Zirconium dioxide (respirable fraction)

MAK Value Documentation, supplement – Translation of the German version from 2019

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated zirconium dioxide [1314-23-4]. Zirconium dioxide is a biopersistent granular dust. Therefore, the respirable fraction of zirconium dioxide dust is classified in Carcinogen Category 4 and a maximum concentration at the workplace (MAK value) of 0.3 mg/m³ × material density is established for the respirable fraction in analogy to the other biopersistent granular dusts. Additionally, this fraction is classified in Peak Limitation Category II with an excursion factor of 8. As zirconium dioxide is not systemically distributed and accumulates only locally in the lungs, no developmental toxicity is expected to occur at the MAK value of 0.3 mg/m³ × material density (respirable fraction). Accordingly, zirconium dioxide is classified in Pregnancy Risk Group C. Zirconium dioxide is not a sensitizer and is not taken up via the skin in toxicologically relevant amounts.
MAK value (2018)  
0.3 mg/m$^3 \times \text{material density } R^{a)}$

Peak limitation (2018)  
Category II, excursion factor 8

Absorption through the skin  
–

Sensitization  
–

Carcinogenicity (2018)  
Category 4

Prenatal toxicity (2018)  
Pregnancy Risk Group C

Germ cell mutagenicity  
–

Synonyms  
baddeleyite  
zirconia  
zirconic anhydride  
zirconium(IV) oxide

Chemical name  
zirconium dioxide

CAS number  
1314-23-4  
12036-23-6 (baddeleyite)

EINECS No.  
215-227-2  
234-843-2 (baddeleyite)

ZVG No.  
4000

Molecular formula  
ZrO$_2$

Molar mass  
123.22 g/mol

Mohs’ hardness  
6.5 (baddeleyite)  
8–8.5 (zirconia)

Melting point  
about 2680°C (IFA 2018)

Boiling point  
about 5000°C (IFA 2018)

log $K_{OW}$  
–

Solubility  
< 1 mg/l water (20°C) (IFA 2018)  
< 55 µg/l water (ECHA 2018)

Density  
modification:  
monoclinic 5.7 g/cm$^3$  
tetragonal 6 g/cm$^3$  
cubic 6.3 g/cm$^3$

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$^{a)}$ The effect of zirconium dioxide is based on the effect of biopersistent granular dusts. The value of 0.3 mg/m$^3$ for the R (respirable) fraction applies to a material density of 1 g/cm$^3$.

Note: except for ultrafine particles; see List of MAK and BAT Values, Section Vh (DFG 2020)

**General Characteristics**

Zirconium dioxide (ZrO$_2$) is poorly soluble and occurs naturally as zirconia and baddeleyite. Besides ZrSiO$_4$ (zircon), it is one of the most frequently occurring zirconium minerals. Zirconium dioxide is of technical importance as a structural ceramic and ion conductor, for example in lambda probes and fuel cells, and as a refractory material. Fur-
thermore, zirconium dioxide ceramic is used as a dental replacement material. Other uses are in products for (metal) surface treatment, polishes and waxes, coating products and metal-working fluids (ECHA 2018).

**Chemical and physical properties**

Zirconium dioxide has a very high chemical and physical resistance to acids and bases. ZrO\(_2\) crystallizes in three different modifications. The monoclinic modification, stable at room temperature, changes into a tetragonal modification at 1050 °C and into a cubic modification at 2400 °C and above. For technical applications the tetragonal and cubic modification can be stabilized at room temperature by doping with CaO or Y\(_2\)O\(_3\).

1 **Toxic Effects and Mode of Action**

Zirconium dioxide particles are chemically inert. They are poorly soluble dusts, which have general particle effects corresponding to those of the biopersistent granular dusts. Like other inhaled poorly soluble dusts, the particles can accumulate in the lungs and lymph nodes and cause impairment of the clearance function of the lungs (Hartwig 2014).

No genotoxic effects of zirconium dioxide are known.

