
Zirconium and zirconium compounds

(CAS No: 7440-67-7)

Health-based Reassessment of Administrative
Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of zirconium and its compounds by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AD Wientjes, M.Sc. and Ir PMJ Bos (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of zirconium and compounds has been based on the review by American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the on-line databases Medline, Toxline, and Chemical Abstracts covering the period 1966 to 26 April 1999 (19990426/UP), 1965 to 29 January 1999 (19990129/ED), and 1967 to 24 April 1999 (19940424/ED), respectively, and using the following key words: zirconium, zircon, 7440-67-7, 1291-32-3, 7699-43-6, 13762-26-0, 12164-98-6, and 1314-23-4. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO00a-e, NLM00a-d). The final literature search was carried out in April 1999.

In September 2001, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland). These comments were taken into account in deciding on the final version of the document.

2 Identity

Data on zirconium and some selected zirconium compounds are presented below.

name	: zirconium	zirconium oxide	zirconium silicate	zirconium tetrachloride	zirconium dichloride	zirconium sulphate	zirconium oxychloride	
synonyms	:	zirconia; baddeleyite	zircon	zirconium(IV) chloride (1;4); tetrachloro-zirconium; zirconium chloride; zirconium chloride, tetra-		zirconium sulphate; disulfatozirconic acid; sulphuric acid, zirconium (VI) salt (2:1); zirconium disulphate; zirconium (IV)sulfate (1:2); zirconium orthosulphate; zirconyl sulphate	basic zirconium chloride; chlorozirconyl; dichlorooxo-zirconium; zirconium oxide chloride; zirconium, dichlorooxo-; zirconium oxydichloride; zirconyl chloride	
molecular formula	:	Zr	ZrO ₂	ZrSiO ₄	ZrCl ₄	ZrCl ₂	Zr(SO ₄) ₂ ·4H ₂ O	ZrOCl ₂
CAS number	:	7440-67-7	1314-23-4	10101-52-7	10026-11-6	13762-26-0	14644-61-2	7699-43-6

Data from ACG99a, Lid94, NIO00a-e, NLM00a-d, Ric94.

3 Physical and chemical properties

Physical and chemical properties of some selected zirconium compounds are listed below.

name	: zirconium	zirconium oxide	zirconium silicate	zirconium tetrachloride	zirconium dichloride	zirconium sulphate	zirconium oxychloride
molecular weight	: 91.22	123.22	183.3	233.03	162.13	355.4	178.13
boiling point	: 4377°C	-	-	-	-	-	210°C
melting point ^a	: 1853°C	2715°C	2550°C	350°C: d	437°C ²⁵	135-150°C (-3H ₂ O)	150°C
flash point	: -	-	-	-	-	-	-
vapour pressure	: -	-	-	-	-	-	-
solubility in water ^b	: i	i	i	cold: s hot: d ^c	d ^e	vs	vs
Log P _{octanol/water}	: -	-	-	-	-	-	-

^a Number in superscript represents the atmospheric pressure in atm at which the presented value is determined; d: decomposes.

^b d: decomposes; i: insoluble; s: soluble; vs: very soluble.

^c Decomposes into hydrochlorid acid and zirconium oxychlorid.

^d Decomposes evolving H₂.

Data from ACG99, Lid94, NIO00a-e, NLM00a-d, Ric94.

Elemental zirconium is a bluish-black, amorphous metallic powder or a greyish-white lustrous metal. Zirconium is corrosion resistant and is not attacked by cold concentrated acid. However, it reacts slightly with hot concentrated acids. Zirconium powder is flammable and explosive in air when mixed with oxidising agents (ACG99).

4 Uses

Zirconium metal is used in nuclear technology, in photoflash bulbs, as a scavenger in steel manufacture, and in vacuum tubes to remove traces of gases. Zirconium oxide is employed as a colourant for ceramics and for dispersion-hardening of platinum and ruthenium, and it has been used clinically as a radio-opaque compound for X-rays of the gut. The tetrachloride is used as a textile water repellent and as a tanning agent. Zircon, a natural zirconium silicate, is employed in making refractories, enamels, porcelain, and abrasives, and as a coating for casting moulds. Water-soluble salts (e.g., zirconium lactate) and zirconium oxide have been used in cosmetics, deodorants, and topical ointments (ACG99).

