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Zirconium and its compounds (except zirconium dioxide)

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

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Keywords

zirconium; zirconium compounds; sensitization; chronic toxicity; hazardous substance

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) for zirconium and its compounds [7440-67-7]. No new data are available that would be relevant for the derivation of a MAK value for zirconium compounds, with the exception of zirconium dioxide (see documentation "Zirconium dioxide"). Therefore, zirconium and its compounds (except zirconium dioxide) are listed in Section II b of the List of MAK and BAT Values. Based on the new human and animal data, zirconium and its compounds (except zirconium dioxide) are not regarded as sensitizers. Dermal absorption does not contribute to systemic toxicity.

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MAK value (2018)	**not yet established, see List of MAK and BAT Values, Section II b**
Peak limitation	–
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–

Chemical name	zirconium
CAS number	7440-67-7
Molecular formula	Zr
Melting point	1852 °C
Boiling point	4377 °C
Density at 25 °C	6.5 g/cm^3

Documentation from 1998 is available for zirconium and its compounds (Greim 1999) and a supplement on peak limitation from 2002 (Greim 2002, available in German only).

Since the documentation from 1998 (Greim 1999) a MAK value of 1 mg/m^3 I (inhalable fraction) has applied for zirconium and its insoluble compounds, whereas no MAK value could be derived for soluble zirconium compounds and these were assigned to Section II b of the List of MAK and BAT Values.

Zirconium dioxide was assessed separately in 2018 and assigned to the group of biopersistent granular dusts with a MAK value of 0.3 mg/cm^3 R (respirable fraction) × material density (Hartwig and MAK Commission 2021). This supplement examines whether the MAK value established in 1998 for zirconium and insoluble zirconium compounds can be retained.

Zirconium and its compounds have also been designated with "Sah" (for substances which cause sensitization of the skin and airways) since 1998. In the meantime, new findings from animal experiments and in vitro studies of contact sensitization, most of which were negative, have become available, but no new data in humans. The additional "Sah" designation must therefore be re-assessed, also in the light of the new criteria recently formulated.

Effects in Humans

Since the documentation of 1998 (Greim 1999) no new studies have been published on the effects of zirconium and soluble and insoluble zirconium compounds (except zirconium dioxide) in humans.

Sensitization

No new data for sensitization in humans are available. However, the findings reported in the documentation of 1998 (Greim 1999) have to be re-assessed according to the criteria formulated in the meantime.

Sensitizing effects on the skin

Allergic contact dermatitis after exposure to zirconium compounds has not been described. In the USA, granulomatous reactions were reported in the 1960s as a result of the use of **zirconium dioxide** in the treatment of dermatitis caused by Toxicodendron radicans ("poison ivy") and other Toxicodendron or Rhus species (see Hartwig and MAK Commission 2021).

Also, after the application of deodorant sticks containing the water-soluble **sodium zirconium lactate**, nodular, inflammatory changes were observed at the application site in some people; these receded only very slowly over the course of months. Histological examination revealed epithelioid cell granulomas (Epstein 1967; Epstein et al. 1962; Rubin et al. 1956; Shelley and Hurley 1958; see also Greim 1999). Regarding these granulomatous reactions to sodium zirconium lactate it should be noted that the application of the deodorant sticks did not take place on inflammatory, pre-damaged skin, as in the case of zirconium dioxide, but (mostly) on shaved skin and that the granulomatous changes occurred (mainly) in the area abraded by shaving. As far as carried out, patch tests on intact skin yielded negative results both in the investigations with preparations of **zirconium dioxide** (see Hartwig and MAK Commission 2021) and in the investigations with preparations of **sodium zirconium lactate**. However, reactions in which granulomas were formed occurred after testing if the skin barrier was impaired, for example when testing after the removal of the upper horny layer, or with intradermal testing.

There have also been isolated reports of individuals who developed axillary granulomas after the application of antiperspirants containing uncharacterized **aluminium zirconium complexes** (Montemarano et al. 1997) or **aluminium zirconium tetrachlorohydrex gly** (complex aluminium zirconium tetrachlorohydrate in which some water molecules are replaced by glycine) (Skelton et al. 1993).

