoms; 18.8 mg V/kg body weight: body weights ↓; 25.9 mg V/kg body weight: ruffled fur, lung weights ↓, thymus weights ↓

^{a)} Unless specified otherwise, the changes listed are statistically significant.

^{b)} The animals of the two high concentration groups were exposed for only 8 days.

V: vanadium

The haematological examination of groups of 5 male and 5 female Charles River rats given gavage doses of **vanadium carbide nitride** of 0, 30, 300 or 1000 mg/kg body weight and day in corn oil (7 days/week) for 4 weeks revealed minimal effects at doses of 300 mg/kg body weight and above. However, like the minimal changes in the organ weights, the

authors did not consider these effects adverse. Other effects were not observed (ECHA 2022 d). The NOAEL (no observed adverse effect level) for **vanadium carbide nitride** was 1000 mg/kg body weight and day.

Groups of 12 male Sprague Dawley rats were given daily gavage doses of **sodium metavanadate** of 0, 4.1, 8.2 or 16.4 mg/kg body weight and day (0, 1.71, 3.42 or 6.84 mg vanadium/kg body weight and day) over a period of 8 weeks. The motor activity (open field) and learning behaviour (2-way shock avoidance test) of the animals were examined for 3 weeks beginning the day after administration of the last dose. The activity levels were decreased with statistical significance at the medium dose and above. The learning behaviour of the animals was tested on 3 consecutive days. Delayed reactions were observed in all exposed animals on day 3. The body weights of the animals in the high dose group were reduced with statistical significance as from week 3. The vanadium levels were determined after a subsequent 3-week test phase without administration; the vanadium concentrations in the liver, spleen, kidneys, brain, bones and muscles were increased with statistical significance at the low dose and above (Sanchez et al. 1998). A LOAEL (lowest observed adverse effect level) for vanadium of 1.71 mg/kg body weight and day was derived based on the study findings; this dose is equivalent to a concentration in air of 0.95 mg/m³ over a 6-hour exposure period (conversion: see footnote for Table 14).

Groups of 7 female Wistar rats were given feed that contained **sodium metavanadate** (NaVO₃) in concentrations of 0, 50 or 100 mg/kg (about 0, 4.5 or 9 mg NaVO₃/kg body weight and day, conversion factor 0.09 (subchronic) according to EFSA (2012), about 0, 1.875 or 3.75 mg vanadium/kg body weight and day) over a period of 10 weeks. The body weight gains of the exposed animals were decreased with statistical significance. Vanadium levels in the liver and kidneys increased with the dose and the metallothionein levels in the kidneys were increased. In the high dose group, the ALT, cholinesterase and alkaline phosphatase activities in the plasma were decreased. The haemoglobin and haematocrit values were decreased with statistical significance, but without dose dependency (Adachi et al. 2000 a).

Groups of 8 male Sprague Dawley rats were given **sodium metavanadate** concentrations of 0, 500, 1000 or 2000 mg/l with the drinking water for 12 weeks in daily doses of about 0, 45, 90 or 180 mg sodium metavanadate/kg body weight (conversion factor 0.09 (subchronic) according to EFSA (2012), about 0, 18.83, 37.5, 75.31 mg vanadium/kg body weight and day). The Morris water maze test was carried out 4 days after the final administration via the drinking water. The escape latency was increased in the animals of the middle dose group with statistical significance and the animals crossed the platform less frequently. The effects observed in the striatum at the low dose and above were a dose-dependent accumulation of vanadium that reached statistical significance and an increase in the neurotransmitters acetylcholine (ACh), 5-hydroxytryptamine (serotonin, 5-HT) and gamma-aminobutyric acid (GABA). The expression of the protein synapsin-1 was reduced with statistical significance from the lowest dose (Sun et al. 2017). Toxicokinetic data was used to extrapolate the LOAEC for vanadium of 18.83 mg/kg body weight and day to obtain a concentration in air of 10.5 mg/m³ for the exposure of rats over a 6-hour period (conversion, see footnote for Table 14).

Groups of 35 SD rats were given **vanadyl sulfate** in daily gavage doses of 0, 0.25 or 1.2 mg/kg body weight and day (0, 0.08 or 0.38 mg vanadium/kg body weight and day) for 24 weeks. The glucose levels in the plasma, the insulin levels in the serum and the high-density lipoprotein levels were decreased with statistical significance. However, the cholesterol and low-density lipoprotein levels were increased (Hussain Shah et al. 2016).

Groups of 8 male Wistar rats were given **vanadyl sulfate** in concentrations of 0, 500, 750, 1250 or 1500 mg/l with the drinking water (about 0, 45, 67.5, 112.5 or 135 mg/kg body weight, conversion factor 0.09 (subchronic) according to EFSA (2012), about 0, 14.1, 21.1, 35.2 or 42.25 mg vanadium/kg body weight and day) over a period of 52 weeks. The AST and ALT activities in the plasma and the urea levels did not differ from the values determined in the controls after the end of exposure and after an observation period of 16 weeks. The histopathological examination of a large number of organs did not reveal any adverse changes (Dai et al. 1994).

Haematological effects were studied by giving vanadium to groups of 8 male Wistar rats with the drinking water for 12 weeks either in the form of **vanadyl sulfate hydrate** at a dose level of 0.15 mmol vanadium/kg body weight and day (7.65 mg vanadium/kg body weight and day) or in the form of **ammonium metavanadate** at a dose level of 0.19 mmol vanadium/kg body weight and day (9.69 mg vanadium/kg body weight and day). Blood tests were performed before the

beginning of the study and in weeks 1, 2, 4, 8 and 12. The values obtained for the haematological parameters did not differ with statistical significance (Dai et al. 1995).

In a study, female and male rats and mice were given **sodium metavanadate** concentrations of 0, 31.3, 62.5, 125, 250 or 500 mg/l or **vanadyl sulfate** concentrations of 0, 21.0, 41.9, 83.8, 168 or 335 mg/l with the drinking water for 3 months. In male mice, haematological effects and hyperplasia of the gastrointestinal tract were observed even at the low sodium metavanadate concentration of 31.3 mg/l (2.8 mg sodium metavanadate/kg body weight and day, 1.4 mg vanadium/kg body weight and day). In the groups exposed to vanadyl sulfate, effects were evident only at higher concentrations (NTP 2023).

Groups of 6 male Sprague Dawley rats were given **sodium metavanadate** for 6 months in concentrations of 0, 1, 10 or 40 mg/l drinking water (about 0, 0.09, 0.9 and 3.6 mg/kg body weight and day, conversion factor 0.09 (subchronic) according to EFSA (2012), about 0, 0.038, 0.38 or 1.5 mg vanadium/kg body weight and day). In a second test, the rats were given drinking water for 180 days that contained sodium metavanadate in concentrations of 0 or 1 mg/l. No effects were found in the histopathological examination of the brain, liver, lungs, heart or blood vessels. In the high dose group, the lumen of the proximal tubules was constricted and contained amorphous material. Hydropic degeneration was observed in several proximal and distal tubules. The Na⁺-K⁺-ATPase activity was reduced with statistical significance. The urinary kinase I and II activities were increased with statistical significance and the potassium levels were decreased with statistical significance at concentrations of 10 mg/l and above. Creatinine, total nitrogen, protein and sodium were excreted with the urine at levels that were within the normal range. The blood pressure was increased with statistical significance in all exposed animals and the heart rate remained unchanged (Boscolo et al. 1994).

5.2.3 Dermal application

There are no data available.

5.2.4 Intraperitoneal injection

Groups of 17 male rats (strain not specified) were given **sodium metavanadate** in doses of 0 or 3 mg/kg body weight and day (0 or 1.25 mg vanadium/kg body weight and day) by intraperitoneal injection on 5 consecutive days. The sodium metavanadate was dissolved in saline solution. The control animals were given only saline solution. No changes in body weights or brain weights were observed. A statistically significant decrease in locomotor activity, reduced grooming and piloerection were observed the day following the last administration. The myelin fibre density was reduced in several areas of the brain. In the hippocampus and cerebellum, lipid peroxidation was increased with statistical significance and the generation of free radicals mediated by vanadium was observed (García et al. 2004, 2005).

Groups of 20 male Wistar rats were given **sodium metavanadate** in doses of 0, 3 or 7.2 mg/kg body weight (0, 1.25 or 3 mg vanadium/kg body weight and day) by intraperitoneal injection on 5 consecutive days. In the high dose group, OH radicals were increased with statistical significance in the cerebellum, but not in the hippocampus. The Cu/Zn SOD and catalase activities were not increased in the cerebellum or in the hippocampus; however, the GSH/GSSG ratio was decreased (Cuesta et al. 2011).

Groups of 12 male BALB/c mice were given **sodium metavanadate** in doses of 0 or 3 mg/kg body weight and day (0 or 1.25 mg vanadium/kg body weight and day) by intraperitoneal injection on 7 consecutive days. Memory loss, restricted locomotor activity and impaired coordination were observed in the exposed mice. Reduced SOD and catalase activities and increased malondialdehyde and H₂O₂ levels were found in the hippocampus (Adebiyi et al. 2018).

Groups of 12 male BALB/c mice were given **sodium metavanadate** in doses of 0 or 3 mg/kg body weight and day (0 or 1.25 mg vanadium/kg body weight and day) by intraperitoneal injection 3 times a week over the course of 3, 6, 9 or 12 months. The results of the Morris water maze test revealed memory loss after only 3 months. Learning deficits and reduced motor skills in the forelimb grip strength test were not observed (Folarin et al. 2016).

Groups of 12 male BALB/c mice were given **sodium metavanadate** in doses of 0 or 3 mg/kg body weight and day (0 or 1.25 mg vanadium/kg body weight and day) by intraperitoneal injection 3 times a week over a period of 18 months.

Another group received a dose of 3 mg/kg body weight and day by intraperitoneal injection 3 times a week over a period of 3 months and the animals were then observed for 15 months. The vanadium concentrations in the olfactory bulb, in the brain stem and in the cerebellum increased over time; the vanadium concentrations were still increased in the observation group 15 months after the last administration. Morphological changes in the frontal lobe and cell degeneration and death in the hippocampus and cerebellum were observed in the group of animals that was exposed for 18 months. A significant neuropathological change that was found in the older animals, including those in the observation group, was microgliosis, while the progressive astrogliosis that had been observed earlier became more attenuated (Folarin et al. 2017).

In a follow-up study using the same test conditions as described in Folarin et al. (2017), the concentrations of malondialdehyde, as a marker for lipid peroxidation, and hydrogen peroxide and nitric oxide were increased with statistical significance in the brains of the mice as from month 6 of exposure. These effects intensified over time (up to 18 months). The effects were reversible if exposure to vanadium was stopped after 3 months (Folarin et al. 2018). The evidence does not clearly support the reduction in SOD, GSH peroxidase, GSH-S-transferase and GSH activities after 6 months that was described by the authors because there was considerable variation in the control values.

5.3 Local effects on skin and mucous membranes

Exposure of animals to **divanadium pentaoxide** dust induced inflammation in the conjunctiva and in the mucosa of the nose, pharynx, oesophagus, bronchia and the lungs (Greim 2009; NTP 2002). There are no data available for other vanadium compounds.

5.3.1 Skin

In a study carried out according to OECD Test Guideline 404, **ammonium metavanadate** and **divanadyl pyrophosphate** (ECHA uses CAS number 65232-89-5 for this substance; however, this CAS number has been assigned to vanadium hydroxide oxide phosphate (vanadyl phosphate) of indeterminate composition (IFA 2022)) did not cause skin irritation in rabbits (ECHA 2019 a, 2020). Vanadyl pyrophosphate (**divanadyl pyrophosphate**), which was applied as a powder and not as a paste, likewise did not produce reactions on the skin of 3 rabbits. The skin of the animals was black in colour up to 24 to 72 hours after treatment. According to the REACH dossier, the discoloration did not hinder the analysis of the skin reactions (ECHA 2014).

An EpiSkinTM test carried out in 2019 using a method similar to OECD Test Guideline 439 found that **vanadium metal powder**, **sodium metavanadate**, **ammonium trivanadium octaoxide**, **divanadium trioxide** and **divanadium pentaoxide** did not cause skin irritation (ECHA 2021 b, c, 2022 a, e). **Vanadyl sulfate pentahydrate**, on the other hand, caused irritation when tested using this method. Negative results were obtained from an in vitro study that was carried out according to OECD Test Guideline 435 to investigate corrosive effects on the skin (in vitro membrane barrier test method for skin corrosion). In this study, the substance was not tested in the form of a paste and the results were not regarded as suitable for demonstrating a corrosive effect in aqueous solution (ECHA 2022 g). **Vanadium oxalate complexes**, applied in crystalline form, were not found to have skin corrosion potential in this test (ECHA 2021 d), while **divanadium trisulfate** in powder form was found to be corrosive (ECHA 2022 b).

No studies were carried out to investigate the skin irritation potential of **vanadyl trichloride** because of its physico-chemical properties (HCl formation) and experience with this substance. REACH registrants classified the substance as corrosive to the skin according to the CLP Regulation (Classification, Labelling and Packaging of Substances and Mixtures) (ECHA 2022 h). The same applies to **vanadium trichloride** (ECHA 2018).