5 Biotransformation and kinetics

The daily oral intake (food and water) of total zirconium by man has been estimated to be ca. 4 mg (Sch66). Most of it is excreted in the faeces (4 mg) and hardly any in the urine (0.15 mg) (Gre99). Levels in tissues are generally below 10 µg/g (wet weight). Highest amounts were found in fat (19 µg/g) and gall bladder (14 µg/g). Levels in erythrocytes amounted to ca. 6 µg/g (data from 4 deceased; Sch66). Binding to albumin and globulins has been demonstrated (Gre99).

In coal miners, the presence of zirconium has been demonstrated in the lungs, pulmonary lymph nodes, blood, and urine (Bel94). Biological half-lives of zirconium in human lung of ca. 70 and 225 days have been reported (Gre99). In several animal species, zirconium was demonstrated to be deposited and retained primarily in the lungs and pulmonary lymph nodes following exposure by inhalation to its oxide and oxychloride. Concentrations in these tissues were of similar order of magnitude but varied largely among species. Concentrations in kidney, liver, and femur were only a few tenths of a per cent of those in the lung. Twenty-four weeks post-exposure, there were still significant amounts in

the lungs and lymph nodes of rats (other species not examined). Generally, in this experiment, no difference was found regarding amounts deposited and pattern of distribution between the insoluble oxide and the soluble oxychloride (Spi56).

In one rat study, the maximal uptake of various zirconium compounds from the gastrointestinal tract into the bloodstream was reported to be 0.2 % of the elemental zirconium dose while in another study, only 0.001% of the zirconium dose ($ZrCl_4$) was taken up from the gastrointestinal tract into the blood (no more data presented) (Gre99). In a chronic study, tissue levels of exposed rats receiving ca. 500 $\mu\text{g}/\text{kg}$ bw/day were similar to those of controls receiving ca. 160 $\mu\text{g}/\text{kg}$ bw/day. Highest levels were found in the spleen (Sch68a).

6 Effects and mechanism of action

Human data

Cases of lung fibrosis and granulomatous interstitial pneumonia in workers exposed to zirconium compounds have been described. Significant amounts of zirconium-containing particles were present in the lungs (Bar91, Lii93, Kot92, Rom94; see also Gre99).

In 178 men working at a plant in Manchester (UK) with zirconium compounds, principally zirconium silicate, effects on the lungs were evaluated by chest radiographs (in 1975, 1978, and 1982) and lung function (FEV_1 , FVC) measurements (from 1975-1988). Of these 178 men, 144 entered the study at the start in 1975, having a mean age at that time of 37.6 years (range: 17-61 years) and a mean employment time of 10.0 years (range: 0-38; 58% less than 10 years); of the total group of 178 men, 37 had been exposed for more than 20 years. Static air sampling performed in 1974 and in 1991-1992 showed total dust levels ranging from 0.5-8.8 and 0.4-9.8 mg/m^3 , respectively. Total dust levels (8-hour time-weighted average) obtained from personal air sampling for 7 different operators in 1974 ranged from 2.5 to 30.0 mg/m^3 , while the highest respirable dust level measured amounted to 3.4 mg/m^3 . Particle size, distribution, and composition were not reported. Each man was interviewed to obtain a general medical and work history and a summary of current symptoms and smoking habits. In addition, specific attention was paid with respect to dust exposure (such as in coal mining, foundry work, cotton milling) in previous jobs. Based on job titles, work locations, and the number of years spend in a job, a cumulative dust exposure score was calculated for each man. No

granulomas were seen. In 12/175 men, there were calcified nodules read in their films but there was no correlation found between the presence of these nodules and exposure duration, cumulative dust exposure, or age. Overall, the study did not reveal any evidence of a relation between (cumulative) zirconium exposure and abnormal chest radiographs or impaired pulmonary function (Mar96).

A group of 32 hand finishers of nuclear fuel components were exposed to zirconium metal and silicon carbide, binding agent, and general dusts for 1 to 17 years. Breathing zone sampling resulted in dust levels of 5.75 to 14.7 mg/m³ consisting of 25% zirconium. Analysis of the high volume sample showed that 85% of the particles had a diameter less than 10 µm. Of samples between 0.67 and 3.2 mg/m³ of zirconium, 95% had a diameter less than 10 µm. When compared to a control group selected from the same plant (considered not to be exposed to dusts or respiratory irritating substances, and matched for age and for current and total smoking history), no significant differences were found concerning respiratory questionnaire and chest x-ray findings. The values of the various expiratory lung function tests were consistently, but not statistically significantly lower for the exposed group when compared to those for the controls (Had81).