In experimental studies, 30 test persons applied a deodorant stick containing about 5% **sodium zirconium lactate** for 8 weeks by vigorously rubbing it onto the area of one axil for 5 minutes each day. On the other axil, a zirconium-free preparation was used for comparison. In one of the volunteers, non-inflammatory papules developed after about 4 weeks, which were histologically classified 2 weeks later as (early) epithelioid cell granulomas. In another test, in which a preparation containing 10% sodium zirconium lactate was used, granulomatous reactions occurred in 1 of 20 test persons. A 0.5% formulation applied in parallel led to no reactions. In both experiments, the subjects shaved their axillae every other day. The patch test results with the formulations containing zirconium were negative also in the two subjects who were probably sensitized. In contrast, intradermal tests with 1% and 0.1% sodium zirconium lactate led to granulomatous reactions within 2 weeks. One of the two volunteers even reacted to a concentration of as little as 0.01%. Corresponding tests with a 1% preparation in 20 persons not pre-treated yielded negative results. In addition to these granulomatous reactions induced in 2 cases, 3 volunteers from each of the two treated groups produced transient, in some cases inflammatory, papular reactions, but no granulomatous reactions after 6 to 8 weeks (in one of these cases after 2 weeks), which healed quickly (Shelley and Hurley 1958).

In other investigations, granulomatous reactions were described after multiple intradermal applications of 4% aqueous **zirconium lactate suspensions**; these were interpreted as a consequence of sensitization. In total, 5 of several hundred (no other details) subjects were presumably sensitized. In these 5 persons, healing primary lesions (no other details) suddenly flared up 6 weeks to 6 months after the treatment, and only then were epithelioid cells detectable histologically. These 5 volunteers were then treated repeatedly with intradermal injections of some soluble and poorly soluble zirconium salts (sodium zirconium lactate, zirconyl citrate and the zirconium lactate originally used). In total they were given 12 to 25 injections of 0.1 ml each of the 1% or 0.1% preparations in physiological saline solution. Histological examinations were performed up to 10 months after this renewed treatment. The 0.1% preparations triggered delayed reactions only in the previously sensitized subjects. Higher concentrations also led to (foreign body) granulomas in subjects not sensitized. The differentiation of the reactions was based mainly on histology and the course of the reaction. The reactions of the persons not sensitized were similar to those of the sensitized persons during the first two to three weeks. They did not then increase in intensity, however, but healed within 6 to 8 months. In contrast, the reactions of the sensitized persons initially intensified further and healed only after at least 10 to 12 months.

The authors noted that the soluble zirconium salts led to significantly less pronounced reactions and only incomplete formation of epithelioid granulomas (Epstein 1960, 1967; Epstein et al. 1962).

On the other hand, investigations in which differently soluble test substances were applied to intact skin yielded no evidence that the tested zirconium compounds have a sensitizing potential:

No granulomas were found in 54 volunteers after topical application of **zirconyl chloride** (no other details) (ACGIH 1992).

In a study with incomplete data, neither a patch test nor an intradermal test could trigger an allergic reaction after repeated occlusive application (no other details) of a 10% preparation of **zirconium lactate** in carbowax to the irritated skin of 30 test persons (Epstein 1960).

Maximization tests in volunteers, in which 25% preparations of **zirconium sulfate** or **zirconium lactate** were used for induction and 10% preparations for the challenge treatment, led to a reaction in 1 of 24 and none of 22 subjects, respectively (no other details) (Kligman 1966).

Conclusion: There is no reliable evidence of sensitizing effects of zirconium compounds on intact skin. Although the histological findings and the course of the granulomatous reactions occurring after intradermal application or after the exposure of previously damaged skin indicate an immunological genesis and sensitization, no further immunological findings are available and an unequivocal classification of these reactions is therefore not possible.