5.3.2 Eyes

In compliance with OECD Test Guideline 405, 100 mg of **divanadium pentaoxide** was instilled into the conjunctival sac of 1 eye of each of 3 male Himalayan rabbits. The untreated eye of the animals served as the control. The treated eye was rinsed 1 hour after instillation. All 3 animals exhibited corneal opacity (index ≤ 3 on a scale with a maximum

of 4), iritis (index ≤ 1.5 (1/3) or ≥ 1.5 (2/3) of a maximum of 3), conjunctival redness (index 3 (2/3) of a maximum of 3) and conjunctival oedema (index 2 (3/3) of a maximum of 4). Testing was terminated after 72 hours because the effects became increasingly more severe over the course of the observation period. Divanadium pentaoxide was classified as severely irritating based on GHS criteria and assigned to Category 1 (irreversible effects on the eyes) (ECHA 2022 a). **Ammonium trivanadium octaoxide** caused serious eye damage in the exposed animals, leading to the termination of the study after 5 days. The substance was likewise classified in Category 1 (irreversible effects on the eyes) (ECHA 2021 a). **Divanadyl pyrophosphate** (see above) caused serious damage to the eyes in a study with 6 rabbits; the damage was not reversible within 28 days (ECHA 2019 a). The substance that is listed in the ECHA dossier as vanadyl pyrophosphate was classified as irritating to the eyes based on a second study that was carried out according to OECD Test Guideline 405 (ECHA 2014).

In a study carried out according to OECD Test Guideline 437 (bovine cornea opacity and permeability test, BCOP), 750 μl of a 20% **ammonium metavanadate** or **sodium metavanadate** suspension in an 0.9% sodium chloride solution was applied to the corneas of 3 cattle for 240 minutes. Neither of the substances were corrosive or severely irritating to the eyes of the cattle. Eye irritation tests subsequently carried out in groups of 3 rabbits in compliance with OECD Test Guideline 405 found corneal opacity and conjunctival redness and oedema as reversible effects and classified the substance as irritating to the eyes (Category 2 according to GHS criteria) (ECHA 2020, 2021 c). **Vanadium oxalate complexes**, by contrast, caused corrosion or serious irritation when tested in vitro in the bovine cornea test (ECHA 2021 d).

Divanadium trioxide was likewise classified as an eye irritant based on studies carried out according to OECD Test Guideline 405. **Vanadium metal powder** was not evaluated as irritating to the eyes (ECHA 2021 b, 2022 e). **Vanadyl sulfate pentahydrate** would not be classified as corrosive or severely irritating to the eyes based on the results of a BCOP test carried out in compliance with OECD Test Guideline 437. In aqueous solution, however, the substance has a $\text{pH} < 2$ and thus meets the criteria for classification as causing serious damage to the eyes (ECHA 2022 g). No studies were carried out to assess the skin and eye irritation potential of **vanadyl trichloride** because of its physicochemical properties (acidification) and experience with the substance. REACH registrants classified the substance as causing serious damage to the eyes according to the CLP Regulation (ECHA 2022 h). The same applies to vanadium trichloride (ECHA 2018).

Table 10 provides an overview of the results of the studies described above.

Tab. 10 Findings of studies investigating irritation of the skin and eyes caused by various vanadium compounds

Compound	Physicochemical properties	Findings of studies carried out according to OECD Test Guidelines 404, 435, 439, 405, 437
Vanadium V		in vitro: does not cause skin irritation in vivo: does not cause eye irritation
Ammonium metavanadate NH_4VO_3		in vivo: does not cause skin irritation in vitro: does not cause corrosion/serious eye irritation in vivo: eye irritation
Ammonium trivanadium octaoxide $\text{NH}_4\text{V}_3\text{O}_8$		in vitro: does not cause skin irritation in vivo: irreversible damage to the eyes
Sodium metavanadate NaVO_3		in vitro: does not cause skin irritation in vitro: does not cause corrosion/serious eye irritation in vivo: eye irritation
Divanadium trioxide V_2O_3		in vitro: does not cause skin irritation in vivo: eye irritation
Divanadium pentaoxide V_2O_5		in vitro: does not cause skin irritation in vivo: serious eye irritation
Divanadyl pyrophosphate $(\text{VO})_2\text{P}_2\text{O}_7$		in vivo: does not cause skin irritation in vivo: eye irritation or serious eye irritation

Tab. 10 (continued)

Compound	Physicochemical properties	Findings of studies carried out according to OECD Test Guidelines 404, 435, 439, 405, 437
Vanadyl trichloride VOCl_3	formation of HCl in aqueous solution: corrosive	not tested
Vanadium trichloride VCl_3	formation of HCl in aqueous solution: corrosive	not tested
Vanadyl sulfate pentahydrate $\text{VOSO}_4 \times 5 \text{H}_2\text{O}$	formation of acid in aqueous solution: severely damaging to the eyes	in vitro: skin irritation
Divanadium trisulfate $\text{V}_2(\text{SO}_4)_3$		in vitro: skin corrosion
Vanadium oxalate complexes $\text{VO}(\text{C}_2\text{O}_4)$		in vitro: does not cause skin corrosion in vitro: corrosion/serious eye irritation

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

A maximization test to assess **divanadium trioxide** was carried out with 10 female Dunkin Hartley guinea pigs in compliance with OECD Test Guideline 406. The test used a 0.01% aqueous solution for intradermal induction and a 50% aqueous suspension for topical induction. None of the animals produced positive reactions 24 or 48 hours after the challenge with a 25% aqueous suspension (ECHA 2021 b).

The REACH dossiers for vanadium and various vanadium compounds (such as ammonium trioxovanadate, ammonium trivanadium octaoxide, divanadium pentaoxide, potassium metavanadate) include a maximization test that was carried out with **vanadyl sulfate pentahydrate** according to OECD Test Guideline 406. Induction in 10 male Dunkin Hartley guinea pigs was performed with a 0.01% aqueous solution for intradermal induction and a 10% aqueous solution for topical induction. The challenge was carried out with a 0.5% aqueous solution. None of the animals produced a positive reaction after 24 or 48 hours (ECHA 2022 e).

A maximization test that was carried out with vanadyl pyrophosphate (**divanadyl pyrophosphate**, see Section 5.3.1 for the identity of the substance) according to OECD Test Guideline 406 yielded positive results. Twenty Dunkin Hartley guinea pigs were treated for induction by intradermal injection of a 0.5% (w/v) formulation and topical application of a 50% (w/v) test concentration in paraffin oil. The challenge was performed with a 10% and 50% formulation. Eight of 20 tested animals reacted to the 50% formulation after 24 and 48 hours. Overall, 11 of the treated animals, but none of the 20 control animals, reacted to the 50% formulation at one of the time points. None of the controls or pre-treated animals reacted to the 10% formulation (ECHA 2014). It is unclear whether the reactions observed in the exposed animals were caused by impurities. However, the results cannot be used to evaluate the sensitizing effects because of the high concentration chosen for the challenge.

Another maximization test with **divanadyl pyrophosphate** (see Section 5.3.1 for the identity of the substance) yielded positive results. Induction in 20 Dunkin-Hartley guinea pigs was performed by intradermal injection of a 0.5% (w/v) formulation and epicutaneous application of 0.6 ml of a 30% (w/v) formulation in water. The challenge was performed with 0.03 ml of a 5% or 30% formulation. In the group of 20 control animals pre-treated with Freund's complete adjuvant (FCA), 2 animals reacted to the 30% formulation after 24 hours and 1 animal after 48 hours; none of the animals, however, reacted to the 5% formulation. In the group of 20 pre-treated animals, 10 (24 hours) and 5 (48 hours) produced positive reactions to the 30% formulation. Overall, 12 of the exposed animals and 3 of the 20 control animals reacted to the 30% formulation at one of the time points. After 24 hours, the 5% formulation induced a positive reaction in 3 of 20 animals. However, none of the animals produced a positive reaction after 48 hours (ECHA 2019 a). It is unclear whether the reactions observed in the exposed animals were caused by impurities. Moreover, the results cannot be used to evaluate

the sensitizing effects based on the available information because a high concentration was chosen for the challenge and reactions were observed in the control animals.

A publication reported positive results from a test carried out with **vanadyl sulfate** in guinea pigs that did not conform with the test guidelines. The substance was administered by a single intradermal injection or by repeated non-occlusive application (Roshchin et al. 1982). These results are not included in the evaluation because of the unusual design of the study and the inadequate documentation.

Another maximization test with **sodium metavanadate** was carried out in 10 Dunkin Hartley guinea pigs in compliance with OECD Test Guideline 406. A 0.01% aqueous solution was used for intradermal induction and a 1% aqueous solution for topical induction. None of the animals reacted to the challenge with a 0.05% aqueous solution after 24 and 48 hours (ECHA 2021 c). This test is also included in the registration dossiers of other vanadium compounds (vanadium, ammonium trioxovanadate, ammonium trivanadium octaoxide, divanadium pentaoxide, potassium metavanadate).

5.4.2 Sensitizing effects on the airways

A study that was already included in the 2006 addendum (Greim 2009) was carried out with monkeys to investigate changes in the reactivity of the lungs after repeated inhalation of **divanadium pentaoxide** dust. Subchronic exposure did not increase the reactivity of the lungs in comparison with that found in the control group. The results of the cytological and immunological examinations and skin tests did not provide any evidence of an allergic reaction (Knecht et al. 1992).

No other studies investigating the sensitizing effects on the airways are available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

Generation studies for vanadium and its inorganic compounds were not available.

Fertility was impaired in male and female mice after oral administration of **ammonium metavanadate**. Sperm damage was found in mice given **sodium metavanadate** (Greim 2009).

In the studies below, male CD1 mice were exposed whole-body to 0 or a nebulized 0.02 M suspension of **divanadium pentaoxide** (about 1.4 mg/m³; 0.8 mg V/m³) twice a week for 1 hour, over a period of 12 weeks. These exposure conditions were chosen because the half-life of vanadium in the blood is 48 hours. As the animals were exposed whole-body, the substance was probably also absorbed orally during grooming.

The exposure group consisted of 60 animals. Five of the animals of the exposure group and 3 of the animals of the control group were examined each week. The exposed animals developed necrosis in the spermatogonia, spermatocytes and Sertoli cells. After a week, the vanadium concentrations in the testes remained stable and were in the range of 1.63 ± 0.15 µg/g dry weight in the exposed animals and 0.05 ± 0.02 µg/g in the control animals (Fortoul et al. 2007).

To investigate the effects of vanadium on the male reproductive organs, male CD1 mice were exposed to the substance according to the protocol described above. Examinations were carried out on a weekly basis. Starting in week 3 of exposure, immunohistochemical changes in the form of reduced actin levels in testicular cells were observed in the animals. This effect was statistically significant and dependent on exposure and time. The authors suggest that this effect may explain the decrease in fertility that was caused by exposure (Rodríguez-Lara et al. 2016 b).

Another study that investigated spermatogenesis determined the expression of connexin 43 in the seminiferous tubules. Connexin 43 underwent redistribution and was present in the membranes in reduced levels. The histological examination additionally revealed severe cell damage in the epithelium of the seminiferous tubules (Bizarro-Neves et al. 2016).

The administration (probably by gavage) of oral doses of **vanadyl sulfate** of 100 mg/kg body weight and day (31.25 mg V/kg body weight and day) for 60 days led to a reduction in the relative weights of the testes and epididymis, seminal

vesicles and the prostate glands in male Wistar rats (7 per group). The body weights of the exposed animals, compared with the values determined in the control animals, did not increase; instead, the body weights were reduced, but not to a statistically significant degree. The number and motility of the sperm in the epididymis were decreased with statistical significance compared with the findings in the control group. The histopathological examination revealed atrophy in the seminiferous tubules and a decrease in diameter of the seminiferous tubules and Leydig cell nuclei. The protein and sialic acid levels in the testes and seminiferous tubules were reduced, the cholesterol levels in the testes were increased and the fructose levels in the seminal vesicles were reduced. Each male was mated with 2 females during the last 5 days of exposure; 50% of the females conceived (5/10, controls 10/10). The litter sizes were reduced. This study shows that vanadyl sulfate in high doses impairs fertility (Jain et al. 2007).

5.5.2 Developmental toxicity

Vanadium compounds pass the blood–brain and placental barriers (demonstrated for tetravalent and pentavalent compounds) (see Section 2.2.1 and Section 3.1.2). Vanadyl sulfate pentahydrate given to mice by gavage significantly increased the vanadium concentrations in the placenta and to a lesser degree in the foetus (Paternain et al. 1990).

5.5.2.1 Prenatal and postnatal developmental toxicity

Several developmental toxicity studies are available. The studies that are relevant for the evaluation are shown in Table 11. Additional studies were published in Greim (2009).