Twenty-two workers involved in the production of zirconium for 1 to 5 years were examined clinically (history, physical examination, vital capacity determination) and chest radiographically. The workers were stated to be exposed to fumes but concentrations and composition were not reported. Further, they were exposed to dusts of zirconium tetrachloride (which hydrolyses to zirconium oxychloride), zirconium oxide, and to metallic zirconium as well as to 'low and non-toxic' concentrations of hydrochloric acid, chlorine, phosgene, and magnesium, aluminium, titanium, and hafnium oxides and chlorides. However, exposure characteristics (levels, particle size and distribution, etc.) were not mentioned. Fifteen out of the 22 workers did not have symptoms of lung disease. Of the remaining 7, 2 had mild bronchial asthma and 5 had chronic bronchitis which required medical treatment. The vital capacity was affected in 2 men, both among those having chronic bronchitis. Chest radiography did not reveal striking abnormalities such as pulmonary granulomatosis. Slightly increased peripheral lung markings were seen in 4 workers; 3 of them were among the cases with chronic bronchitis. The authors concluded that this study did not show effects attributable to exposure to zirconium. The effects found were thought to be chlorine related (Ree56).

Pneumoconiosis (small — Categories 1 to 3 — densities on chest X-rays) was reported in 8 workers of a zirconium process plant adjacent to an antimony

smelting plant in the UK (McC67). This aforementioned group of zircon workers was included in a study carried out to examine the mortality among a group of workers exposed to antimony in this UK smelter (study period: 1960-1992). Other study groups included maintenance workers and a group consisting of office workers and management staff. The total cohort consisted of 1420 men; figures for the subgroups were not given. Data on exposure levels were not presented. As to the zircon workers, there were no statistically significant findings. Mortality from all causes, from all neoplasms, from lung cancer, and from respiratory disease were all lower than expected based on local rates (56 vs. 68.6, 14 vs. 20.1, 5 vs. 8.8, and 6 vs. 8.2, respectively) while mortality from ischaemic heart disease and from other circulatory diseases was similar to that expected (Jon94).

Both clinical and experimental reports of allergic reactions appearing as epithelioid granulomas at the site of applying deodorants containing both water soluble and insoluble zirconium compounds have been published (Mon97, Ske93; see also Gre99). ACGIH referred to a study in which no granulomas were found in 54 volunteers topically treated with zirconium oxychloride (ACG99).

Animal data

Irritation and sensitisation

The committee did not find experimental animal data on possible skin- and eye-irritating properties of zirconium or its compounds.

Sodium zirconium lactate was positive in 3 methods of immunisation (Split adjuvant, Maximisation, and Polak). In these tests, 6 guinea pigs (outbred Hartley strain) per test were used. Reactions at 24 and 48 hours were typically erythematous. These delayed hypersensitivity-like reactions developed into nodular lesions which reached peak intensity at 8 days and histologically contained histiocytes with an epithelioid cell appearance and giant cells (Tur77).

In a study designed to address the potential sensitising and granulomagenic capacities of selected metallic salts, white New Zealand rabbits of both sexes (bw: 2 to 3 kg) were inoculated intradermally with zirconium aluminium glycinate (ZAG) or sodium zirconium lactate (NZL) by single and multiple injections. One group of animals was exposed to 10.0 mg ZAG or NZL in complete Freund's adjuvant (0.4 mL/animal) via the toe pad route while animals

of another group were injected intradermally with 100 µg of each compound in saline solution, twice weekly for 6 weeks (0.1 mL/rabbit). The initial injections for weeks 1 and 4 consisted of 200 µg of each compound in saline solution administered via the toe pad route (0.4 mL/rabbit). The total cumulative dose in each subgroup was 1.4 mg of either ZAG or NZL. A third untreated group served as controls for skin testing, lymphocyte stimulation, assays, and histological observations. Neither single nor multiple injections of ZAG resulted in clear-cut positive skin reaction, macrophage migration inhibitory factor (MIF) production, or lymphocyte stimulation. Rabbits inoculated with multiple injections of NZL showed some marginally positive macrophage migration inhibition and skin reactivity. Histologically, ZAG induced well-organised foreign-body granulomas after intradermal injection in both normal and inoculated rabbits. NZL also induced skin granulomas, but these were less organised (Kan77).