Sensitizing effects on the airways

There are no classical findings regarding respiratory sensitization. In a few reports already mentioned in the 1998 documentation (Greim 1999) granulomatous changes in the lungs were described, but more detailed immunological investigations from which respiratory sensitization caused by zirconium could be deduced were not carried out:

In a 25-year-old female employee who was exposed to dusts containing zirconium for 3.5 years, epithelioid granulomatous interstitial pneumonia with mild fibrosis developed. Pronounced lung function impairment was found, with values for the one-second capacity (FEV1) and forced vital capacity (FVC) of 32% and 34% of the expected value, respectively. The bronchoalveolar lavage fluid contained 4.95×10^8 cells/litre, of which 29% were lymphocytes, 18% neutrophils and 10% eosinophils. The burden of dust in the lung was examined in a tissue sample and was found to be nearly 100 times the normal background level with about 4.4×10^6 particles per gram dry weight. The particles consisted mainly of **zirconium silicate** (30%), clay (37%), potassium feldspar (11%) and quartz (9%). The dust concentration at the workplace, where glazes were used, was 0.8 to 5.8 mg/m^3 during the last 1.5 years of employment, with a proportion of 10% to 30% zirconium silicate and 15% silicon dioxide. In the two previous years, there was exposure to 0.5 to 2.6 mg dust/m^3 (no other details) with levels of up to 8.6 mg dust/m^3 for one month (no other details) (Liippo et al. 1993).

A female worker in a nuclear plant who spent 16 years carrying out welding work on the cladding of fuel rods containing zirconium, tin, iron and chromium developed inflammatory changes in the lungs, which the authors interpreted as symptoms of exogenous allergic alveolitis. Histologically, different stages of foreign body-induced epithelioid cell granulomatosis with the inclusion of foreign bodies in giant cells and with fibrotic changes were observed in the lungs. Zirconium (in addition to iron, chromium and silicon) was found to be an essential component of these foreign bodies. Granulomatous changes were also found in older scar tissue of the skin of the mamma and in the axillary lymph nodes (Kotter and Zieger 1992; Schneider et al. 1994; Werfel et al. 1998).

Another case of interstitial lung disease with non-confluent granulomas after zirconium exposure (eight years, dust containing zirconium silicate, 1.1 mg/m^3) was described. Pulmonary function tests were inconspicuous, and the histological examination of transbronchial biopsy tissue revealed small interstitial nonconfluent granulomas with epithelioid and giant cells (Romeo et al. 1994).

Conclusion: Further studies that examined the respiratory tract after repeated exposure to zirconium or zirconium compounds (see Greim 1999; Hartwig and MAK Commission 2021) did not report positive immunological findings or the occurrence of epithelioid granulomas.

It cannot be deduced therefore from the few available findings whether these isolated cases of granulomatous reactions in the lungs are, as in the case of beryllium, an immunological phenomenon in the sense of a cell-mediated allergic reaction of the delayed type.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

The previous MAK value of 1 mg/m^3 I (inhalable fraction) for zirconium and insoluble zirconium compounds was based on the study by Brown et al. (1963). In this study, groups of 10 guinea pigs, 10 Wistar rats and 10 hamsters were exposed to respirable **zirconium lactate** concentrations of 15 mg/m^3 (group A) or 150 mg/m^3 (group B) or respirable **barium zirconate** at 15 mg/m^3 (group C) for 7 hours a day, on 5 days a week, for 225 days. The measured average concentrations were 18.8, 145.1 and 18.2 mg/m^3 (corresponding to 4.7, 36.3 and 5.4 mg zirconium/m^3, respectively). Lung weights were increased in all groups in all species. In rats and hamsters, body weight development was reduced compared with that in the control animals. In all three species there was an increase in the zirconium content in the lungs and pathological signs of diffuse interstitial pneumonitis with only minor fibrogenic effects were found. The changes were more pronounced in the animals of groups A and C than in the animals of group B. In some animals of groups A and C degenerative changes were observed in the epithelium of the bronchi and bronchioles. Two guinea pigs of group A died on days 200 and 209 of exposure, respectively. In these animals the degenerative changes were particularly pronounced. Some of the animals exposed to barium zirconate were observed for 3 months; notable regression of the lung changes was not observed. Giant cells but no granulomas were found in group B animals. Histological examinations of the liver, spleen and kidneys did not yield pathological findings in any of the animals (Brown et al. 1963). From the results of this study, which was incompletely documented, particularly with regard to histological findings, no NOAEC is discernible for either of the two compounds investigated, especially since there was no dose–response relationship. Furthermore, respirable particles were tested. A MAK value cannot be derived from these data for zirconium or insoluble zirconium compounds.