Tab. 11 Developmental toxicity studies with administration of inorganic vanadium compounds that are relevant for the evaluation

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 20 ♀, 20 ♂	60 days before mating (♂), 2 weeks before mating, during mating (♀) up to GD 14 or PND 21 (♀), length of exposure: ♂: 6 weeks, ♀: 6 or 10 weeks, 0, 5, 10, 20 mg NaVO ₃ /kg body weight and day (0, 2.1, 4.2, 8.4 mg V/kg body weight and day), gavage, purity 99%, about half of the animals examined on GD 14 and half on PND 21	8.4 mg V/kg body weight: NOAEL maternal toxicity; 4.2 mg V/kg body weight: NOAEL perinatal toxicity; 8.4 mg V/kg body weight: fetuses, offspring: number of litters ↓ (14, 14, 12, 8 litters/group), body weights and body length decreased on PND 1, 4 and 21, no other effects on litter parameters	Domingo et al. 1986
rat, Sprague Dawley, 20 ♀	GD 6–14, 0, 5, 10, 20 mg NaVO ₃ /kg body weight and day (0, 2.1, 4.2, 8.4 mg V/kg body weight and day), gavage, purity: reagent grade, vehicle: distilled water, examination on GD 20	maternal toxicity: compare with Domingo et al. (1986), same research group, same rat strain; 4.2 mg V/kg body weight: NOAEL developmental toxicity; resorptions ↑, but resorption incidence unchanged; 8.4 mg V/kg body weight: fetuses: number of litters ↓ (14, 14, 12, 8 litters/group), 2 fetuses with hydrocephalus (2%; 0 in the other groups, but at the same time litter size reduced), facial haemorrhage ↑; haemorrhage not increased with dose dependency in other areas (not specifically attributable to developmental toxicity), no other noticeable effects: number of corpora lutea and implantations, foetal body weights and length, sex ratio, resorption incidence, number of living and dead fetuses, no teratogenicity	Paternain et al. 1987

Tab. 11 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, Swiss, 20 ♀	GD 6–15, 0, 37.5, 75, 150 mg VOSO ₄ × 5 H ₂ O/kg body weight and day (0, 7.6, 15.1, 30.2 mg V/kg body weight and day), gavage, purity not specified, vehicle: distilled water, examination on GD 18, OECD TG 414	no NOAEL for maternal toxicity, developmental toxicity; 7.6 mg V/kg body weight: dams: 2 animals died (probably due to incorrect administration); 7.6 mg V/kg body weight and above: body weight gains ↓ (GD 6–15, GD 0–18), body weights decreased by 20%, gravid uterine weights ↓, foetuses: number of early resorptions/litter ↑, body weights ↓, crown rump lengths ↓, overall increase in the total number of external defects and in delayed ossification per foetus and also per litter; 15.1 mg V/kg body weight: dams: absolute liver and kidney weights ↓; 30.2 mg V/kg body weight: dams: body weights decreased by 25%, placental weights ↓; foetuses: overall increase in the total number of external defects (cleft palate, micrognathia) and in delayed ossification per foetus and also per litter; dose-dependent increase in the vanadium concentrations in the liver, kidneys, placenta and spleen of the dams and in the foetuses	Paternain et al. 1990
mouse, Swiss, 20 ♀	GD 6–15, 0, 7.5, 15, 30, 60 mg Na ₃ VO ₄ /kg body weight and day (0, 2.1, 4.2, 8.3, 16.6 mg V/kg body weight and day), gavage, purity not specified, vehicle: distilled water, examination on GD 18	2.1 mg V/kg body weight: NOAEL maternal toxicity; 4.2 mg V/kg body weight: NOAEL developmental toxicity; 4.2 mg V/kg body weight and above: dams: feed consumption decreased on GD 0–18; 8.3 mg V/kg body weight: dams: 4/18 died; 8.3 mg V/kg body weight and above: dams: body weight gains decreased by 20% from GD 6–15, foetuses: delayed ossification of the sacral vertebrae, distal phalanges of the fingers and toes, no embryoletality and teratogenicity; 16.6 mg V/kg body weight: dams: 17/19 died, no other examinations	Sanchez et al. 1991
Prenatal and postnatal exposure, postnatal examination			
rat, Sprague Dawley, at least 14 ♀	GD 0–PND 21, 0, 75 mg V/kg feed, given as NaVO ₃ (ca. 0, 9 mg V/kg body weight and day ^{a)}), purity not specified, examination on PND 21	9 mg V/kg body weight: dams: feed consumption during gestation ↓, body weight gains during gestation ↓ (109 g, controls: 135 g), offspring: survival during lactation ↓, body weight gains during lactation ↓ (PND 20: 34% lower than the controls), diarrhoea and lethargy ↑, relative liver, brain and testis weights ↑	Elfant and Keen 1987

^{a)} Conversion factor 0.12 (subacute) according to EFSA (2012)

GD: gestation day; PND: postnatal day; V: vanadium

Vanadium given in oral doses to rats in the form of **sodium metavanadate** reduced the number of litters per group and the foetal body weights at 8.4 mg/kg body weight and day (Domingo et al. 1986; HSE 2002; WHO 2001). In mice treated with oral doses of **vanadyl sulfate pentahydrate**, reduced body weights, reduced crown rump lengths, an increase in the total number of external defects and in delayed ossification were observed in the foetuses at vanadium doses of 7.6 mg/kg body weight and day and above (Paternain et al. 1990). In the same species, ossification of the sacral vertebrae and the distal phalanges of the fingers and toes was delayed in the foetuses after exposure to vanadium as **sodium orthovanadate** in doses of 8.3 mg/kg body weight and day and above (Sanchez et al. 1991). Exposure of the dams (Sprague Dawley rats) to sodium metavanadate concentrations of 500 mg/l drinking water (equivalent to about 22.4 mg V/kg body weight and day) led to increased mortality of the dams and foetuses at the end of gestation (GD 22) and of the offspring during lactation. No effects were observed after exposure to low concentrations of sodium metavanadate or after exposure to vanadyl sulfate (no other details; NTP 2023).

In mice given vanadium by intraperitoneal injection as **sodium metavanadate** at dose levels of 0.8 mg/kg body weight and day and above from gestation days 6 to 15, increased embryoletality and reduced body weights were observed. A NOAEL of 0.4 mg/kg body weight and day was derived for vanadium (Gomez et al. 1992). Intraperitoneal administration is regarded as the worst case because 100% of the substance is absorbed.

5.5.2.2 Developmental neurotoxicity

Vanadium impaired myelination and motor function in neonatal/juvenile rats. In vitro and in vivo studies with Sprague Dawley rats found that oligodendrocyte progenitor cells are more sensitive to vanadium than astrocytes or mature oligodendrocytes (Todorich et al. 2011). Another study with exposure of rats 3 days before birth until postnatal day 100 found that the working memory of the offspring was impaired at the age of 4 weeks (Poggioli et al. 2001). The findings of these studies are described in detail in Table 12.

Tab. 12 Studies of neurodevelopmental toxicity with administration of inorganic vanadium compounds

Species, strain, number per group	Exposure	Findings	References
Postnatal examination			
rat, Wistar, 5 ♀ dams, 20 offspring each (10 ♂, 10 ♀)	3 days before birth–PND 100, 0, 300 mg VOSO ₄ /l drinking water (0, 10 mg V/kg body weight and day), both groups additionally 5000 mg NaCl/l; control group not given vanadium or NaCl, examination of offspring: age 1 month: locomotor activity, open field test	10 mg V/kg body weight: offspring: number of living animals at weaning ↓, body weights at weaning ↓, ♂: water consumption ↑, open field test: impaired working memory (reduced outer ambulation), reduced rearing behaviour and grooming activity, increased defecation; no noticeable effects: locomotor activity; no data for maternal toxicity, small number of animals, NOAEL cannot be derived because only one dose; not suitable for evaluation	Poggioli et al. 2001
rat, Sprague Dawley, 5 offspring (no other data)	PND 1–PND 15, exposure of offspring 0, 3 mg NaVO ₃ /kg body weight and day (1.25 mg V/kg body weight and day), intraperitoneal, vehicle: phosphate buffered saline solution, examination of offspring: PND 15: rotarod, immunohistology	1.25 mg V/kg body weight: offspring: rotarod test: impaired motor function, corpus callosum: number of NG2-positive oligodendrocyte progenitor cells ↓ and increased number and extensive branching of astrocytes (thus cytotoxic for oligodendrocytes, stimulation of astrogliosis); hypomyelination; NOAEL cannot be derived because only one dose; in vitro experiments: oligodendrocyte progenitor cells more sensitive to vanadium than astrocytes or mature oligodendrocytes; oligodendrocyte progenitor cells: ROS generation ↑, annexin V labelling ↑ (signs of apoptosis), mechanism: signs of interference with iron assimilation into oligodendrocytes; NOAEL cannot be derived because only one dose	Todorich et al. 2011

NG2: antibody used as a marker for oligodendrocyte progenitor cells; PND: postnatal day; ROS: reactive oxygen species; V: vanadium

5.5.2.3 Exposure via lactation

Wistar rats were exposed from postnatal days 10 to 21 via the milk from dams given vanadium by intraperitoneal injection (4 animals/group; 0, 3 mg **sodium metavanadate**, equivalent to 0, 1.25 mg vanadium/kg body weight and day, vehicle: distilled water). The offspring were examined every 48 hours (surface righting reflex, negative geotaxis, hindlimb support tests). A delay in eye opening and decreased muscle strength were observed in the offspring. In the open field test carried out on postnatal day 21, the number of crossings was decreased, which is evidence of reduced locomotor activity. The histochemical and immunohistochemical examinations on postnatal day 22 revealed decreased myelination in the corpus callosum and cerebellum. A NOAEL cannot be derived because only one dose was tested (Soazo and Garcia 2007).

In neonatal/juvenile CD1 mice (PND 1 to PND 15 or PND 22) exposed to vanadium via the milk from dams given vanadium (3 mg **sodium metavanadate**/kg body weight and day; 1.25 mg vanadium/kg body weight and day, intraperitoneal) impaired oligodendrocyte maturation, astrocyte activation and myelin damage were observed. During lactation, the exposed animals exhibited reduced locomotor activity and negative geotaxis in the open field test at most examination time points (Mustapha et al. 2014). In another study, mice were exposed via lactation to the same dose from postnatal days 1 to 21. At the end of this period, the animals continued to be treated with this dose, which was administered 3 times a week for 3 months by intraperitoneal injection. The animals were examined on postnatal day 90. Myelin

damage was found in the brain in the region of the neocortex and the hippocampus. Hypomyelination was observed also in the corpus callosum and in other areas. Activated microglia and astrocytes and signs of neuroinflammatory processes were likewise observed. Locomotor impairment was detected in the open field test on postnatal days 60 and 89 (Azeez et al. 2016).

5.5.2.4 Summary

Findings in vitro and in rats demonstrated that oligodendrocyte progenitor cells are more sensitive to vanadium exposure than mature oligodendrocytes (Todorich et al. 2011). While myelination was first observed in rats on postnatal day 10 (and lasted up to postnatal day 90), this effect was already noticeable in humans in utero (gestation day 135) and continued to be evident into the early postnatal period (Semple et al. 2013; Zeiss 2021). Therefore, the effects observed in neonatal/juvenile rats are relevant for exposure of humans in utero. The oligodendrocyte progenitor cells are distributed throughout the CNS and represent a pool of migrating and proliferative adult progenitor cells that can differentiate into oligodendrocytes (Kuhn et al. 2019). In neonatal/juvenile rats and mice, oligodendrocyte impairment is associated with effects on myelination and motor impairment (Azeez et al. 2016; Mustapha et al. 2014; Soazo and Garcia 2007; Todorich et al. 2011). A NOAEL for these types of effects cannot be derived from the available studies. Effects induced by vanadium, such as demyelination and motor impairment, can occur after exposure via lactation (Azeez et al. 2016; Mustapha et al. 2014; Soazo and Garcia 2007).

5.6 Genotoxicity

5.6.1 In vitro

The following results were obtained in the studies evaluated in 2006: Gene mutation studies in bacteria and mammalian cells yielded mostly negative results. Inconsistent results were reported by studies that investigated sister chromatid exchange and chromosomal aberrations. Vanadium compounds inhibited the repair of DNA damage caused by UV light or bleomycin in vitro and induced DNA strand breaks (comet assay) and aneuploidy (micronucleus test) (Greim 2009).

The data that were published after 2006 or were not included in the addendum support these findings (Greim 2009):

Divanadium pentaoxide did not induce mutagenic activity in the *Salmonella typhimurium* strains TA97, TA98, TA100, TA102 and TA1535 either with (0.03–333 µg/plate) or without (0.03–10 µg/plate) a metabolic activation system. The highest concentration was cytotoxic in the presence of a metabolic activation system (NTP 2002).

Sodium metavanadate and **vanadyl sulfate** yielded negative results in the *Salmonella typhimurium* strains TA98 and TA100 and in *Escherichia coli* uvrA(pKM101) both in the presence and in the absence of a metabolic activation system. Sodium metavanadate was tested in the strain TA98 in concentrations of 0.5 to 100 µg/plate (with and without metabolic activation) and in the strain TA100 in concentrations of 0.5 to 100 µg/plate (without metabolic activation) and of 1 to 500 µg/plate (with metabolic activation). In each case, the highest concentration was cytotoxic. Concentrations of 40 to 6000 µg/plate (with and without metabolic activation) were tested in *Escherichia coli*. Vanadyl sulfate was tested in the strains TA98 and TA100 in concentrations of 0.4 to 100 µg/plate; the highest concentration induced cytotoxic effects in TA98. Concentrations in the range of 4 to 6000 µg/plate were tested in *Escherichia coli* (NTP 2023).

In the human cell lines HepG2 and LS-174T, **vanadium trichloride** (1–1000 µM) did not increase phosphorylation of the histone H2AX (γH2AX) and thus did not lead to DNA damage. The cell lines represent the liver and the colon, respectively (Kopp et al. 2018). H2AX is phosphorylated during DNA repair. This is usually triggered by DNA double strand breaks; however, also single strand breaks may be involved, caused, for example, by UV light or oxidative stress (Mishima 2017). DNA damage occurring during proliferation or apoptosis leads to the phosphorylation of H2AX.

Sodium metavanadate decreased phosphorylation of the histone H2AX (γH2AX) in HepaRG cells, with a LOEC (lowest observed effect concentration) of 1.25 µM, and increased DNA damage (alkaline unwinding test), with a LOEC of 5 µM (Desaulniers et al. 2021).

The induction of DNA strand breaks appears to be specific to certain types of cells. **Divanadium pentaoxide**, **sodium orthovanadate** and **vanadyl sulfate** yielded positive results in fibroblasts and lymphocytes in the comet assay but negative results in nasal mucosal epithelial cells and leukocytes isolated after incubation of the whole blood. HeLa cells (cultivated cancer cells) reacted with greater sensitivity than lymphocytes (AGS 2015; ATSDR 2018).