Inbred 4-month old female CBA/J strain agouti mice were injected (0.02-0.05 mL) intradermally in the foot pads and the pinnae, or intraperitoneally with zirconium lactate (an insoluble salt in 10% suspension in physiological saline solution) and sodium zirconium lactate (as water soluble complex). Control injections were made using a mixture of sodium stearate (0.2 M) and lactic acid. Biopsy specimens of the foot pads and ears as well as autopsy material from the liver, kidney, spleen were taken. The intradermal and intraperitoneal injections produced local foreign body granulomas which regularly persisted for over 8 months. None of the animals exhibited evidence of the late delayed immune type of epithelioid cell granulomatous hypersensitivity. Benign chondromas developed locally in the ear cartilage in 87/182 of the mice receiving zirconium oxychloride and 12/24 mice receiving sodium zirconium lactate (She71).

Contact sensitisation capacity of zirconium tetrachloride was evaluated in the guinea pig maximisation test (GPMT) as well as in the adjuvant and patch test (APT) using 5 adult female Hartley strain guinea-pigs per test, and in a sensitive mouse lymph node assay (SLNA) using 5 female BALB/c strain mice (6-8-week old). In none of these tests, zirconium tetrachloride caused any sensitisation responses (Ika96).

Acute toxicity

The acute oral toxicity of inorganic zirconium salts was concluded to be very low due to their poor gastrointestinal absorption: LD₅₀ values ranged between

700 and 3500 mg/kg bw. Oral LD₅₀ values in rats were 1690 mg/kg bw for zirconium tetrachloride and >10,000 mg/kg bw for basic zirconium carbonate (ACG99).

Subacute and subchronic toxicity

Dogs (n=2), rabbits (n=6), and rats (n=20) were exposed to zirconium oxide dust (average particle size: 1.5 µm) at concentrations of 75 mg Zr/m³, for 60 days, and cats (n=4/group), dogs (n=8/group), guinea pigs (n=20/group), rabbits (n=19 or 20), and rats (n=72/group) to zirconium oxide dust at 11 mg Zr/m³, for 30 days, or to a mist of zirconium tetrachloride dissolved in water (average particle size: 0.6 µm) at an average concentration of 6 mg Zr/m³, for 60 days. All groups were exposed 6 hours/day, 5 days/week. Zirconium oxide produced no significant changes in the end points examined, viz., mortality, growth rate, blood non-protein nitrogen or fibrinogen, urinary protein, haematological values, or histological parameters. Exposure to zirconium tetrachloride — which was converted into zirconium oxychloride upon being dissolved — increased mortality rates in rats (8/72) and guinea pigs (3/20), but not in rabbits, cats, or dogs. The cause of death, although not well established, was stated to be an intercurrent respiratory infection. Post-mortem examination showed varying congestion, oedema, and haemorrhage in the lungs of one-half of the exposed animals, but similar changes were seen in the control animals. Apart from borderline reductions in haemoglobin content and erythrocyte count in dogs, no other changes were found. Overall, only effects were noted following inhalation of zirconium tetrachloride at 6 mg/m³, which presumably were due to the liberation of hydrogen chloride. The study did not include cat, dog, or guinea pig control groups (Spi56).

Chronic toxicity and carcinogenicity

Rats, hamsters, and guinea pigs (n=10/group; strain and sex not reported) were exposed to 15 or 150 mg/m³ of zirconium lactate (according to Gre99 ca. 5 and 36 mg Zr/m³) (particle size: 82% <0.3 µm) or to 15 mg/m³ barium zirconate (ca. 5 mg Zr/m³; see Gre99) (particle size: 91% <1.2 µm, 79% <0.6 µm, 50% <0.3 µm), 7 hours/day, 5 days/week, for 225 days. Apart from the death of 3 guinea pigs exposed to 15 mg/m³ of the lactate, no mortality occurred. Body weights of the rats and hamsters were lower when compared to controls; those of guinea pigs exposed to 150 mg/m³ were higher while the body weights of the animals

of the other groups were similar when compared to controls. No statistical evaluation was presented. At necropsy, a chronic interstitial pneumonitis with associated hypertrophy of the media of the arterioles was found in all exposed groups. These changes were stated to be more pronounced in the animals exposed to the zirconate. Only very little histological changes were seen in the lungs of the control animals. They consisted of minimal thickening of the alveolar walls and a minimal amount of round cell infiltration. There was no evidence of changes in the bronchial or vascular tissues. Data presented on lung, liver, and kidney weights were not very informative since only absolute weights were given and no statistical evaluation was made. No abnormalities were seen in liver, spleen, and kidneys (Bro63).