Allergenic effects

Sensitizing effects on the skin

In vivo studies

In addition to the earlier studies with intradermal induction and challenge treatment already evaluated in the 1998 documentation (Greim 1999), several more recent experimental studies of the skin sensitization potential of differently soluble zirconium compounds, some of which were carried out according to test guidelines, are now available. These studies in mice and guinea pigs did not provide any evidence of skin sensitization according to known mechanisms. However, the reactions of the animals were assessed only after the usual time periods; information on reactions which may have occurred later is not available.

A local lymph node assay carried out according to OECD Test Guideline 442B (BrdU variant) with 25%, 50% and 100% of a 40.7% solution of **zirconium acetate** in acetone/olive oil (4:1) yielded stimulation indices of 1.02, 1.06 and 0.72, respectively, and thus a clearly negative result (ECHA 2018 c).

In a modified local lymph node assay, likewise with negative results, groups of 3 BALB/c mice were given intradermal injections into the abdomen of 50 µl of a 0.02%, 0.2% and 2% preparation of **zirconium tetrachloride**. After 5 days, 25 µl of a 5% test substance preparation in 70% dimethyl sulfoxide was applied non-occlusively to both ears on three

further consecutive days. One day after the last application, the auricular lymph nodes were removed and the lymphocyte proliferation was determined. The determined stimulation indices are given as 0.94, 0.90 and 1.09, respectively (Ikarashi et al. 1996).

A negative result was reported for a maximization test in 10 female LAL/HA/BR guinea pigs with **zirconium dinitrate oxide** (induction: 0.25% intradermal and 25% topical; challenge: 25%; in physiological saline with 1% methylcellulose in each case). None of the animals produced a reaction 24 and 48 hours after the challenge treatment (ECHA 2018 f). It was not stated whether sodium lauryl sulfate had been applied prior to the topical induction.

A maximization test with **zirconium acetate** (induction: 5% intradermal and 20% topical; challenge: 20%; in water in each case) likewise did not lead to a reaction in the 20 animals used, either at the first or after a second challenge treatment (ECHA 2018 e).

Also a maximization test in 20 guinea pigs with **aluminium zirconium tetrachlorohydrex gly** yielded negative results. For intradermal induction treatment a 0.5% preparation in water was used, and for topical induction treatment and challenge a 50% aqueous preparation (ECHA 2018 a). Maximization tests with solutions of **aluminum zirconium tetrachlorohydrate** and **aluminum zirconium pentachlorohydrate** (concentrations not specified) did not lead to sensitization in any of the 20 guinea pigs used in each case. Both test substances were used as 1% aqueous preparations for intradermal induction, and undiluted for topical induction and challenge treatment (ECHA 2018 a).

Zirconium tetrachloride proved to be non-sensitizing in a modified maximization test with only 5 female Hartley guinea pigs. The intradermal induction was performed with a 1% solution in physiological saline, the topical induction with a 5% preparation in petrolatum and the challenge treatment with 1%, 2% and 5% preparations in ethanol (Ikarashi et al. 1996).

An incompletely documented maximization test with **zirconium tetrakis(isobutyrate)** in 20 female Dunkin Hartley guinea pigs likewise yielded negative results. The intradermal induction treatment was performed with a 0.5% preparation of the test substance in acetone and the topical induction treatment and challenge treatment with a 25% preparation in the same vehicle (ECHA 2018 b).