Since zirconium dioxide particles belong to the poorly soluble granular dusts, particle-related tumour formation is to be expected if lung clearance is overloaded.

There is no evidence that zirconium dioxide has skin-sensitizing effects on intact skin. However, if the intact skin barrier is evaded, both zirconium dioxide and other poorly soluble zirconium compounds may lead to granulomatous reactions, which are presumably of immunological genesis. Granulomatous changes in the lungs as a result of exposure to zirconium dioxide have not been reported.

2 **Mechanism of Action**

See supplement "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)” (Hartwig 2014).

3 **Toxicokinetics and Metabolism**

There is no information available.

Due to its poor solubility, significant dermal absorption of zirconium dioxide is not expected.

Zirconium dioxide chloride (from which zirconium dioxide is formed in aqueous solution at physiological pH) is absorbed by rats and mice to the extent of 0.01% to 0.05% after oral administration. This absorption rate can be assumed the worst case scenario for zirconium dioxide (ECHA 2018).

4 **Effects in Humans**

4.1 **Single exposures**

There are no data available.
4.2 Repeated exposure

In a study, 32 workers were exposed to dust in concentrations of 5.75 to 14.7 mg/m$^3$ containing 25% zirconium (Hadjimichael and Brubaker 1981). No significant effects were observed in lung x-rays, lung function tests or on respiratory symptoms. There is no quantitative information on the zirconium dioxide content of the dust, so the study is of limited value.

A case of pulmonary fibrosis following exposure to zirconium dioxide was reported, but there was also exposure to other substances such as talc, asbestos, alumina and silica. The worker mixed a powder containing 90% zirconium dioxide and 10% silica without using a respirator. Over the course of 25 years, the employee developed increasing dyspnoea. Lung function tests revealed a restrictive pattern and a lung capacity of 56% of the expected value. No granulomas were found in lung biopsy samples. Tests for zirconium-specific lymphocyte proliferation with peripheral lymphocytes and lymphocytes from the bronchoalveolar lavage fluid (BALF) yielded negative results (Bartter et al. 1991).

In 178 men who handled substances containing zirconium (especially zirconium silicate) for several years (no other details), no conspicuous x-ray findings or changes in lung function were found. Determinations made about 15 years after the installation of a ventilation system yielded static dust concentrations of between 0.4 and 9.8 mg/m$^3$. Analyses carried out two years before the installation of the ventilation system yielded similar values of 0.5 to 8.8 mg/m$^3$. Personal air sampling carried out at that time yielded hourly average values for total dust concentrations of between 2.5 mg/m$^3$ in the area of the zirconium silicate smelting furnaces and 30 mg/m$^3$ in the area of the zirconium oxide furnaces. The highest concentration of inhalable dust of 3.4 mg/m$^3$ was found in the filling area. More detailed information on the composition of the dusts is not available (Marcus et al. 1996).

No pulmonary granulomas were observed in 22 workers exposed to zirconium oxide, zirconium chloride and zirconium metal for one to five years (no information on the exposure level). Two workers had mild bronchial asthma, five others had chronic bronchitis. Some of them were, however, also exposed to chlorine (Reed 1956).

4.3 Local effects on skin and mucous membranes

There are no data available.

4.4 Allergenic effects

4.4.1 Sensitizing effects on the skin

Allergic contact dermatitis following exposure to zirconium dioxide has not been described and there have been no reports of positive patch tests, although 0.1% preparations of zirconium dioxide in petrolatum are available as commercial test substances.

In a study of 50 ceramics workers who performed manual glazing activities and 190 employees from five companies in the ceramics industry (126 enamellers and 64 decorators), none reacted to undiluted “zirconium oxide” three days after patch tests had been carried out (Gaddoni et al. 1993; Motolese et al. 1993). There is no information as to whether delayed papular or granulomatous reactions occurred later in the test area.