In the comet assay with human leukocytes, vanadium compounds in 3 different oxidation states (**divanadium trioxide**, **divanadium tetraoxide**, **divanadium pentaoxide**) induced DNA single strand breaks under strongly alkaline conditions (pH 13) and treatment with divanadium tetraoxide at a pH of 9 led also to DNA double strand breaks (Rodríguez-Mercado et al. 2011). Chromosomal aberrations (visual analysis), however, were induced in primary human lymphocytes only by **divanadium tetraoxide**, but not by trivalent or pentavalent vanadium compounds (**divanadium trioxide**, **divanadium pentaoxide**). All 3 compounds cause cytotoxic effects (Rodríguez-Mercado et al. 2010). The DNA damage could be repaired; however, the cells treated with **divanadium tetraoxide** took longer to return to the range of the DNA damage found in the controls (120 minutes in comparison with 90 minutes after treatment with **divanadium trioxide** or **divanadium pentaoxide**). The authors assume that the damage caused by **divanadium tetraoxide** was of a different kind (Rodríguez-Mercado et al. 2011).

Sister chromatid exchange was not induced after the incubation of human leukocytes for 48 hours with **divanadium trioxide** concentrations of up to 16 µg/ml; however, there was a statistically significant increase in cells with premature chromatid separation. In addition, the mitotic and replication indices were decreased and the average generation time (AGT) was increased. The latter 2 parameters are used to determine the number of replications in a cell population and the time required for replication. The authors suggest that an effect was induced at the centromere level that led to aneuploidy (Mateos-Nava et al. 2017).

Micronuclei were induced by **divanadium pentaoxide** in V79 cells and by **sodium metavanadate**, **ammonium metavanadate**, **sodium orthovanadate** and **vanadyl sulfate** in human lymphocytes at vanadium concentrations of 0.5 µg/ml and above; most of the micronuclei contained a single centromere, which is a sign of aneugenicity (Greim 2009). More recently published studies likewise found that divanadium pentaoxide, divanadium trioxide and vanadyl sulfate have clastogenic properties at higher concentrations (no other details; AGS 2015).

In vitro gene expression studies are described in Section 2.

Summary: The new findings confirm the evaluation made in 2006 (Greim 2009) that the genotoxicity of vanadium compounds, like that of other metal compounds, is triggered by clastogenic and by aneugenic effects. Most of the studies that investigated DNA strand breaks and micronuclei reported positive results. Vanadium compounds are therefore considered genotoxic in vitro.

5.6.2 In vivo

The set of data available for genotoxicity in 2006 was summarized in the documentation as follows: Oral administration of **vanadyl sulfate** caused an increase in structural chromosomal aberrations as well as aneuploidies in mice. Micronuclei in polychromatic erythrocytes were induced in mice after single oral administration of vanadium(IV) and vanadium(V) compounds. Micronuclei were also demonstrated in mice after repeated inhalation exposure and subcutaneous or intraperitoneal administration of **divanadium pentaoxide**. Intraperitoneal administration of divanadium pentaoxide induced DNA strand breaks in the testes of mice. One positive result each has been published for the dominant lethal test after intraperitoneal administration of divanadium pentaoxide to mice and after oral administration of **ammonium metavanadate** to rats (Greim 2009).

To evaluate the genotoxicity and to determine whether the observed genotoxic effects are high-dose effects, Table 13 lists all the valid studies that are relevant for the evaluation, including studies that were already described in Greim (2009).

Tab. 13 In vivo studies of genotoxicity induced by inorganic vanadium compounds

Test system	Species, strain, number per group	Exposure	Results	Cytotoxicity/Comments	References
Somatic cells					
SCE, bone marrow	mouse, CD-1, groups of 4 ♂	single, 0, 5.75, 11.5, 23 mg V ₂ O ₅ /kg body weight (0, 3.2, 6.4, 12.8 mg V/kg body weight), intraperitoneal, examination 24 hours after treatment, purity: 99.6%	–		Altamirano-Lozano et al. 1993
DNA damage (comet assay, alkaline), liver, kidneys, lungs, spleen, heart, bone marrow	mouse, CD-1, groups of 4 ♂	see above	+ : liver, heart, lungs, bone marrow: 3.2 mg V/kg body weight and above, kidneys: 6.4 mg V/kg body weight and above, spleen: 3.2, 12.8 mg V/kg body weight	tested doses: 1/4, 1/2 or acute LD ₅₀ , viability: dose-dependent decrease in the liver (12.8 mg/kg body weight: 44%), all other organs ≥ 70%	Altamirano-Lozano et al. 1999
DNA damage (comet assay, alkaline), spleen, bone marrow, peripheral blood	mouse, CD-1, groups of 5 ♂	5 weeks, 0, 0.75, 7.5, 75, 750, 1500 mg Na ₃ VO ₄ /l (0, 0.06, 0.57, 5.49, 20.8, 33 mg V/kg body weight and day), drinking water, purity: > 90%	+ : spleen: 33 mg V/kg body weight, – : bone marrow, NOAEL: 20.8 mg V/kg body weight and day	20.8 mg/kg body weight and above: body weight gains ↓, water consumption ↓, lethargy during the last 2 weeks, absolute spleen weights ↓; 33 mg/kg body weight: 1 animal died (week 3), PCE/NCE unchanged in the micronucleus test	Leopardi et al. 2005
oxidative DNA damage (HPLC-MS/MS), lungs	mouse, B6C3F1, groups of 6 ♀	7 or 16 days, 6 hours/day, 0, 0.25, 1, 4 mg V ₂ O ₅ /m ³ (0, 0.14, 0.56, 2.25 mg V/m ³), inhalation, nose-only, purity: 99.8%	+ : 0.56 mg V/m ³ and above, NOAEC: 0.14 mg V/m ³	8-oxo-dG/10 ⁶ nucleosides: controls: 0.24 ± 0.04, 0.14 mg/m ³ : 0.26 ± 0.07, 0.56 mg/m ³ : 0.43 ± 0.14*, 2.25 mg/m ³ : 0.49 ± 0.11**, concentration-dependent increase, dCyd341 unchanged, 8-oxo-dAdo, 5-OH-dCyc, ThdGly, 5-hmdUrd, EdGuo, EdAdo not detectable, GSH: 0.14 mg/m ³ ↓, GSSG: 0.14 mg/m ³ and above ↑ (159%, 223%, 215%), GSH/(2 × GSSG) ↓ (53%, 55%, 53% of the controls), no consistent changes in α-tocopherol and F2 isoprostane	Schuler et al. 2011
DNA damage (comet assay, alkaline), lungs, BAL cells	see above	see above	– NOAEC: 2.25 mg V/m ³	0.56 mg V/m ³ and above: lung weights ↑, histopathological damage to the lungs, 2.25 mg/m ³ : body weights ↓ (week 1)	

Tab. 13 (continued)

Test system	Species, strain, number per group	Exposure	Results	Cytotoxicity/Comments	References
DNA damage (comet assay, alkaline), bone marrow, testes (see germ cells)	mouse, CD-1, groups of 8–10 ♂	5 weeks, 0, 2, 10, 100, 500, 1000 mg VOSO ₄ × 5 H ₂ O/l (0, 0.519, 1.96, 26.8, 72.3, 148 mg/kg body weight and day (0, 0.105, 0.395, 5.4, 14.6, 29.9 mg V/kg body weight and day)), drinking water, purity: 99.99%	– NOAEL: 29.9 mg V/kg body weight and day	2 experiments: 1) 10, 100, 500, 1000 mg/l 2) 2, 10 mg/l V levels ↑ (bone marrow (linear, dose-dependent) > spleen, liver, kidneys, testes; not detectable in intestines and stomach), 14.6 mg/kg body weight and above: water consumption ↓, Experiment 2: water consumption increased at 0.105 mg/kg body weight	Villani et al. 2007
DNA damage (comet assay, alkaline), peripheral blood	rat, Sprague Dawley, 31–33, sex not specified	24 weeks, probably daily administration, 0, 0.25, 1.2 mg VOSO ₄ /kg body weight and day (0, 0.08, 0.38 mg V/kg body weight and day), gavage	+ : 0.08 mg V/kg body weight and day and above, no NOAEL, LOAEL: 0.08 mg V/kg body weight and day	0.08 mg V/kg body weight and above: ALT ↑, MDA in the serum ↑, DNA damage increased with the dose, sex not specified, incomplete description of method	Hussain Shah et al. 2019
CA, structural and numerical, bone marrow	mouse, CD-1, groups of 3 ♂, control 4 ♂	single, 0, 75 mg Na ₃ VO ₄ /kg body weight (21 mg V/kg body weight), gavage, examination after 24 and 36 hours	– : structural CA, + : hypoploidy or hyperploidy	PCE/NCE unchanged	Ciranni et al. 1995
		single, 0, 50 mg NH ₄ VO ₃ /kg body weight (22 mg V/kg body weight)	– : structural CA + : hypoploidy or hyperploidy	PCE/NCE unchanged	
		single, 0, 100 mg VOSO ₄ /kg body weight (31 mg V/kg body weight)	+ : structural CA, hypoploidy or hyperploidy	structural CA: effects after 24 hours greater than after 36 hours, PCE/NCE ↓	
CA, numerical, bone marrow	mouse, ICR, groups of 5 ♀, hormonal stimulation	single, 0, 5, 15, 25 mg Na ₃ VO ₄ /kg body weight (1.4, 4.2, 6.9 mg V/kg body weight), intraperitoneal, examination after 18 hours	+ : 1.4 mg V/kg body weight and above	1.4 mg V/kg body weight and above: dose-dependent increase in tetraploid cells; 6.9 mg V/kg body weight: 20% of the animals lethargic, hyperploid cells ↑, cells with premature centromere division ↑	Mailhes et al. 2003
MN, bone marrow	mouse, 102/El × C3H/El)F1, groups of 5 ♂	single, 0, 1, 5, 15, 25 mg Na ₃ VO ₄ /kg body weight (0.2, 1.4, 4.2, 6.9 mg V/kg body weight), intraperitoneal, examination after 24 hours	–	PCE/NCE unchanged	Attia et al. 2005
MN, bone marrow	mouse, CD-1, groups of 3 ♂, control 4 ♂	single, 0, 75 mg Na ₃ VO ₄ /kg body weight (21 mg V/kg body weight), gavage, examination after 6, 12, 18, 24, 30, 36, 42, 48, 72 hours	+	PCE/NCE unchanged	Ciranni et al. 1995
		single, 0, 50 mg NH ₄ VO ₃ /kg body weight (22 mg V/kg body weight)	+	PCE/NCE unchanged	
		single, 0, 100 mg VOSO ₄ /kg body weight (31 mg V/kg body weight)	+	PCE/NCE ↓ (6, 36, 48 hours)	

Tab. 13 (continued)

Test system	Species, strain, number per group	Exposure	Results	Cytotoxicity/Comments	References
MN, bone marrow	mouse, Balb-c, no other details	single, 0, 20 μM $\text{NH}_4\text{VO}_3/\text{kg}$ body weight (23.4 mg V/kg body weight), intraperitoneal, no other details	–	PCE/NCE unchanged	AGS 2015
MN, bone marrow	mouse, CD-1, groups of 5 ♂	5 weeks, 0, 0.75, 7.5, 75, 750, 1500 mg $\text{Na}_3\text{VO}_4/\text{l}$ (0, 0.06, 0.57, 5.49, 20.8, 33 mg V/kg body weight and day), drinking water	+ : 20.8 mg V/kg body weight and day and above	20.8 mg V/kg body weight and above: body weight gains ↓, water consumption ↓, lethargy during the last 2 weeks; 33 mg V/kg body weight: 1 animal died (week 3), PCE/NCE unchanged, vanadium detected in the bone marrow	Leopardi et al. 2005
MN, peripheral blood (reticulocytes)	see above	examination: 0, 1, 3, 5 weeks	+ : 5.49 and 20.8 mg V/kg body weight and day (week 3), + : 0.57, 5.49 and 20.8 mg V/kg body weight and day (week 5), – : 0.06, 0.57 (week 3); 33 mg V/kg body weight and day	examination of dependency on time, + means: values increased in the group with statistical significance relative to the values at the beginning of treatment, no dose dependency, only 1000 reticulocytes counted per animal, published only as a graph	
MN, bone marrow	mouse, CD-1, groups of 8–10 ♂	5 weeks, 0, 2, 10, 100, 500, 1000 mg $\text{VOSO}_4 \times 5 \text{H}_2\text{O}/\text{l}$ (0, 0.519, 1.96, 26.8, 72.3, 148 mg/kg body weight and day (0, 0.105, 0.395, 5.4, 14.6, 29.9 mg V/kg body weight and day)), drinking water, purity: 99.99%	–	2 experiments: 1) 10, 100, 500, 1000 mg/l 2) 2, 10 mg/l PCE/NCE unchanged, see comet assay for further comments	Villani et al. 2007
MN, peripheral blood (reticulocytes)	see above	examination on day 0, 7, 14, 21, 28 and 35	+ / – + : 0.105 mg V/kg body weight and day (weeks 3 and 4), + : 0.395 mg V/kg body weight and day (weeks 4 and 5), – : ≥ 5.4 mg V/kg body weight and day	not dependent on dose and time, RNA content of the cytoplasm (cytotoxicity) unchanged	
MN, peripheral blood (erythrocytes)	mouse, B6C3F1, groups of 10 ♂ and groups of 10 ♀	3 months, 6 hours/day, 5 days/week, 0, 1, 2, 3, 8, 16 mg $\text{V}_2\text{O}_5/\text{m}^3$ (0, 0.56, 1.12, 1.68, 4.48, 8.96 mg V/m^3), inhalation, whole-body	– NOAEC: 8.96 mg V/m^3	PCE/NCE unchanged, additional oral uptake probable	NTP 2002