The earlier studies in mice, guinea pigs and rabbits, which were already evaluated in the 1998 documentation (Greim 1999) and were not performed according to the test guidelines, are not suitable for the evaluation, or only to a very limited extent, due to the intradermal induction and challenge treatment:

The intradermal injection of a 10% **zirconium lactate** suspension in physiological saline into 48 CBA/J mice and of an 8% to 20% **sodium zirconium lactate** solution in a 0.2 molar sodium stearate preparation into 58 CBA/J mice (0.02–0.05 ml injected intradermally into the four footpads) and of a 10% solution of sodium zirconium lactate in physiological saline solution into 12 CBA/J mice (injected into both ears) led to the formation of local foreign body granulomas in all 48, in 47 of the 58 and in all 12 animals that persisted for more than 8 months. However, epithelioid cell granulomas, which could indicate sensitization, were not observed. The animals pre-treated with zirconium lactate were also treated 6 weeks later with an intradermal injection of 0.1% zirconyl chloride into the ear pinnae. Histological evidence of granuloma formation was not found in any of the animals after 3.5 to 5.5 months (Shelley and Raque 1971).

Six Hartley guinea pigs were immunized with a total of 1 mg **sodium zirconium lactate**/animal (1.25 mg/kg body weight), with 4 injections into the footpads and one into the neck. After 2 weeks, the animals were given intradermal injections of 25 µg sodium zirconium lactate in 0.1 ml physiological saline once a week for up to 13 weeks. In week 5, 24 hours after the injections, 2 guinea pigs produced reactions (erythema with a diameter of more than 8 mm or an increase in skin thickness of over 0.7 mm) (the remaining 4 produced such reactions in week 8), which the authors interpreted as an expression of sensitization. Subsequently, nodular granulomas also formed. Similar results were obtained in a modified split adjuvant test and a modified maximization test with a single intradermal induction treatment, in which the animals were subjected to repeated intradermal challenge treatments as described above. In the split adjuvant test, 1 of 6 animals reacted after 3 weeks and 6 of 6 animals after 8 weeks. In the maximization test, 1 of 6 animals reacted after 6 weeks and 4 of 5 animals after 8 weeks (Turk and Parker 1977 b; Turk et al. 1978).

After intradermal injection of 0.05, 0.5 or 5 mg **zirconium carbonate**, no granulomas developed in guinea pigs; after the administration of the same amounts of an **aluminium zirconium glycine complex**, on the other hand, granulomas were observed. However, the authors attributed this to the aluminium, as the changes were similar to the granulomas formed after the injection of aluminium hydroxide (Turk and Parker 1977 a).

New Zealand White rabbits were given single injections of preparations of 1.42 mg **aluminium zirconium glycinate** (group A) or 0.31 mg **sodium zirconium lactate** (group B) in 0.4 ml of Freund's complete adjuvant into the paws. Further groups were given intradermal injections of 100 µg of the test substances in 100 µl physiological saline twice a week over a period of 6 weeks. At the first injections of the first and fourth week, twice the amount of the test substance was injected into the animals' paws. The cumulative amount administered was 1.4 mg/animal (groups C and D). Within 7 days after the induction phase, the animals of groups C and D underwent challenge treatment with 5, 50 and 500 µg test substance in 100 µl physiological saline; the reactions were monitored over a period of 5 days. Challenge with 50 µg aluminium zirconium glycinate resulted in only slightly more pronounced reactions in group C after 48 hours than in the control group (on average about 4.5 mm compared with about 3.5 mm; in 2 of 10 animals larger than 6 mm). The reactions to sodium zirconium lactate were more pronounced in group D with an average of about 7 mm (compared with about 3 mm). In this group, 3 of 9 animals produced a reaction with a diameter of over 6 mm. The reactions were morphologically described as small bright indurated papules "without histological characteristics of delayed hypersensitivity". The results of lymphocyte transformation tests with 1 µg test substance were negative with lymphocytes from all groups. The results of tests for macrophage migration inhibition factor (MIF) with 10 µg aluminium zirconium glycinate, with 10 µg sodium zirconium lactate and with 25 µg aluminium zirconium glycinate were negative, but weakly positive in 2 of 8 animals given 50 µg sodium zirconium lactate (Kang et al. 1977).