Schroeder et al. administered 5 ppm zirconium sulphate to the drinking water of Long-Evans rats (56 males and 58 females) from the time of weaning until natural death. Treatment did not affect survival and longevity. The body weights of the exposed females were generally higher than those of controls throughout the study, reaching statistical significance at 30, 150, and 540 days (the last measurement point listed). Exposed males were heavier in the first 180 days of the study while statistically lower body weights were observed in the following part at 360 and 540 days. Upon post-mortem examinations, there were no differences between exposed and control animals concerning the incidences of grossly visible tumours. Mean absolute and relative heart weights were higher and lower in females and males, respectively, when compared to controls. No other data on organ weights or macroscopic or microscopic lesions were presented. An increased incidence of glycosuria was found in the male animals (52% vs. 23% in controls). The authors estimated the mean daily zirconium intake to be 510 µg/kg bw for the exposed animals. Since the food contained some zirconium, the control animals received 160 µg/kg bw/day (Sch70). In a separate paper, Schroeder et al. reported on the possible effects of the aforementioned exposure level of zirconium on serum cholesterol levels of these rats. In mature rats (age: 893 days; n=12/sex), the serum cholesterol levels were decreased in males (89.7±5.6 vs. 122.9±8.17 mg/100 mL in controls; p<0.01) and increased in females (100.7±9.0 vs. 94.5±11.19 mg/100 mL) (Sch68a).

The group of Schroeder reported the results for mice (Charles River CD-1; 54 males, 53 females) receiving a similar treatment — 5 ppm zirconium sulphate in the drinking water from weaning until death — as described above for rats in 2 separate papers. Treatment caused shortening of life span (mean,

median, and 75% life span) when compared to controls. Body weights were generally comparable to those of controls; at 540 days of age, the last observation presented, body weights were significantly lower for both treated males and females. There was no difference in tumour incidence between treated and control groups. Apart from a somewhat higher incidence of hepatic fatty degeneration in the zirconium-treated animals (36.7% vs. 22.2% in controls), no other data on organ weights and non-neoplastic macroscopic and microscopic lesions were presented. The authors estimated the mean daily zirconium intake to be 510 µg/kg bw for the exposed animals. Since the food contained some zirconium, the control animals received 160 µg/kg bw/day (Kan69, Sch68b).

When a single dose of ca. 20 µg of zirconium oxychloride (octahydrate) (vehiculum: aqueous 0.9% sodium chloride solution) was injected into the dorsa of the ear lobes of female ICR and CBA/J mice (n=10/strain), all treated mice showed ecchondromas (outgrowths from the cartilaginous plate) at post-mortem examinations after 2 and 5 months, respectively. These chondromas were not seen in a separate group of 10 female CBA/J mice sacrificed 2 weeks after the treatment (She73).

Mutagenicity and genotoxicity

Zirconium tetrachloride was reported to be negative when tested in *S. typhimurium* strains TA98, TA100, TA102, TA1537, and TA2637. Experimental details such as concentrations, metabolic activation, etc., were not given. Zirconium tetrachloride was co-mutagenic — in strains TA1537 and TA2637 only — when tested at concentrations of 1-10,000 µmol/plate in the presence of the mutagen 9-aminoacridine (100 µmol/plate). At the optimal concentration of 10 µmol/plate, zirconium tetrachloride produced 1.6 times more revertants than aminoacridine alone (Oga87). Zirconium oxychloride was negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 both in the presence and absence of a metabolic activating system derived from rat and hamster liver (Mor86). Zirconocene dichloride ((C₅H₅)₂ZrCl₂) (dose range: 100-10,000 µg/plate) was found positive when tested without metabolic activation in *S. typhimurium* strains TA98 and TA100 and weakly positive in strain TA97 with a hamster liver S9 mix added (with rat liver S9: negative). Negative results were obtained at testing in strains TA98 and TA100 with rat or hamster liver S9 mix added, in strain TA97 without metabolic activation, and in

strain TA1535 with and without metabolic activation (both rat and hamster) (Zei88).