Tab. 13 (continued)

Test system	Species, strain, number per group	Exposure	Results	Cytotoxicity/Comments	References
MN, peripheral blood (reticulocytes)	rat, Sprague Dawley, groups of 5 ♂ and 5 ♀	3 months, 0, 31.3, 62.5, 125, 250, 500 mg NaVO ₃ /l (♂: 0, 2.8, 5.5, 10.9, 36.2 mg NaVO ₃ /kg body weight and day (0, 1.17, 2.3, 4.55, 15.13 mg V/kg body weight and day); ♀: 0, 3.2, 6.5, 12.7, 21.4, 37.9 mg/kg body weight and day (0, 1.34, 2.72, 5.31, 8.94, 15.94 mg V/kg body weight and day)), drinking water	– NOAEC: ♂: 15.13 mg V/kg body weight and day; ♀: 15.94 mg V/kg body weight and day	♂: % PCE ↑ (marker for erythropoiesis stimulation)	NTP 2023
MN, peripheral blood (erythrocytes)	mouse, B6C3F1/N, groups of 5 ♂ and 5 ♀	3 months, 0, 31.3, 62.5, 125, 250, 500 mg NaVO ₃ /l (♂: 0, 3.3, 6.7, 13.1, 26.6, 46.6 mg NaVO ₃ /kg body weight and day (0, 1.38, 2.8, 5.47, 11.12, 19.47 mg V/kg body weight and day); ♀: 0, 3.2, 6.7, 13.5, 25.9, 45.6 mg/kg body weight and day (0, 1.34, 2.8, 5.64, 10.81, 19.1 mg V/kg body weight and day)), drinking water	– NOAEC: ♂: 19.47 mg V/kg body weight and day; ♀: 19.1 mg V/kg body weight and day	♂ and ♀: % PCE ↑ (marker for erythropoiesis stimulation)	NTP 2023
MN, peripheral blood (reticulocytes)	rat, Sprague Dawley, groups of 5 ♂ and 5 ♀	3 months, 0, 21, 41.9, 83.8, 168, 335 mg VOSO ₄ /l (♂: 0, 1.9, 3.7, 7.2, 13.9, 25.2 mg/kg body weight and day (0, 0.59, 1.16, 2.25, 4.34, 7.88 mg V/kg body weight and day); ♀: 0, 2.1, 4.5, 9.2, 17.1, 29.9 mg/kg body weight and day (0, 0.66, 1.41, 2.88, 5.53, 9.34 mg V/kg body weight and day)), drinking water	– NOAEC: ♂: 7.88 mg V/kg body weight and day; ♀: 9.34 mg V/kg body weight and day		NTP 2023
MN, peripheral blood (erythrocytes)	mouse, B6C3F1/N, groups of 5 ♂ and 5 ♀	3 months, 0, 21, 41.9, 83.8, 168, 335 mg VOSO ₄ /l (♂: 0, 2.3, 4.8, 9.5, 20.0, 34.4 mg/kg body weight and day (0, 0.72, 1.5, 2.97, 6.25, 10.75 mg V/kg body weight and day); ♀: 0, 2.3, 4.3, 8.3, 17.1, 34.5 mg/kg body weight and day (0, 0.72, 1.34, 2.59, 5.34, 10.78 mg V/kg body weight and day)), drinking water	– NOAEC: ♂: 10.75 mg V/kg body weight and day; ♀: 10.78 mg V/kg body weight and day	♂ and ♀: % PCE ↑ (marker for erythropoiesis stimulation)	NTP 2023
MN, peripheral blood	mouse, CD-1, groups of 3 ♂ and 3 ♀	4 weeks, 1 hour/day, 2 days/week, 0.02 M V ₂ O ₅ (1.4 mg V ₂ O ₅ /m ³ (0.78 mg V/m ³ , extrapolated to 6 hours/day, 5 days/week: 0.05 mg V/m ³)), inhalation, whole-body, 24 hours after last exposure per week	+ : ♂ (even after 1st exposure) – : ♀	time-dependent induction of MN increased in ♂ compared with ♀, leukocyte count unchanged, reticulocyte count ↓, no clinical symptoms, protective effect of oestrogen? inconsistent data for length of exposure (abstract: 2 hours/day, methods section: 1 hour/day), additional oral uptake probable	Rojas-Lemus et al. 2014

Tab. 13 (continued)

Test system	Species, strain, number per group	Exposure	Results	Cytotoxicity/Comments	References
MN, peripheral blood	mouse, Hsd:ICR, groups of 5 ♂	single, 0, 40 mg V ₂ O ₅ /kg body weight (0, 22.5 mg V/kg body weight), intraperitoneal, MN: examination 0, 24, 48, 72 hours after treatment, apoptosis and cell viability: 48 hours	+	apoptotic and necrotic cells ↑, administration of ascorbic acid or alpha-tocopherol (antioxidant), 4 hours prior to treatment with V → no MN induced by V	García-Rodríguez et al. 2016
gene mutation (PCR and sequencing, <i>Kras</i> , Codon 12, 13, 61), lungs	mouse, B6C3F1, (40, ♂/♀, no other details)	2 years, 6 hours/day, 5 days/week, 0, 1, 2, 4 mg V ₂ O ₅ /m ³ (0, 0.56, 1.12, 2.24 mg V/m ³), inhalation, whole-body, 40 lung tumours, (♂/♀, no other details): 0.56 mg/m ³ : 11; 1.12 mg/m ³ : 15; 2.24 mg/m ³ : 14 (compared with 84 tumours in the historical controls)	+: mutation incidence <i>Kras</i> ↑ (Codon 12)	all 40 tumours compared in sum with historical controls; <i>Kras</i> mutation incidence: controls: 25/84 (30%); V ₂ O ₅ : 29/40 (73%); Codon 12: V ₂ O ₅ : GGT → GTT: 7/40 (18%) GGT → GAT: 12/40 (30%) controls: GGT → GTT: 1/84 (1%) GGT → GAT: 9/84 (11%) Codon 13 and 61 increased without statistical significance, additional oral absorption probable	NTP 2002
loss of a <i>Kras</i> allele, lungs	see above	exposure: see above 0 mg/m ³ : 2; 0.56 mg/m ³ : 11; 1.12 mg/m ³ : 15; 2.24 mg/m ³ : 14	+	comparison only with the concurrent control; 19/40 (48%), of these 17/19 (or 16/18; Zhang et al. 2001) with <i>Kras</i> mutation, controls: 0/2 (0%), additional oral absorption probable	NTP 2002; Zhang et al. 2001
gene mutation (ACB-PCR, <i>Kras</i> , Codon 12, mutations GGT → GAT, GGT → GTT), lungs	mouse, BigBlue® B6C3F1, groups of 6 ♂	4 weeks, 6 hours/day, 5 days/week, 0, 0.09, 1.18 mg V ₂ O ₅ /m ³ (0, 0.05, 0.66 mg V/m ³), inhalation, nose-only, purity: 100%	–	0.66 mg V/m ³ : lung weights ↑	Banda et al. 2015
		8 weeks, 6 hours/day, 5 days/week, 0, 0.1, 1.04 mg V ₂ O ₅ /m ³ (0, 0.06, 0.58 mg V/m ³)	– NOAEC: 0.58 mg V/m ³	0.58 mg V/m ³ : lung weights ↑	
gene mutation (<i>cII</i>), lungs	see above	4 weeks, (see Banda et al. 2015)	–	0.66 mg V/m ³ : lung weights ↑, mutation incidence ($\times 10^{-6}$): controls: 30 ± 4.2, 0.05 mg/m ³ : 39 ± 7.9, 0.66 mg/m ³ : 24 ± 4.4	Manjanatha et al. 2015
		8 weeks, (see Banda et al. 2015)	– NOAEC: 0.58 mg V/m ³	controls: 29 ± 3.4, 0.06 mg/m ³ : 48 ± 14.3, 0.58 mg/m ³ : 17 ± 2.8	

Tab. 13 (continued)

Test system	Species, strain, number per group	Exposure	Results	Cytotoxicity/Comments	References
mutations (genome sequencing), lungs, liver	mouse, B6C3F ₁ , (3 lung tumours (controls from other NTP studies))	2 years (see NTP 2002), 0, 1.12, 2.24 mg V/m ³ , 3 lung tumours: 2 ♂: 1.12 mg/m ³ , 1 ♀: 2.24 mg/m ³ , 6 liver tumours: 4 ♂: 2.24 mg/m ³ , 2 ♀: 1 × 1.12 mg/m ³ , 1 × 2.24 mg/m ³	compared with spontaneous tumours: lungs: +: SNV –: DBS/INDELs –: substance-specific mutational signature liver: –: SNV –: DBS/INDELs –: substance-specific mutational signature	see text: lungs: SNV: increased with statistical significance (not liver); DBS/INDEL: lungs/liver: not different from spontaneous tumours; lungs: no substance-specific mutational signatures; agreement with human mutational signatures: SBS1, 5, 17, 40: correlation with age; SBS18: ROS-induced; chromothripsis detected in 1 lung tumour; liver: new liver-specific, but not substance-specific, mutational signature, not detected in human tumours (COSMIC), aetiology unknown (APOBEC, AID)	Riva et al. 2020
mutations (299 different cancer driver mutations such as <i>Kras</i> , <i>Trp53</i> , <i>Hras</i> , <i>Braf</i> , <i>Ctnnb1</i>), lungs, liver	see above	see above	– not different from spontaneous tumours	lungs: <i>Kras</i> , <i>Trp53</i> , liver: <i>Hras</i> , <i>Braf</i> , <i>Ctnnb1</i>	
Germ cells					
DNA damage (comet assay, alkaline), testes	mouse, CD-1, groups of 4 ♂	single, 0, 5.75, 11.5, 23 mg V ₂ O ₅ /kg body weight (0, 3.2, 6.4, 12.8 mg V/kg body weight), intraperitoneal, examination 24 hours after treatment, purity: 99.6%	–	tested doses: 1/4, 1/2 or acute LD ₅₀ ; viability: dose-dependent decrease in the liver (12.8 mg/kg body weight: 44%), all other organs ≥ 70%	Altamirano-Lozano et al. 1999
DNA damage (comet assay, alkaline), testes	mouse, CD-1, ♂, no other details	see above	+ : 3.2 mg V/kg body weight and above	tested doses: 1/4, 1/2 or acute LD ₅₀ ; whole testis minced (connective tissue, Sertoli cells, all germ cell stages, blood vessels, etc.) and analysed	Altamirano-Lozano et al. 1993

Tab. 13 (continued)

Test system	Species, strain, number per group	Exposure	Results	Cytotoxicity/Comments	References
DNA damage (comet assay, alkaline), testes	mouse, CD-1, groups of 5 ♂	5 weeks, 0, 0.75, 7.5, 75, 750, 1500 mg Na ₃ VO ₄ /l (0, 0.06, 0.57, 5.49, 20.8, 33 mg V/kg body weight and day), drinking water, purity: > 90%	–	20.8 mg/kg body weight and above: body weight gains ↓, water consumption ↓, lethargy during the last 2 weeks, absolute spleen weights ↓; 33 mg/kg body weight: 1 animal died (week 3); PCE/NCE unchanged in the micronucleus test	Leopardi et al. 2005
DNA damage (sperm chromatin structure assay (SCSA test)), epididymal spermatozoa	see above	see above	–	testis weights, DNA content in the testicular cells, chromatin structure of the sperm and cell population of the testes unchanged	
DNA damage (structural, no other details), testes	mouse, CD-1, groups of 5 ♂	12 weeks, 1 hour/day, 2 days/week, 0, 0.02 M V ₂ O ₅ (0, 1.4 mg V ₂ O ₅ /m ³ (0, 0.8 mg V/m ³)), inhalation, whole-body, examined weekly after last exposure	+	in addition to the main study objective (changes to the testicular actin cytoskeleton), histopathological observation of structural DNA damage (no other data), possibly resulting from changes to the cytoskeleton during cell division, additional oral uptake probable	Rodríguez-Lara et al. 2016 a
DNA damage (comet assay, alkaline), testes	mouse, CD-1, groups of 8–10 ♂	5 weeks, 0, 2, 10, 100, 500, 1000 mg VOSO ₄ × 5 H ₂ O/l (0, 0.519, 1.96, 26.8, 72.3, 148 mg/kg body weight and day (0, 0.105, 0.395, 5.4, 14.6, 29.9 mg V/kg body weight and day)), drinking water, purity: 99.99%	– NOAEL: 29.9 mg V/kg body weight and day	2 experiments: 1) 10, 100, 500, 1000 mg/l 2) 2, 10 mg/l V levels ↑ (bone marrow (linear, dose-dependent) > spleen, liver, kidneys, testes; not detectable in intestines and stomach), 14.6 mg/kg body weight and above: water consumption ↓, Experiment 2: water consumption ↑ at 0.105 mg/kg body weight	Villani et al. 2007
DNA damage (sperm nuclear DNA fragmentation index), sperm	rat, Sprague Dawley, groups of 6 ♂	90 days, 0, 1 mg NaVO ₃ /kg body weight and day, intraperitoneal	+	markedly reduced with concurrent administration of antioxidant glucosyl hesperidin, malondialdehyde, SOD, catalase ↓, testosterone in the serum, sperm count, motility ↓, abnormal sperm morphology ↑, histopathological damage to the testes	Vijaya Bharathi et al. 2015
CA, oocytes	see above	see above	–	disruption of maturation (premature anaphase)	Mailhes et al. 2003
CA, numerical (FISH, DNA probes for chromosome 8, X, Y), sperm	mouse, 102/El × C3H/El)F1, groups of 5 ♂	single, 0, 5, 15, 25 mg Na ₃ VO ₄ /kg body weight (0, 1.4, 4.2, 6.9 mg V/kg body weight), intraperitoneal, examination after 22 days	+ : 4.2 mg V/kg body weight and above	sperm count, body weights, testis weights unchanged, 4.2 mg V/kg body weight and above: dose-dependent increase in hyperhaploid sperm	Attia et al. 2005