In rabbits, the subcutaneous and intracutaneous administration of 0.5 ml and 0.1 ml of a 42% **sodium zirconium lactate** solution, respectively, on the back and ear led to acute inflammatory and granulomatous reactions. Preparations of 12.6%, 10.5%, 8.4%, 6.3% and 4.2% sodium zirconium lactate led to similar but less pronounced reactions. In the pre-treated animals, inflammatory reactions occurred also after occlusive application of a preparation of 9.2% sodium zirconium lactate and 0.5% hexachlorophene. Repeated applications led to more pronounced reactions (no other details). However, due to the incompletely documented method, the findings are not suitable for assessing the sensitizing potential (Prior et al. 1957).

In 2 of 2 and 1 of 2 rabbits, 24 hours after a single subcutaneous injection of 100 mg and a single intracutaneous injection of 10 mg of **zirconium tetraisopropoxide**, respectively, slight reddening of the skin was observed. Seven weeks later, the repeated injection of the substance resulted in slight reddening of the skin in 1 of 2 animals in each case; this disappeared after 48 hours. The formation of granulomas was not observed and topical application produced no effects (Prior and Cronk 1959).

The non-occlusive application of a 21% ointment preparation of hydrated **zirconium carbonate** once a week over a period of 12 weeks did not cause sensitization in 10 guinea pigs (Harrisson et al. 1951).

In vitro studies

In vitro tests with **zirconium bis(hydrogen)phosphate** yielded negative results in the direct peptide reactivity assay (DPRA) carried out according to OECD Test Guideline 442C and positive results in the hCLAT and LuSens assays carried out according to OECD Test Guidelines 442E and 442D (ECHA 2018 d).

Sensitizing effects on the airways

After three intratracheal instillations of 10 mg **aluminium zirconium glycinate** or 10 mg **sodium zirconium lactate** at intervals of 3 days, acute inflammatory effects on the lungs occurred in female New Zealand White rabbits (one day after the last treatment: mild to moderately severe bronchiolitis, infiltrate with polymorphonuclear leukocytes and macrophages), which subsided within 28 days. Aluminium zirconium glycinate led to more pronounced effects than the aluminium chlorohydrate also investigated, and sodium zirconium lactate produced the least effects (a few areas

of lymphocytic infiltrates; after 14 and 28 days the pulmonary histology was normal). Skin tests with intradermal injection of 25 to 100 µg of the test substances in physiological saline and MIF assays did not reveal any differences between pre-treated and naive animals (Stankus et al. 1978).

Manifesto (MAK value/classification)

MAK value. The study by Brown et al. (1963) used in the 1998 documentation (Greim 1999) is, after re-evaluation, not suitable for establishing a MAK value for zirconium and its insoluble compounds as a NOAEC cannot be derived from it and there is no dose–response relationship. In addition, respirable particles were used. Therefore, the previous MAK value of 1 mg/m^3 for zirconium and its insoluble compounds has been suspended and they are assigned to Section II b of the List of MAK and BAT Values, as are the soluble zirconium compounds. Thus, the previous peak limitation category and Pregnancy Risk Group D are no longer applicable.

Absorption through the skin. There are no data available for absorption through the skin. A NOAEC for systemic toxicity is not known. Therefore, zirconium and its compounds (except zirconium dioxide) are not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no positive clinical findings which indicate that zirconium or zirconium compounds can cause contact sensitization of the intact skin. The granulomatous reactions to some zirconium compounds described in the earlier clinical literature are mostly related to application on previously damaged skin. The described reaction courses and histological findings point to an immunological genesis. However, the sensitization suspected from these findings is not supported by further immunological findings. Neither in experimental studies in humans with topical application of zirconium compounds nor in more recent experimental studies in animals, some of which were carried out according to test guidelines, could sensitization be demonstrated. Therefore, skin sensitization after occupational exposure to zirconium or zirconium compounds cannot be sufficiently validated. Whether the granulomatous changes in the lungs after exposure to zirconium or zirconium compounds are associated with sensitization cannot be deduced from the few findings available, so that sensitization of the airways can also not be validated. Zirconium and zirconium compounds are therefore not designated with "Sh" (for substances which cause sensitization of the skin) or "Sa" (for substances which cause sensitization of the airways).

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.

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