Zirconium oxychloride (10-20 µg/mL culture medium) induced an increase in frequency of cell division (mitotic index), chromosomal aberrations, and SCE's *in vitro* in cultured human peripheral blood leukocytes (Gho91a).

In vivo, zirconium oxychloride caused an increase in the percentage of mitotic cells in the bone marrow of mice (albino Swiss; n=5/group) of the mid- and high-dose groups sacrificed 24 hours after giving single oral doses of 220, 734, and 2200 (females) or 225, 750, and 2250 mg/kg bw (males). Treatment induced a dose-related increase in the percentage of total aberrant metaphases including both chromosomal aberrations (mainly chromatid and chromosome breaks) and spindle disturbances (polyploidy) (Gho90). In a follow-up experiment using similar doses, statistically significant increases in the frequency of chromosomal aberrations and breaks per cell, excluding gaps, were found in male mice sacrificed 12 and 24 hours and in female mice sacrificed 6, 12, and 24 hours after exposure. The increases were dose and, to a lesser extent, duration related (Gho91b).

Reproduction toxicity

The committee did not find data on the potential reproduction toxicity of zirconium or its compounds.

Immunotoxicity

The effects of zirconium on the humoral immune response were studied by measuring the level of IgM-plaque forming cells (IgM-PFC) against sheep red blood cells (SRBC) in the spleen of C57 BL mice intraperitoneally injected with zirconium oxychloride. One group (n=25/dose) was treated with a single injection (total n=125) of zirconium oxychloride of 1.7, 3.4, 17, or 34 mg/kg bw (i.e., 1/100, 1/50, 1/10, and 1/5 of the LD₅₀), while another group (n=10/treatment) received doses of 2.125, 4.25, or 8.5 mg/kg bw (i.e., 1/80, 1/40, 1/20 of the LD₅₀), every other day for 2 or 4 weeks. In case of a single injection, zirconium oxychloride was administered either on days -1, 0, +1, +2, or +3 in relation to SRBC immunisation. The control group was injected with saline. Both single and repeated treatment enhanced the IgM response to sheep red blood cells (Shi87).

Similar immunostimulating effects were reported in an abstract for zirconium oxychloride, zirconium oxide, and zirconium silicate after single or repeated (every other day for 2, 4, or 6 months) injections into the thorax cavity or the peritoneum of mice, respectively (Ric94). In addition, in an *in vitro* study, zirconium sulphate was found to exhibit a mitogenic effect in mouse splenocytes (an increased ³H-thymidine incorporation into lymphocyte DNA) (Pri86).

7 Existing guidelines

The current administrative exposure limit (MAC) for zirconium and zirconium compounds in the Netherlands is 5 mg/m³, 8-hour TWA.

Existing occupational exposure limits for zirconium in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Zirconium was found in lungs, pulmonary lymph nodes, and blood and urine of miners, indicating that it can be absorbed from the lungs. Biological half-lives in human lung of ca. 70 as well as 225 days were reported. Daily human intake via food, water, etc., is about 4 mg. The predominant excretion route is via the faeces; hardly any is excreted in the urine. Tissue levels are generally below 10 µg/g wet tissue. Highest amounts were found in fat (19 µg/g) and gall bladder (14 µg/g). Animal experiments showed a similar picture. Following oral absorption, absorption percentages of 0.2 and 0.001% were reported.

Clinical and experimental reports indicated that zirconium compounds can induce allergic reactions appearing as epithelioid granulomas at the site of exposure. A study on a group of workers exclusively exposed to zircon (zirconium silicate) — as part of a more extensive investigation among workers of an antimony smelter — did not show evidence of an increased mortality from all causes, all cancer, or respiratory or circulatory diseases. No evidence of a relation between (cumulative) zirconium dust exposure and abnormal chest radiographs or impaired pulmonary function was found in a group of 178 men with mean employment time of 10.0 years. Results from static air sampling performed in 1974 and in 1991-1992 suggest that exposure was similar throughout these years with total dust levels ranging from ca. 0.5-10 mg/m³. Personal air sampling performed for 7 workers in 1974 showed total dust levels (8-hour TWA) ranging from 2.5 to 30.0 mg/m³ with highest respirable dust

levels amounting to 3.4 mg/m³. However, particle size, distribution, and composition of the dust were not given. In another study on 32 workers exposed to zirconium metal for 1 to 17 years, no significant differences were found in respiratory questionnaires and chest X-ray findings when compared to controls matched for age and smoking habits. The values of the various expiratory lung function tests were consistently, but not statistically significantly lower for the exposed group when compared to the controls. Breathing zone air sampling resulted in dust levels of ca. 6 to 15 mg/m³ consisting of 25% zirconium. Although the results suggest that some marginal effects may have been induced at these dust levels, workers were exposed to silicon carbide as well. Therefore, the committee feels that no firm conclusions can be drawn from this study with respect to a dose-response relationship for zirconium.