Tab. 13 (continued)

Test system	Species, strain, number per group	Exposure	Results	Cytotoxicity/Comments	References
dominant lethal test	rat, Sprague Dawley, groups of 10 ♂	70 days, 0, about 20 mg NH_4VO_3 /kg body weight and day (0, 8.7 mg V/kg body weight and day), drinking water, each ♂ mated for 5 days with 2 untreated ♀	+	post-implantation losses ↑ (47.36%, controls 0.92%), fertility reduced in treated ♂, pre-implantation losses ↑ (29.63%, controls 0.9%) (probably due to reduced sperm count and dominant lethal effects), results typical for high doses of strong germ cell mutagens	Greim 2009; Morgan and El-Tawil 2003
dominant lethal test	mouse, CD-1, groups of 15–20 ♂	60 days, treated every third day, 0, 8.5 mg V_2O_5 /kg body weight and day (0, 4.7 mg V/kg body weight and day), intraperitoneal, each ♂ mated for 5 nights with 2 untreated ♀	+	dose: 1/2 subchronic LD_{50} , terminal body weights ↓ (20%), post-implantation losses ↑ (0.41, controls 0.04), cytotoxicity: fertility reduced in treated ♂, pre-implantation losses ↑ (29.63%, controls 0.9%), marked dominant lethal effects in addition to cytotoxicity	Altamirano-Lozano et al. 1993; Greim 2009

*p < 0.01; **p < 0.001

–: negative results; +: positive results; +/-: unclear results; ABC-PCR: allele-specific competitive blocker PCR; ALT: alanine aminotransferase; APOBEC/AID: apolipoprotein B editing complex/activation induced cytidine deaminase; CA: chromosomal aberrations; DBS: doublet/dinucleotide base substitution; EdAdo: etheno-2'-deoxyadenosine; EdGuo: etheno-2'-deoxyguanosine; FISH: fluorescence in situ hybridization with centromere-specific DNA samples; GSH: glutathione; GSSG: glutathione disulfide; 5-hmdUrd: 5-hydroxymethyl-2'-deoxyuridine; 5-OH-dCyc: 5-hydroxy-2'-deoxycytidine; INDEL: insertions/deletions; MDA: malondialdehyde; MN: micronuclei; NCE: normochromatic erythrocytes; 8-oxo-dAdo: 8-oxo-2'-deoxyadenosine; 8-oxo-dG: 8-oxo-2'-deoxyguanosine; PCE: polychromatic erythrocytes; ROS: reactive oxygen species; SBS: single base substitution; SCE: sister chromatid exchange; SNV: single nucleotide variants; SOD: superoxide dismutase; ThdGly: thymine glycol; V: vanadium

A long-term inhalation study carried out by the NTP (2002) analysed the bronchoalveolar lung carcinomas of B6C3F1 mice exposed to **divanadium pentaoxide** for mutations in the *Kras* gene or the loss of a *Kras* allele. All exposure groups were evaluated together. The loss of heterozygosity was compared with 2 control tumours of the same NTP study, the mutations with historical controls. Exposure to divanadium pentaoxide increased the number of mutations in the *Kras* gene in comparison with the number found in the historical controls. The greatest increase was observed in the frequency of GGT to GTT and GGT to GAT mutations in codon 12. There was no increase in mutations in codon 13 and 61. The authors suggest that this non-specific type of mutation may be induced by divanadium pentaoxide via the formation of reactive oxygen species or the promotion of endogenous mutations. Exposure to divanadium pentaoxide led to the loss of a *Kras* allele in 19 of 40 tumours (48%); the remaining allele had a mutation in 17 of these 19 tumours (NTP 2002) and in 16 of 18 tumours (Zhang et al. 2001), respectively. The 2 controls did not have a *Kras* allelic imbalance. The discrepancies between the data published by NTP (2002) and by Zhang et al. (2001) are difficult to understand. The examination of 10 tumours (no other details) did not provide clear evidence of the induction of mutated p53 protein (NTP 2002). Although the authors reported that they selectively examined mutated p53, the antibody used detects both wild-type and mutated p53 (MGI 2022).

The occurrence of somatic mutations in the lung and liver tumours of mice from the NTP study (NTP 2002) was investigated by sequencing. Tumours that had developed spontaneously in untreated animals in various NTP studies, but not from the control animals of the divanadium pentaoxide study, were used as the controls, in addition to healthy tissue from 29 mice. The frequency of somatic single-nucleotide variants (SNV) was increased with statistical significance (1.7-fold) in the lung tumours, but not in the liver tumours, of animals exposed to divanadium pentaoxide. The mutational signatures extracted from the mutation spectra by hierarchical cluster analysis did not differ from those observed in spontaneously occurring tumours. The analysis of orthologs from 299 human “hotspot mutations in cancer driver genes” did not reveal driver mutations specific for vanadium pentaoxide. A lung tumour in the divanadium

pentaoxide group revealed chromothripsis, a very rare event involving multiple chromosomal rearrangements. This mutation was not found in any of the control tumours. Overall, genomic sequencing revealed that the tumours induced by divanadium pentaoxide had slightly more SNVs, but qualitatively the same type of mutations (mutational signatures, driver mutations) as spontaneously occurring tumours. As the mutational signatures found in the tumour tissue of mice (spontaneous and substance-induced) have been detected also in the tumours and healthy tissue of humans, the authors suggest that they may be attributed to a disruption of endogenous processes (Riva et al. 2020). However, this hypothesis is qualified by the circumstance that only 3 lung tumours were sequenced for divanadium pentaoxide and the control tumours were taken from other NTP studies. However, qualitative differences were not found in the mutational signatures of the control tumours.

Summary in vivo: In the available studies, DNA damage in the comet assay, oxidative DNA damage, clastogenic and aneugenic effects (chromosomal aberrations, micronuclei) were induced by several different vanadium compounds in mice and rats after exposure by inhalation, administration with the drinking water and by intraperitoneal injection. (Oxidative) DNA damage was induced at lower concentrations or doses than micronuclei or chromosomal aberrations. After nose-only inhalation exposure of BigBlue® mice to vanadium concentrations of up to 0.58 mg/m³ for up to 8 weeks, there was no increase in the mutation frequency in the *Kras* and *cH* genes of the lungs. In the lung tumours that developed in mice after 2-year inhalation exposure there was an increase in G → T transversions in *Kras*, which is a marker for ROS. The additional occurrence of G → A transitions suggests that different mechanisms of tumourigenesis are involved.

With respect to the whole genome, the mutation frequency in lung tumours was increased only slightly after 2-year exposure to vanadium concentrations of up to 2.24 mg/m³; however, the type of mutation did not differ from that occurring in spontaneous tumours.

Table 14 includes only studies with oral or inhalation exposure that can be used to derive a NOAEL(C) or a LOAEL(C).

The study with the lowest LOAEC (Hussain Shah et al. 2019) has numerous shortcomings and weaknesses in the areas of documentation and plausibility. For example, the methods section does not include information about how the comets were scored or the examination time points and provides incorrect values for the tail moment. Furthermore, it is unclear whether the animals were administered the substance on a daily basis. For these reasons, the results of this study were not taken into consideration for the determination of the lowest NOAEC or LOAEC.

A 5-week drinking water study investigated time as a factor in the induction of micronuclei in the peripheral blood of mice treated with **sodium orthovanadate**. The publication compared the statistically significant changes that were detected in each group after 3 and 5 weeks with the values obtained at the beginning of exposure. The incidences in the groups exposed to vanadium doses of 5.49 and 20.8 mg/kg body weight were increased with statistical significance compared with the values determined at the beginning of exposure. After exposure for 5 weeks, an increase was observed at doses as low as 0.57 mg/kg body weight and above. The values determined in the highest dose group at the beginning of exposure did not change with statistical significance over the entire examination period. A comparison with the concurrent control was not documented (Leopardi et al. 2005). In a figure published with the study, the micronuclei in the peripheral blood almost doubled compared with the values of the concurrent controls after 3-week exposure to vanadium doses of 5.49 mg/kg body weight and above. After 5-week exposure, the incidence of micronuclei had at least doubled in the 2 low-dose groups, but not in the medium and high dose groups. As no dose dependency was evident, only 1000 reticulocytes per animal were evaluated and the findings were not analysed statistically, this aspect of the study is not taken into consideration for the determination of the NOAEL or LOAEL.

A micronucleus test using the peripheral blood of male and female mice that were exposed by inhalation to **divanadium pentaoxide** (about 1.4 mg/m³; 0.78 mg V/m³; converted to 6 hours/day, 5 days/week: 0.052 mg V/m³) for 1 hour a day, twice a week, over a period of 4 weeks yielded positive results for male mice (Rojas-Lemus et al. 2014). These results were not included in the evaluation of genotoxic effects for the following reasons: The method used to determine the level of exposure was poorly described, the aerosol generator was a commercially available device used in the health sector and the specified concentration may not have been properly prepared and analysed. Furthermore, a suspension was prepared with divanadium pentaoxide powder, which was then nebulized. Only one concentration was tested.

In contrast, a micronucleus test carried out by the NTP using the peripheral blood of mice yielded negative results. In this study, the animals were exposed to vanadium powder in a concentration of up to 8.96 mg/m³ for 6 hours a day, on 5 days a week, for 3 months (NTP 2002).

Tab. 14 Overview of NOAEC and LOAEC values obtained from valid studies for the genotoxic effects of inorganic vanadium compounds

End point, organ	Species, exposure	NOAEL / NOAEC (for V)	LOAEL / LOAEC (for V)	Toxicity	References
DNA damage (comet assay, alkaline, unless specified otherwise)					
spleen, testes, bone marrow, peripheral blood	mouse, CD-1, 5 weeks, drinking water, Na ₃ VO ₄ , 0.06–33 mg V/kg body weight and day	20.8 mg/kg body weight (6.6 mg/m ³) ^{a)}	33 mg/kg body weight (spleen) (10.5 mg/m ³) ^{a)}	≥ 20.8 mg/kg body weight: lethargy, body weight gains ↓, water consumption ↓, absolute spleen weights ↓	Leopardi et al. 2005
lungs, BALF	mouse, B6C3F1, 7 or 16 days, inhalation, 6 hours/day, V ₂ O ₅ , 0.14–2.24 mg V/m ³	2.24 mg/m ³	no LOAEC	≥ 0.56 mg/m ³ : lung weights ↑, histopathological lung damage; 2.24 mg/m ³ : body weights ↓ (week 1)	Schuler et al. 2011
lungs (oxidative DNA damage)	see above	0.14 mg/m ³	0.56 mg/m ³	8-oxo-dG increased with concentration dependency, dCyd341 unchanged, 6 others not detectable, GSH: ≥ 0.14 mg/m ³ ↓, GSSG ≥ 0.24 ml/m ³ ↑, GSH/2 × GSSG: ↓	
bone marrow, testes	mouse, CD-1, 5 weeks, drinking water, VOSO ₄ × 5 H ₂ O, 0, 0.105, 0.395, 5.4, 14.6, 29.9 mg V/kg body weight and day	29.9 mg/kg body weight (9.5 mg/m ³) ^{a)}	no LOAEL	≥ 14.6 mg/kg body weight and day: water consumption ↓, Experiment 2: water consumption increased at 0.105 mg/kg body weight	Villani et al. 2007
Micronucleus test					
bone marrow	mouse, CD-1, 5 weeks, drinking water, Na ₃ VO ₄ , 0.06–33 mg V/kg body weight and day	5.49 mg/kg body weight (1.74 mg/m ³) ^{a)}	20.8 mg/kg body weight (6.6 mg/m ³) ^{a)}	PCE/NCE unchanged, ≥ 20.8 mg/kg body weight: systemic toxicity, V detected in bone marrow	Leopardi et al. 2005
bone marrow	mouse, CD-1, 5 weeks, drinking water, VOSO ₄ × 5 H ₂ O, 0, 0.105, 0.395, 5.4, 14.6, 29.9 mg V/kg body weight and day	29.9 mg/kg body weight (9.5 mg/m ³) ^{a)}	no LOAEL	PCE/NCE unchanged, see comet assay for further comments	Villani et al. 2007
peripheral blood	mouse, B6C3F1, 3 months, inhalation, 6 hours/day, 5 days/week, V ₂ O ₅ , 0, 0.56, 1.12, 1.68, 4.48, 8.96 mg V/m ³	8.69 mg/m ³	no LOAEC	PCE/NCE unchanged, additional oral uptake probable	NTP 2002
Mutations					
Kras mutations in codon 12 GGT → GAT, GGT → GTT, lungs	mouse, BigBlue® B6C3F1, 4, 8 weeks, inhalation, 6 hours/day, 5 days/week, V ₂ O ₅ , 4 weeks: 0, 0.05, 0.66 mg V/m ³ 8 weeks: 0, 0.06, 0.58 mg V/m ³	0.58 mg/m ³	no LOAEC	0.58 and 0.66 mg V/m ³ , respectively: lung weights ↑	Banda et al. 2015
(cII), lungs	see above	0.58 mg/m ³	no LOAEC	0.58 and 0.66 mg V/m ³ , respectively: lung weights ↑	Manjanatha et al. 2015

^{a)} inhaled concentration (mg/m³) that would be equivalent to the orally administered dose after 6 hours: oral dose (mg/kg body weight and day) / (respiratory minute volume (RMV) of the species × 60 minutes × 6 hours / oral absorption / 1000) / inhalation absorption (RMV: mouse: 1.4 l/min/kg body weight, rat: 0.8 l/min/kg body weight (Bide et al. 2000), oral absorption: 16% (see Section 3.1), inhalation absorption: 100%)

BALF: bronchoalveolar lavage fluid; GSH: glutathione; GSSG: glutathione disulfide; NCE: normochromatic erythrocytes; 8-oxo-dG: 8-oxo-2'-deoxyguanosine; PCE: polychromatic erythrocytes; V: vanadium

The lowest NOAEC for the genotoxic effects induced by vanadium is 0.14 mg/m³ and was derived from an inhalation study with B6C3F1 mice with up to 16-day exposure (Table 14). A concentration-dependent increase in 8-oxo-2'-deoxyguanosine was detected by HPLC at the next-higher vanadium concentration of 0.56 mg/m³ and above. Deoxycytosine 341 (dCyd341) remained unchanged; other oxidized bases such as 8-oxo-2'-deoxyadenosine, etheno-2'-deoxyadenosine or etheno-2'-deoxyguanosine were not detected (Schuler et al. 2011).