Zirconium dioxide was temporarily used in the 1960s to treat dermatitis caused by Toxicodendron radicans (“poison ivy”) and other Toxicodendron or Rhus species, which was widespread in the USA. There were subsequent reports of granulomatous skin reactions at the application site, and therefore always on inflammatory and pre-damaged skin, which developed in the course of several weeks to months and persisted for a long time (Baler 1965; Cronin 1980, p. 376; Epstein and Allen 1964; LoPresti and Hambrick 1965; Williams and Skipworth 1959). Patch tests on intact skin with preparations of 2% or 4% zirconium dioxide in a lotion or of 4% zirconium dioxide in an ointment yielded consistently negative results. Reactions occurred in tests only after the removal of the upper horny layer or in the case of an impaired skin barrier. Approximately 2 to 4 weeks after such a patch test, mostly reddish-brown papules formed in the test areas, which were histologically characterized as epithelioid granulomas. Two publications also reported
granulomatous reactions after testing with a 1% dilution of the 4% lotion. In other cases, instead of such patch tests with the presumably causative zirconium dioxide, intradermal tests with highly diluted preparations (1:100 to 1:10,000) of other poorly soluble zirconium compounds, especially zirconium lactate, were performed to confirm the diagnosis.

### 4.4.2 Sensitizing effects on the airways

No granulomatous reactions in the lungs resulting from exposure to zirconium dioxide have been reported. The isolated findings of granulomatous reactions in the lungs after exposure to other zirconium compounds do not allow a definitive assessment of whether this is an immunological phenomenon in the sense of a cell-mediated allergic reaction of the delayed type, as in the case of beryllium granulomas.

In a recent publication, investigations in 10 nanotechnology employees with comparable activities and exposures were described. On average, they worked for 11 years (3.5 to 18 years) in the production, surface modification and further processing of oxide nanomaterials (<10 to 100 nm). They were exposed primarily to zirconium oxide, (amorphous and crystalline) silicon dioxide, aluminium oxide and numerous other metal oxides and compounds. Exposure determinations yielded particle concentrations of 6 to 10,000 particles/cm³ (maximum 16,400) for refilling activities with zirconium dioxide powder. For spray painting activities, ventilated respiratory protection hoods were used. Exposure in previous years was assumed, as the processes and protective measures had not yet been optimized. Anamnesis revealed mucosa-associated complaints (impeded nasal breathing or recurrent sinusitis) in 5 of the 10 persons. Activity-associated symptoms were reported by 4 persons, including 2 persons who reported a sore throat and sensations in the eyes, of the skin and in the lungs when handling barium hydroxide or zirconium dioxide materials. In 4 people, anterior rhinoscopy revealed redness of the nasal mucosa. A lymphocyte transformation test (LTT) for zirconium (no other details) yielded a “positive result” (stimulation index (SI) between 2.2 (2×) and 10.2 (1×), no other details) in 5 persons. The person with the highest LTT result also had an SI of 2.4 in the LTT for “molybdenum” and a reaction to 1% “zirconium chloride” in water (no other details) in the prick test (Mittmann-Frank et al. 2010). Due to the unclear validity of the LTT investigations and the questionable suitability of zirconium chloride for prick testing, respiratory sensitization caused by zirconium dioxide cannot be deduced from these findings.

There are no other findings available for sensitization of the respiratory tract (see also Section 4.2).

### 4.5 Reproductive and developmental toxicity

There are no data available.

### 4.6 Genotoxicity

There are no data available.

### 4.7 Carcinogenicity

There are no data available.
5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation
In a study from 2010, carried out in accordance with OECD Test Guideline 436, acute toxicity was determined in 11-week-old rats (3 males and 3 females) exposed to zirconium dioxide at a concentration of 4.3 mg/l over a period of 4 hours. An observation period of 14 days followed with subsequent examination. No mortality was found. Toxicologically significant clinical signs were not observed. Substance deposits around the nose and muzzle were attributed to the exposure. On the first day, the body weights of all the test animals decreased. The body weights returned to normal after one to three days. No other changes were observed (ECHA 2018).