The committee did not find experimental animal data on possible skin- and eye-irritating properties of zirconium or its compounds. Sodium zirconium lactate and zirconium aluminium glycinate demonstrated skin sensitising properties while zirconium tetrachloride did not cause any sensitisation response.

The committee did not find data on the effects of zirconium or its compound following single inhalation exposures. Following single oral administration, LD₅₀ values ranging from 700 to 3500 mg/kg bw were found for inorganic zirconium salts.

Repeated inhalation studies using several animal species reported not to induce changes in mortality or growth rates, haematology or histological parameters following exposure to zirconium oxide dust at concentrations of 75 mg Zr/m³ for 60 days or to 11 mg Zr/m³ for 30 days. Exposure to zirconium tetrachloride (which was converted into zirconium oxychloride upon being dissolved) at an average concentration of 6 mg Zr/m³ caused some histological changes in the lungs — comparable to those found in controls — in 50% of the exposed animals. However, since this study could not be retrieved by the committee, the significance of this study as a (possible) basis for standard setting could not be assessed. In another study in which rats, hamsters, and guinea pigs were exposed to 15 or 150 mg/m³ of zirconium lactate (i.e., ca. 5 and 36 mg Zr/m³) or 15 mg/m³ barium zirconate (i.e., ca. 5 mg Zr/m³) body weight decreases were found in rats and hamsters and chronic interstitial pneumonitis in all exposed groups. However, because of limited design and reporting, the committee considers this study not suitable to serve as a basis in standard setting.

Zirconium tetrachloride appeared to be positive in mutagenicity assays (co-mutagenic in the presence of 9-aminoacridine) using *S. typhimurium* strains TA1537 and TA2637 and zirconocene dichloride is positive in TA98 en TA100 strains of *S. typhimurium* without metabolic activation. Zirconium oxychloride induced chromosomal aberrations in human leukocytes *in vitro* and chromosomal aberrations and polyploidy in bone marrow of orally exposed male mice *in vivo*. The committee considers these positive findings of concern requiring confirmation and further investigation.

The committee did not find data on the reproduction toxicology of zirconium.

The committee considers the toxicological database on zirconium and its compounds too poor to justify recommendation of a health-based occupational limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

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Annex

Occupational exposure limits for zirconium and its compounds in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note ^a	reference ^b
	ppm	mg/m ³				
the Netherlands -Ministry of Social Affairs and Employment	-	5	8 h	administrative		SZW02
Germany -AGS	-	5 ^c	8 h			TRG00
	-	20 ^{c,d}	15 min			
-DFG MAK-Kommission	-	1 ^e	8 h		sens ^{g, h}	DFG02
	-	1 ^e	15 min ^f			
Great-Britain -HSE	-	5	8 h	OES		HSE02
	-	10	5 min			
Sweden	-	-				Arb00b
Denmark	-	5	8 h			Arb00a
USA -ACGIH	-	5	8 h	TLV	A4 ⁱ	ACG02b
	-	10	15 min	STEL		
-OSHA	-	5	8 h	PEL		ACG02a
-NIOSH	-	5 ^j	10 h	REL		ACG02a
		10 ^j	15 min	STEL		
European Union -SCOEL	-	-				CEC00

^a S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

^b Reference to the most recent official publication of occupational exposure limits.

^c Inhalable dust fraction.

^d Holds for zirconium compounds.

^e Inhalable dust fraction; holds for zirconium and its insoluble compounds. The soluble compounds were listed among compounds for which studies of the effects in man and in experimental animals have yielded insufficient information for the establishment of MAK-values.

^f Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

^g For both skin and respiratory tract; holds for the metal, the soluble, and the insoluble compounds

^h Listed among compounds for which the possible risk of damage to the embryo/fetus was investigated but for which classification was not possible.

ⁱ Classified in carcinogenicity category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of a lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.

^j Not for zirconium tetrachloride.