5.7 Carcinogenicity

5.7.1 Short-term studies

To investigate whether divanadium pentaoxide has promoting effects, male animals of the mouse strains A/J, BALB/cJ and C57BL/6J (n=3–15) were given 3-methylcholanthrene as an initiator by intraperitoneal injection in a dose of 10 µg/kg body weight. One week later, they were exposed to **divanadium pentaoxide** doses of 0 or 4 mg/kg body weight and day by **oropharyngeal aspiration** once a week for 5 weeks. Divanadium pentaoxide was suspended in PBS. The control animals were given PBS. Three weeks after the last administration of divanadium pentaoxide, inflammatory signs were increased in the BALF of the mice exposed to divanadium pentaoxide, but not in those that had received a single injection of methylcholanthrene. The animals were examined for tumour formation in the lungs 20 weeks after administration of the initiator. The tumour incidence in the lungs of mice of the strains A/J and BALB/cJ was increased with statistical significance after initiation and treatment with divanadium pentaoxide. The histopathological analysis of the tumours of several animals revealed solid (80%) and papillary (20%) adenomas. Under these study conditions, divanadium pentaoxide did not cause tumours without initiation (NTP 2002; Rondini et al. 2010). The data suggest that divanadium pentaoxide has a tumour-promoting effect.

5.7.2 Long-term studies

In an inhalation study, groups of 50 male and 50 female B6C3F1 mice were exposed to **divanadium pentaoxide** concentrations of 0, 1, 2 or 4 mg/m³ (0, 0.56, 1.12 or 2.24 mg vanadium/m³) for 6 hours a day, on 5 days a week, over a period of 2 years. The incidence of bronchoalveolar carcinomas was increased in both sexes with statistical significance even in the low concentration group (see Table 15). Mortality was significantly increased in the high concentration group. A concentration-dependent decrease in body weight and irregular breathing were observed in all exposed animals. Hyperplasia and metaplasia were observed in the lungs, larynx and nose; their occurrence was dependent on the concentration. The incidence of adenomas and carcinomas in the liver and in the Harderian gland declined at higher concentrations (anti-tumour effects) (Greim 2009; NTP 2002).

Tab. 15 Carcinogenicity study of divanadium pentaoxide in B6C3F1 mice (Greim 2009; NTP 2002)

Author:	NTP 2002				
Substance:	divanadium pentaoxide (dust, > 90% of the particles < 1 µm)				
Species:	mouse, B6C3F1, 50 ♂, 50 ♀ per group				
Administration route:	inhalation, whole-body				
Concentration:	0, 1, 2, 4 mg V ₂ O ₅ /m ³ (0, 0.56, 1.12, 2.24 mg V/m ³)				
Duration:	104 weeks, 5 days/week, 6 hours/day				
Toxicity:	see Table 8, 0.56 mg V/m ³ and above: lungs: inflammation, fibrosis (Section 5.2.1)				
		Exposure concentration [mg V/m ³]			
		0	0.56	1.12	2.24
Surviving animals	♂	39/50 (78%)	33/50 (66%)	36/50 (72%)	27/50 (54%)
	♀	38/50 (76%)	32/50 (64%)	30/50 (60%)	32/50 (64%)
Tumours and pre-neoplasms					
lungs:					
hyperplasia of the alveolar epithelium	♂	3/50 (6%)	41/50 (82%)**	49/50 (98%)**	50/50 (100%)**
	♀	0/50	31/50 (62%)**	38/50 (76%)**	50/50 (100%)**
hyperplasia of the bronchiolar epithelium	♂	0/50	15/50 (30%)**	37/50 (74%)**	46/50 (92%)**
	♀	0/50	12/50 (24%)**	34/50 (68%)**	48/50 (96%)**
bronchoalveolar adenomas	♂	13/50 (26%)	16/50 (32%)	26/50 (52%)*	15/50 (30%)
	♀	1/50 (2%)	17/50 (34%)**	23/50 (46%)**	19/50 (38%)**
bronchoalveolar carcinomas	♂	12/50 (24%)	29/50 (58%)**	30/50 (60%)**	35/50 (70%)**
	♀	0/50	23/50 (46%)**	18/50 (36%)**	19/50 (38%)**
bronchoalveolar adenomas or carcinomas	♂	22/50 (44%)	42/50 (84%)**	43/50 (86%)**	43/50 (86%)**
	♀	1/50 (2%)	32/50 (64%)**	35/50 (70%)**	32/50 (64%)**
lymph nodes:					
hyperplasia of the bronchial lymph nodes	♀	3/39 (7%)	13/40 (32%)**	14/45 (31%)**	20/41 (48%)**
spleen:					
haemangiomas	♂	0/50	0/50	0/50	3/50 (6%)

*p ≤ 0.05; **p ≤ 0.01 (pairwise poly-3 test)

V: vanadium

A retrospective evaluation of the study data by poly-3-adjusted Cochran-Armitage trend test confirmed a statistically significant trend for the incidence of lung tumours. However, it was not possible to derive a concentration–effect relationship for the 3 treatment groups (Starr and MacGregor 2014).

Groups of 62 to 84 male and female mice were exposed to **divanadium pentaoxide** dust in concentrations of 0, 0.5, 2 or 8 mg/m³ (0, 0.3, 1.1 or 4.5 mg vanadium/m³) for 4 hours a day over the course of 1 year. At divanadium pentaoxide dust concentrations of 2 and 8 mg/m³, 2 of 79 animals had papillomatous and 3 of 62 animals adenomatous tumours in the lungs. No tumours were found in the control group and in the group exposed to a divanadium pentaoxide dust concentration of 0.5 mg/m³ (no other details; WHO 2001). The study report does not include any other information about the exposure conditions and the size of the particles.

Groups of 50 male and 50 female F344/N rats were exposed to **divanadium pentaoxide** concentrations of 0, 0.5, 1 or 2 mg/m³ over a period of 2 years. The females in the high concentration group had reduced mean body weights. The incidence of hyperplasia of the alveolar and bronchiolar epithelium was increased with statistical significance in the males at the low concentration and above and in the females at concentrations of 1 mg/m³ and above. The incidence of alveolar metaplasia was increased with statistical significance in both sexes at the high concentration. There was an increased incidence of metaplasia of the bronchoalveolar epithelium, but only in the male animals. Alveolar carcinomas were found in individual males of the exposure groups and in one female of the high concentration group. The incidence of bronchoalveolar adenomas and carcinomas was increased in the male animals; however, these effects were neither statistically significant nor dependent on the concentration. Non-neoplastic lesions were detected in the lungs, larynx and nose of exposed males and females; this effect increased with the concentration. The authors of the NTP study

interpreted the presence of alveolar hyperplasia and metaplasia as some evidence of carcinogenic activity in male rats and as equivocal evidence in female rats (see Table 16) (Greim 2009; NTP 2002).

Tab. 16 Carcinogenicity study of divanadium pentaoxide in F344 rats (Greim 2009; NTP 2002)

Author:	NTP 2002				
Substance:	divanadium pentaoxide (dust, > 90% of the particles < 1 µm)				
Species:	rat, F344/N, 50 ♂, 50 ♀ per group				
Administration route:	inhalation, whole-body				
Concentration:	0, 0.5, 1, 2 mg V ₂ O ₅ /m ³ (0, 0.28, 0.56, 1.12 mg V/m ³)				
Duration:	104 weeks, 5 days/week, 6 hours/day				
Toxicity:	see Table 8, 0.28 mg V/m ³ and above: lungs: inflammation (Section 5.2.1)				
		Exposure concentration [mg V/m ³]			
		0	0.28	0.56	1.12
Surviving animals	♂	20/50 (40%)	29/50 (58%)	26/50 (52%)	27/50 (54%)
	♀	33/50 (66%)	24/50 (48%)	29/50 (58%)	30/50 (60%)
Tumours and pre-neoplasms					
lungs:					
hyperplasia of the alveolar epithelium	♂	7/50 (14%)	24/49 (49%)**	34/48 (71%)**	49/50 (98%)**
	♀	4/49 (8%)	8/49 (16%)	21/50 (42%)**	50/50 (100%)**
hyperplasia of the bronchiolar epithelium	♂	3/50 (6%)	17/49 (35%)**	31/48 (65%)**	49/50 (98%)**
	♀	6/49 (12%)	5/49 (10%)	14/50 (28%)*	48/50 (96%)**
metaplasia of the alveolar epithelium	♂	1/50 (2%)	0/49	0/48	21/50 (42%)**
	♀	0/49	0/49	0/50	6/50 (12%)*
metaplasia of the bronchoalveolar epithelium	♂	0/50	0/49	0/48	7/50 (14%)**
	♀	0/49	0/49	0/50	1/50 (2%)
bronchoalveolar adenomas	♂	4/50 (8%)	8/49 (16%)	5/48 (10%)	6/50 (12%)
	♀	0/49	3/49 (6%)	1/50 (2%)	0/50
bronchoalveolar carcinomas	♂	0/50	3/49 (6%)	1/48 (2%)	3/50 (7%)
	♀	0/49	0/49	0/50	1/50 (2%)
bronchoalveolar adenomas or carcinomas	♂	4/50 (8%)	10/49 (20%)	6/48 (12%)	9/50 (18%)
	♀	0/49	3/49 (6%)	1/50 (2%)	1/50 (2%)
larynx:					
hyperplasia of the respiratory epithelium of the epiglottis	♂	0/49	18/50 (36%)**	34/50 (68%)**	32/49 (64%)**
	♀	0/50	25/49 (51%)**	26/49 (53%)**	33/50 (66%)**

*p ≤ 0.05; **p ≤ 0.01 (pairwise poly-3 test)

V: vanadium

At 8%, the tumour incidence for lung adenomas and adenomas/carcinomas in the male control animals of this study was very high relative to the incidence found in the historical controls, leading to a decrease in the statistical significance. The NTP studies used the following historical control data for the male animals: adenomas 1.34% (2010) and 1.15% (2009), carcinomas 1.34% (2010) and 1.15% (2009), adenomas and carcinomas 2.68% (2010) and 2.29% (2009) (NTP 2020).

Retrospectively published historical control data (NTP 2020), including data from 25 studies that used the same feed as the carcinogenicity study of the NTP (2002), were pooled with the historical control data from the carcinogenicity study. The authors evaluated the results of significance calculations carried out with the pooled data and concluded that the lung tumour incidence was not increased with statistical significance and there was no evidence of carcinogenic effects in rats exposed to **divanadium pentaoxide** (Starr et al. 2012). The historical control data collected from 25 studies (including all routes of administration) for male F344 rats and published by the NTP (2020) show that bronchoalveolar carcinomas occur very rarely in F344 rats. In 24 of the evaluated studies, no or only one bronchoalveolar carcinoma was found in the male control animals (mean value 1.2%, geometric mean 1.2%, standard deviation ± 1.42%). However, one study with dermal application reported 3 cases in 50 control animals. Starr et al. (2012) used this study to establish a range of 0 to 6% for the significance calculations. If only the historical control data of the inhalation studies (n = 6) were used as the basis, the range would be 0 to 2% (NTP 2020). The incidence of bronchoalveolar tumours in male rats

thus lies above the range of the historical controls. As a result, the Commission does not support the conclusions drawn by Starr et al. (2012).

Some authors report anticarcinogenic effects of vanadate(V) ions and organic vanadium complexes, which, however, are not evaluated by the Commission (summarized in Mukherjee et al. (2004); more recent data cited by US EPA (2009)).

5.8 Other studies

Mouse WEHI-3 cells revealed altered macrophage-interferon- γ -binding and interferon- γ -inducible responses after incubation with **ammonium metavanadate** and **divanadium pentaoxide** and the addition of interferon- γ for 4 hours (Cohen et al. 1996 a).

After in vitro incubation with **divanadium pentaoxide**, aggregation inhibition effects were detected in isolated platelets from human blood samples at concentrations of 500 μ M and above (González-Villalva et al. 2011).

6 Manifesto (MAK value/classification)

Vanadium compounds induce tumour-promoting effects in the lungs and lung tumours in mice and rats. Vanadium compounds cause irritation in the upper respiratory tract and may lead to chronic bronchitis and obstructive respiratory disorders. Vanadium compounds have neurotoxic potential.