5.1.2 Oral administration
A mixture of cheese and hydrogenated zirconium carbonate was administered to groups of 5 rats with the diet in different single doses. The zirconium carbonate contained 20.9% zirconium dioxide. The effective doses of zirconium dioxide were 2, 4, 8 and 10 g/kg body weight. The rats were 7 to 8 months old. After exposure, the animals were observed over a period of 60 days. No mortality occurred during the entire test period. The animals' growth was normal, and no changes were observed at necropsy up to the highest dose tested. Even when the study was repeated with the same parameters, but with a total of 50 rats, there were no unusual findings (Harrisson et al. 1951).

5.1.3 Dermal application
No toxic effects were observed after dermal application of an ointment containing 20% hydrogenated zirconium carbonate (1.68 g ZrO$_2$) to the skin of guinea pigs (Harrisson et al. 1951).

5.1.4 Intratracheal instillation
Six to eight months after a single intratracheal instillation of 50 mg of zirconium and zirconium dioxide dust, examination revealed thickening of the alveolar septum, fibrosis, peribronchial and perivascular sclerosis and moderate emphysema as well as slight cell proliferation in the lymph nodes (no other details) in the lungs of rats. The histological changes were similar in both groups, but more pronounced in the animals treated with zirconium dioxide (Egorov and Mogilevskaya 1960; Mogilevskaya 1967).

Rats were given 0.5 or 1.5 µl yttrium-stabilized zirconium dioxide by intratracheal instillation in two aliquots on two consecutive days. On days 3 and 28 after dosing, bronchoalveolar lavage was performed in 6 male rats per group. On day 3 polymorphonuclear neutrophils (granulocytes) were increased by 35% to 50%, suggesting an increased acute inflammatory response (Creutzenberg et al. 2017).

The ZrO$_2$ investigated in the study contains about 12% nano-Y$_2$O$_3$. When the solubility of this technical ZrO$_2$ was tested in simulated lung fluids, zirconium and yttrium were found to have a certain degree of solubility only in the acidic lysosomal fluid. After 96 hours 1.34 mg ZrO$_2$/l and 10.2 mg Y$_2$O$_3$/l had dissolved. It can be assumed that the inflammatory effects in the lungs after intratracheal instillation of the technical ZrO$_2$ used here are due to the nano-yttrium oxide contained in it.
5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

No signs of fibrosis, chronic inflammation or granulomas were observed in the lungs of guinea pigs after exposure (24 hours daily) to zirconium dioxide, zirconium chloride and elemental zirconium (no other details) for 2 to 6 months (Reed 1956).

In a subacute inhalation study, dogs, rabbits and rats were exposed to a zirconium dioxide concentration of 75 mg/m³ for 30 days, while cats, dogs, guinea pigs, rabbits and rats were exposed to 11 mg/m³ in a 60-day study. In both cases exposure was for 6 hours a day, on 5 days a week. Mortality was not increased in any of the experiments compared with that in the control animals. There were no effects on the body weights of the animals, or on the haematology, clinical chemistry or histology. Only deposits of the substance were found in the lungs and pulmonary lymph nodes of the treated animals, with species differences in the quantity of the deposits. The zirconium content was highest in the rat lung (158 µg/g tissue to 361 µg/g tissue). The lowest zirconium content (16 µg/g tissue to 69 µg/g tissue) was found in rabbits (Spiegl et al. 1956).

In a recent inhalation study in rats, various materials were tested, including nano-zirconium dioxide. The rats were exposed to the aerosols for 5 days at concentrations of 0.5, 2.5 and 10 mg/m³ (target concentrations). The measured concentrations were 0.5 ± 0.1, 2.6 ± 0.3 and 9.6 ± 1.2 mg/m³. The aerosols had a particle size of about 25 to 60 nm. An observation period of 14 or 21 days followed. No effects related to the nanoparticle treatment were observed up to the highest concentration tested of 10 mg/m³. There were no unusual findings for BALF parameters, such as proteins, enzymes, cytokines and chemokines, or in the gross-pathological and histological examinations of the respiratory organs. Haematological parameters likewise were not affected. The lung burden on the last day of treatment at the highest concentration tested was about 270 µg/lung; it decreased during the following observation period by up to 75% at the middle concentration. The NOAEC (no observed adverse effect concentration) was established to be 10 mg/m³.

Exposure to coated zirconium dioxide nanoparticles up to a concentration of 50 mg/m³ was also carried out, likewise without adverse effects. Here the NOAEC was 50 mg/m³ (Landsiedel et al. 2014).

5.2.2 Oral administration

There are no data available.

5.2.3 Dermal application

There are no data available.

5.2.4 Intraperitoneal injection

The following studies were conducted to test the release of metals from implants. Male Wistar rats were given single intraperitoneal injections of 16, 1600 or 16,000 mg ZrO₂/kg body weight. The size of the particles was about 1 µm. A 5 to 10-month observation period followed. Histological examinations did not yield unusual findings, except for increased macrophage activity in the liver and kidneys and foci of alveolar macrophages in the lungs after five months at the highest dose tested (Olmedo et al. 2002). The research group repeated the tests in male Wistar rats a few years later. The animals (n = 62) were given a single ZrO₂ dose of 16,000 mg/kg body weight. The particles had an average size of 0.5 µm. After 3, 6 and 18 months the following parameters were examined in the animals: the presence of particles in blood cells, the quantitative determination of zirconium particles in serum, the liver and lungs, the determination of particle deposition in histological sections of the liver and lungs, the generation of oxygen radicals in the lungs and the determination of oxidant/antioxidant balance in homogenates of the lungs and liver. At all three points in time, mononuclear phagocytic cells were observed in the blood. Deposits of the substance were found in the liver and lung parenchyma. These were phagocytized by alveolar macrophages and Kupffer cells (Olmedo et al. 2011). The study does
not provide any usable findings because, on the one hand, the (intraperitoneal) route of exposure is not relevant and, on the other hand, phagocytosis is a physiological process.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin
There are no data available.

5.3.2 Eyes
There are no data available.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin
A maximization test (GPMT) with zirconium dioxide (with 5.15% yttrium oxide; intradermal induction with 2.5% and topical induction with 25% after prior non-occlusive application of 10% sodium lauryl sulfate in petrolatum; challenge with 2.5% and 25% test substance in physiological saline solution) did not result in a reaction in any of the 10 treated female Hartley guinea pigs and the 5 control animals 24 and 48 hours after challenge treatment (ECHA 2018).

The application of a 21% preparation of hydrogenated zirconium carbonate (4.3% zirconium dioxide) in an emulsified base of stearic acid, glycerine and water a total of 12 times at intervals of one week did not cause sensitization in 10 guinea pigs (Harrison et al. 1951).

Also investigations with other zirconium compounds of different solubility did not provide any evidence of skin sensitization.

5.4.2 Sensitizing effects on the airways
There are no studies available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility
There are no data available.

5.5.2 Developmental toxicity
There are no data available.

5.6 Genotoxicity

5.6.1 In vitro
In a gene mutation study, mouse lymphoma L5178Y cells were exposed for 3 hours to zirconium dioxide concentrations of 0.03, 0.1, 0.3, 1, 3, 10, 33, 100 and 333 µg/ml with and without metabolic activation by S9 mix. In a second test the cells were cultured in the presence of ZrO₂ for 24 hours without S9 mix and for 3 hours with S9 mix. The study complies with OECD Test Guideline 476 and EC Test Guideline B17. At 100 µg/ml and above, precipitation of the test substance
occurred because the maximum solubility was exceeded. Zirconium dioxide was not mutagenic at the tested concentrations in either the presence or absence of a metabolic system (ECHA 2018).

### 5.6.2 In vivo

There are no data available.

### 5.7 Carcinogenicity

There are no data available.