Carcinogenicity. There is no evidence available that vanadium compounds have carcinogenic potential in humans. In B6C3F1 mice, **divanadium pentaoxide** increased the incidence of bronchoalveolar adenomas and carcinomas with statistical significance. In F344/N rats, the incidence of bronchoalveolar adenomas and carcinomas was increased, but without statistical significance (NTP 2002). The vanadate(V) ion and the vanadyl(IV) ion, which are in equilibrium with each other under physiological conditions, are considered responsible for the carcinogenic effects. DNA damage in the comet assay, oxidative DNA damage, and clastogenic and aneugenic effects (chromosomal aberrations, micronuclei) were induced by several different vanadium compounds in mice and rats after exposure by inhalation, administration with the drinking water and by intraperitoneal injection.

(Oxidative) DNA damage occurs at lower concentrations and doses than the induction of micronuclei or chromosomal aberrations; furthermore, DNA repair processes are inhibited. Vanadium compounds induce cytotoxicity, which may trigger inflammatory reactions. These may in turn activate signalling cascades, which are responsible for increased proliferation and cell growth, ultimately leading to tumour formation. The aneugenic effects of vanadium compounds are mediated by the inhibition of protein tyrosine phosphatases. Because inflammatory effects, and not a genotoxic mechanism of action, are the primary cause of the carcinogenic effects, and a no-effect concentration can be determined for these effects, vanadium and its inorganic compounds have been classified in Carcinogen Category 4.

MAK value. *Neurotoxicity:* Neurotoxic effects were found in workers who were employed for more than 1 year in the manufacture of products containing vanadium after exposure to a mean vanadium concentration of 0.216 mg/m³. In animal studies, neurotoxic effects and histopathological changes were observed after inhalation exposure to a vanadium concentration of 0.78 mg/m³ and intraperitoneal injection of a vanadium dose of 1.25 mg/kg body weight. As only one concentration or dose was tested, it is not possible to establish a concentration–effect or dose–response relationship.

Carcinogenicity: A NOAEC for carcinogenic effects cannot be derived based on the available studies. A 2-year inhalation study (exposure to **divanadium pentaoxide**) in rats revealed alveolar histiocytic infiltration and hyperplasia in the lungs in addition to increased incidences of adenomas and carcinomas that did not reach statistical significance at vanadium concentrations of 0.28 mg/m³ and above. Chronic inflammation, hyperplasia and degeneration were found in the larynx. In mice, the described effects and increased incidences of adenomas and carcinomas in the lungs that reached statistical significance were observed at the low vanadium concentration of 0.56 mg/m³ and above (NTP 2002). A

NOAEC of 0.14 mg vanadium/m³ was derived for oxidative DNA damage, cell proliferation and histopathological effects in the lungs based on the findings of a 16-day inhalation study carried out in female B6C3F1 mice with a **divanadium pentaoxide** aerosol (respirable fraction). Of all of the studies, this study tested the lowest concentration of **divanadium pentaoxide** (see Table 17) (Schuler et al. 2011).

Tab. 17 Overview of the NOAEC and LOAEC values for the most sensitive end points

End point, organ, species	NOAEC (for V)	LOAEC (for V)
8-Oxo-dG (HPLC-MS/MS), inflammatory and histopathological effects, lungs, mouse	0.14 mg/m³	0.56 mg/m ³
Micronucleus test, bone marrow, mouse (oral) ^{a)}	1.7 mg/m ³	6.6 mg/m ³
Mutations, lungs, BigBlue® mouse	0.58 mg/m ³	no LOAEC
Alveolar histiocytic infiltration, hyperplasia, adenomas/carcinomas, lungs, mouse	–	0.56 mg/m ³
Alveolar histiocytic infiltration, hyperplasia, adenomas/carcinomas, lungs, rats	–	0.28 mg/m ³
Neurotoxicity, mouse	–	0.78 mg/m ³
Neurotoxicity, rat (oral) ^{a)}	–	0.95 mg/m ³

^{a)} Conversion to an inhaled concentration see Table 14

V: vanadium

A subacute NOAEC of 0.14 mg/m³ (respirable fraction) was derived for histopathological inflammatory changes and oxidative DNA damage induced by vanadium in the lungs. On the basis of this NOAEC, and taking into consideration the time extrapolation (1:6), the extrapolation from animals to humans (1:2) and the increased respiratory volume at the workplace (1:2), this results in a vanadium concentration of 0.005 mg/m³ for the respirable fraction. Carcinogenic effects are not expected to occur at this concentration.

Upper respiratory tract (inhalable fraction): A value for the inhalable fraction is derived to protect against cytotoxic effects and irritation, and thus tumour formation, in the upper respiratory tract. Lung tumours are caused by oxidative stress, which leads to cytotoxic effects and to irritation. A NOAEC cannot be derived for histopathological changes in the upper respiratory tract. There are no data for oxidative DNA damage in the upper respiratory tract.

In a Finnish study, 25 of 63 workers who had been exposed to a mean vanadium concentration of 0.028 mg/m³ for at least 4 months and for on average 11 years exhibited wheezing, but not a decline in pulmonary function. A rhinoscopy did not reveal effects on the mucous membrane of the palate, the posterior pharyngeal wall, the larynx or the vocal cords. In the nasal smears, the number of neutrophils was increased in 16 to 21 of 45 to 57 exposed individuals, depending on the evaluation of exposure duration, compared to the control subjects, as was the number of plasma cells and lymphocytes (“round cells”) in the nasal mucosa. A LOAEC of 0.028 mg/m³ was derived from the findings of this study for effects induced by vanadium in the upper respiratory tract.

Only the vanadyl cation (VO²⁺) and the vanadate anion (H₂VO₄⁻) are relevant under physiological conditions (at pH 7 in human tissue), which can easily be converted into each other by redox reactions. It is quite probable that vanadium compounds other than divanadium pentaoxide are able to convert to effective vanadium ions. Data for subchronic or chronic inhalation exposure are available only for divanadium pentaoxide. As the vanadate(V) ion, or the vanadyl(IV) ion, which are in equilibrium with it under physiological conditions, are considered responsible for the cytotoxic effects, irritation and also carcinogenic effects, the inorganic vanadium compounds are evaluated together despite their varying levels of solubility. A NOAEC for effects in the upper respiratory tract cannot be derived on the basis of the data from animal studies or from humans. As a result, the NOAEC of 0.14 mg vanadium/m³ that was obtained for inflammatory, histopathological and oxidative DNA damage in the lungs of mice after subacute exposure is likewise used to derive the value for the inhalable fraction to prevent these effects in the upper respiratory tract. The concentration of 0.005 mg/m³ that was derived for the respirable fraction has been set also as the MAK value for the inhalable fraction.

There are no data for vanadium metal dust. Other metals (for example nickel) are known to be bioavailable in the body and undergo oxidation. This is assumed also for vanadium metal, which is more a base metal, as long as there are no studies that prove otherwise. The MAK value of 0.005 mg vanadium/m³ (inhalable fraction) is used also for vanadium metal and its inorganic compounds.

Peak limitation. Peak Limitation Category II has been assigned because the MAK value was derived based on long-term effects in the lungs. Workplace studies found that effects were induced after many years of exposure to mean vanadium concentrations of 0.028 mg/m³. As a result, an excursion factor of 2 has been set.

Prenatal toxicity. Vanadium passes the blood–brain barrier and crosses the placental barrier.

Developmental toxicity: Vanadium given to rats in oral doses of 8.4 mg/kg body weight and day as **sodium metavanadate** reduced the number of litters and the body weights of the foetuses (Domingo et al. 1986). **Vanadyl sulfate pentahydrate** given to mice in oral doses led to reduced body weights, reduced crown rump lengths and an increased total number of external defects and delayed ossification in the foetuses at doses of 7.6 mg vanadium/kg body weight and day and above (Paternain et al. 1990). In the same species, **sodium orthovanadate** caused delayed ossification in the foetuses of the sacral vertebrae and of the distal phalanges of the fingers and toes at doses of 8.3 mg vanadium/kg body weight and day and above. In conclusion for oral exposure, the margins between the concentration in air extrapolated from the LOAEL for developmental toxicity in rats and mice and the MAK value of 0.005 mg/m³ are > 100. A NOAEL of 4.2 mg/kg body weight was derived for mice (Sanchez et al. 1991); this is equivalent to a 134-fold margin after extrapolation (taking into consideration oral absorption of 16%). In mice given sodium metavanadate from gestation days 6 to 15 by intraperitoneal injection, which is considered the worst-case scenario, an increase in embryoletality and reduced body weights were observed at vanadium doses of 0.8 mg/kg body weight and day and above. This results in a NOAEL for vanadium of 0.4 mg/kg body weight and day (Gomez et al. 1992), which is equivalent to an 80-fold margin to the MAK value after extrapolation to a concentration in the workplace air (assumption: 100% absorption). Overall, classification in Pregnancy Risk Group C would be justified for general developmental toxicity.

Developmental neurotoxicity: In vitro and in vivo studies in rats and mice reported effects on oligodendrocyte progenitor cells, which react with greater sensitivity than astrocytes or mature oligodendrocytes. Impaired oligodendrocytes led to myelination effects and motor impairment in neonatal/juvenile rats and mice (Azeez et al. 2016; Mustapha et al. 2014; Soazo and Garcia 2007; Todorich et al. 2011). A NOAEC for developmental neurotoxicity cannot be derived from the available studies.

The effect dose for vanadium is 1.25 mg/kg body weight and day (Todorich et al. 2011), which represents the worst case because it was obtained in a study that administered the substance by intraperitoneal injection. The following toxicokinetic data are taken into consideration for the extrapolation of this effect dose to a concentration in workplace air: the corresponding species-specific correction value for the rat (1:4), the intraperitoneal absorption (100%), the body weight (70 kg) and the respiratory volume (10 m³) of the person and the assumed 100% absorption by inhalation. A vanadium concentration of 2.2 mg/m³ is calculated from these data, which results in a 440-fold margin to the MAK value of vanadium of 0.005 mg/m³. It is not possible to establish whether this margin is sufficiently large because, as mentioned above, a NOAEC for the effects on oligodendrocyte progenitor cells and motor impairment has not been derived. Valid toxicokinetic data for estimating the body burden of foetuses at exposure levels equal to the MAK value are not available. As a result of this uncertainty, vanadium and its inorganic compounds have been classified in Pregnancy Group D.

Germ cell mutagenicity. Gene mutation studies in bacteria and mammalian cells yielded mostly negative results for several different vanadium compounds. Nose-only inhalation exposure to vanadium concentrations up to 0.58 mg/m³ for a maximum period of 8 weeks did not lead to an increase in the frequency of *Kras* and *cII* mutations in the lungs of BigBlue® mice.

Vanadium compounds induced dominant lethal mutations at very high doses after oral (rat) and intraperitoneal (mouse) administration. DNA damage and numerical chromosomal aberrations were observed in the germ cells of male mice after intraperitoneal administration. The in vitro and in vivo studies reported the induction of DNA damage in the comet assay, oxidative DNA damage, inhibition of the repair of DNA damage (in vitro) induced by UV light or bleomycin, and clastogenic and aneugenic effects (chromosomal aberrations, micronuclei) both in vitro and after exposure of mice and rats by inhalation, administration with the drinking water and by intraperitoneal injection. The (oxidative) DNA damage occurred at lower concentrations and doses than the micronuclei or chromosomal aberrations.

Animal studies detected effects in germ cells only at very high doses. The effect dose determined for vanadium in the dominant lethal test after oral administration in rats was 8.7 mg/kg body weight and day (Morgan and El-Tawil 2003). The following toxicokinetic data are taken into consideration for the extrapolation of this effect dose to a concentration in workplace air: the corresponding species-specific correction value for the rat (1:4), the oral absorption (16%), the body weight (70 kg), the respiratory volume (10 m³) of the human and the assumed 100% absorption by inhalation. Another factor that is taken into consideration is continuous exposure (7 days a week) via the drinking water as opposed to the typical workplace situation (7:5). A vanadium concentration of 3.4 mg/m³ is calculated from these data, which results in a 680-fold margin to the MAK value of vanadium of 0.005 mg/m³. As no noteworthy contribution to the genetic risk of humans is to be expected if this MAK value is observed, vanadium and its inorganic compounds have been classified in Category 5 for germ cell mutagens.

Absorption through the skin. Acute toxicity studies with dermal application to Sprague Dawley rats revealed LD₅₀ values markedly above 1000 mg/kg body weight for 2 water-soluble vanadium salts and for the poorer soluble divanadium pentaoxide. Acute toxicity studies with dermal application to rabbits could not be used to evaluate systemic effects caused by absorption through the skin because of local irritation.

There are no other observational data after application of the substance only to the skin or experimental data for the absorption of vanadium and its compounds through the skin. Model calculations could not be used.

At present there is no evidence available that shows that vanadium and its inorganic compounds are absorbed through the skin. As a result, vanadium and its inorganic compounds have not been designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are several clinical findings of positive reactions to vanadium or vanadium compounds in patch tests. However, as the test formulations were of questionable suitability (see Section 4.4.1), particularly those with vanadium trichloride, these results cannot be evaluated with confidence. Furthermore, with 2 exceptions, the reported findings involve suspected intolerance reactions to metal implants that are not appropriate for assessing the risks of possible topical exposure at the workplace. Overall, the findings from animal studies do not demonstrate contact sensitizing effects. More recently published data for sensitizing effects on the airways are not available. For this reason, vanadium and its inorganic compounds have not been designated with “Sh” or “Sa” (for substances which cause sensitization of the skin or airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

The views expressed in these publications are those of the individual authors acting in their personal capacity as experts and do not represent the positions of their respective institutions or employers.

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