### 5.8 Other effects

In a study, zirconium dioxide was examined in vitro in human BEAS-2B cells. These are epithelial cells infected with Simian virus 40 (SV-40). Particles with sizes in the range from 50 to 100 nm were used. The expression of mRNA of 84 different signalling molecules was investigated. These signalling molecules are characteristic of the following metabolic pathways: DNA damage and repair, oxidative stress, growth arrest and senescence, inflammation, proliferation and carcinogenesis, heat shock and apoptosis. Zirconium dioxide particles induced signalling molecules which are considered to be characteristic of oxidative and metabolic stress. In addition, an increase in apoptosis signalling molecules and the enzyme uracil DNA glycosylase (UNG) was observed. UNG removes uracil from DNA molecules. If this can no longer be guaranteed and uracil remains in the DNA, this leads to mismatching of the DNA bases uracil and adenine and has a mutagenic effect (Helmig et al. 2014).

### 6 Manifesto (MAK value/classification)

**MAK value.** Zirconium dioxide is poorly soluble and after inhalation exposure acts on the lungs in accordance with the general particle effect of biopersistent granular dusts. The available study results do not provide any evidence of substance-specific effects of zirconium dioxide beyond the general particle effect of biopersistent granular dusts. The general threshold limit value for dust of 0.3 mg/m$^3 \times$ material density for the respirable fraction therefore applies to zirconium dioxide.

The previous MAK value for zirconium and its insoluble compounds of 1 mg/m$^3$ I (inhalable fraction) no longer applies, as it was established on the basis of a study in which the animals were exposed to respirable particles of zirconium lactate and barium zirconate.

**Peak limitation.** The critical effect is the effect of biopersistent granular particles on the lungs. Therefore, zirconium dioxide dust, like other biopersistent granular dusts, is classified in Peak Limitation Category II. Since the clearance half-life of biopersistent granular dusts is approximately 400 days, an excursion factor of 8 has been set.

**Prenatal toxicity.** No developmental toxicity studies are available for zirconium dioxide. Since zirconium dioxide is a poorly soluble dust, an embryotoxic effect is not to be assumed if the MAK value of 0.3 mg/m$^3$ R × material density is observed. It is therefore assigned to Pregnancy Risk Group C, in analogy to other biopersistent granular dusts.

**Carcinogenicity.** There are no epidemiological studies available. Zirconium dioxide induces tumours in rats after intratracheal instillation of high doses (see Hartwig 2014). Since zirconium dioxide is a poorly soluble biopersistent granular dust, particle-related tumour formation in rats after inhalation cannot be excluded. This is due mainly to inflammation in the alveolar or bronchial area, which is accompanied by the release of reactive oxygen species. The respirable fraction of the zirconium dust is classified in Carcinogen Category 4, in analogy to other biopersistent granular dusts.

**Germ cell mutagenicity.** The available genotoxicity data do not provide evidence of germ cell mutagenicity caused by zirconium dioxide. It is therefore not classified in one of the categories for germ cell mutagens.
Absorption through the skin. Dermal uptake of zirconium dioxide is not known. The substance is therefore not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts) in analogy to other biopersistent granular dusts.

Sensitization. There are no positive clinical or experimental findings of contact sensitization caused by zirconium dioxide which would show that the substance can lead to sensitization on intact skin. The granulomatous reactions described in the earlier clinical literature are mostly related to applications on previously damaged skin. The course of the reactions and the histological findings indicate an immunological phenomenon and a sensitizing effect, but the observations are not supplemented by further immunological findings. There is no evidence of a skin-sensitizing potential of zirconium dioxide on intact skin or of a sensitizing effect of zirconium dioxide on the lungs. Whether the granulomatous changes in the lungs after exposure to other poorly soluble zirconium compounds are accompanied by sensitization cannot be deduced from the few findings available. There is insufficient evidence, therefore, that zirconium dioxide causes respiratory sensitization. Zirconium dioxide is thus not designated with “Sa” or “Sh” (for substances which cause sensitization of the airways or skin).

Notes

Competing interests

The established rules and measures of the commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

References


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