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Titanium dioxide (respirable fraction)

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

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Keywords

mechanism of action, toxicokinetics, metabolism, (sub)acute toxicity, (sub)chronic toxicity, irritation, allergenic effects, genotoxicity, carcinogenicity, peak limitation, prenatal toxicity, germ cell mutagenicity, absorption through the skin, sensitization, occupational exposure, maximum workplace concentration, MAK value, toxicity, hazardous substance

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated titanium dioxide [13463-67-1]. Titanium dioxide causes lung tumours in rats at high concentrations. In 2009, titanium dioxide was evaluated and, because a maximum concentration at the workplace (MAK value) could not be established, it was classified in Carcinogen Category 3A. Titanium dioxide is a biopersistent granular dust and, in a later evaluation, inhalation studies with titanium dioxide were used to derive the general threshold limit value for granular biopersistent dusts. Therefore, the respirable fraction of titanium dioxide dust is reclassified in Carcinogen Category 4 and a MAK value of 0.3 mg/m^3 × material density is established for the respirable fraction according to the general threshold value for biopersistent granular dusts. Reclassification in Carcinogen Category 4 is justified because the lung tumours are regarded as a consequence of the inflammatory mechanism of action, for which a threshold can be defined. Direct genotoxic effects appear to be of subordinate relevance for the carcinogenicity of biopersistent granular dusts. By analogy with the biopersistent granular dusts, Peak Limitation Category II is established for titanium dioxide with an excursion factor of 8. Since titanium dioxide is not systemically distributed and accumulates only locally in the lungs, damage to the embryo or foetus is unlikely when the MAK value is not exceeded. Titanium dioxide is classified accordingly in Pregnancy Risk Group C. Titanium dioxide is not expected to be a sensitizer and is not taken up via the skin in toxicologically relevant amounts.

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MAK value (2018)	**0.3 mg/m³ R × material density[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	–
BAT value	–
Chemical name	titanium(IV) oxide
Synonyms	titanic anhydride
CAS number	13463-67-7 (titanium dioxide) 1317-70-0 (anatase) 13463-67-7 (brookite) 1317-80-2 (rutile)
Molecular formula	TiO_2
Molar mass	79.9 g/mol
Melting point	decomposes at 1860 °C
Density	3.9 g/cm³ (anatase) 4.1–4.2 g/cm³ (brookite) 4.25 g/cm³ (rutile) (Holleman and Wiberg 2007; Ramdohr and Strunz 1978; Rösler 1991)
Mohs' hardness	5½–6 (anatase) 5½–6 (brookite) 6–6½ (rutile)
Crystallographic class/structure	ditetragonal dipyramidal $^4/_m{}^2/_m{}^2/_m$ (anatase) rhombodipyramidal $^2/_m{}^2/_m{}^2/_m$ (brookite) ditetragonal dipyramidal $^4/_m{}^2/_m{}^2/_m$ (rutile)
log K_{OW}	–
Solubility	insoluble in water, organic solvents and diluted acids; soluble in lyes, concentrated hot sulfuric acid and in hydrofluoric acid (Holleman and Wiberg 2007; IFA 2018; Matthes 1990; Ramdohr and Strunz 1978; Rösler 1991)

[a)] the effects of titanium dioxide are based on the effects of biopersistent granular dusts. The value of 0.3 mg/m³ for the R (respirable) fraction applies for a material density of 1 g/cm³.

Note: Evaluation except for ultrafine particles; see Section V h of the List of MAK and BAT Values.

Since the supplement from 2009 (translated 2014, Hartwig 2014 a) in 2012 the supplement "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)" (translated 2014, Hartwig 2014 b) was published, which refers extensively to studies with titanium dioxide. In this supplement, therefore, titanium dioxide is evaluated solely on the basis of the results of studies published since 2012.

General characteristics

The annual production volume of titanium dioxide in the EU amounts to 10^6 to 10^7 tonnes. It is a white, crystalline, odourless solid of inorganic nature. The particle size varies greatly, and titanium dioxide can be processed to form also nanotubes and nanofibres (ECHA 2016, 2018).

The substance is used in many different ways.

1 Toxic Effects and Mode of Action

See supplement 2009 (Hartwig 2014 a) and supplement "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)" 2012 (Hartwig 2014 b).

There are no clinical findings of allergic contact dermatitis as a result of topical exposure to the substance and no positive results from studies with animals. There is also no evidence of sensitizing effects on the airways.

2 Mechanism of Action

See supplement 2009 (Hartwig 2014 a) and supplement "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)" 2012 (Hartwig 2014 b).

3 Toxicokinetics and Metabolism

There are no new data available.

4 Effects in Humans

4.1 Single exposures

There are no new data available.

4.2 Repeated exposure

A short-term study in workers from a factory which processed titanium dioxide was carried out at the Peking University from 19th June 2009 to 18th July 2009 to investigate the effects of the occupational exposure on the cardiopulmonary functions (Zhen et al. 2012). Seven male workers who had worked at the factory for the previous three years took part in the study. Exclusion criteria were chronic heart and lung disease, liver and kidney disease, a family history of high blood pressure or other cardiopulmonary illnesses. The 4 smokers had to minimize the number of cigarettes smoked during work to control the effects of inhaled smoke. The average age was 36.57 years (29–48) and the average duration of employment was 8.64 years (3–23). All worked in the usual 8-hour shifts. The measured particles were classified in three size categories: 14.5% > 10 µm, 69.6% 1–10 µm, 12.3% < 1 µm. The study

revealed a significant relationship between the exposure and a reduction in pulmonary function and an increase in blood pressure. The average lung function parameters for the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1.0), peak expiratory flow (PEF), maximum voluntary ventilation (MVV) and maximum mid expiratory flow (MMEF) before work were 4.57, 3.70, 6.53, 144.02 and 3.67 l/s and after work were 4.54, 3.67, 6.45, 144.05 and 3.64 l/s. The systolic blood pressure increased from 131.1 to 131.6 mm Hg and the diastolic blood pressure from 75.5 to 76.6 mm Hg. In view of the variations in the measurements (which were within a very small, hardly determinable and always physiological range) and the small cohort of only 7 persons, the meaningfulness of the study is limited.

At three American plants that processed titanium dioxide, the mortality of the exposed workers employed there was investigated. The factories were situated in Delaware, Tennessee and Mississippi; the study began in 1935 and ended in 2005. The minimum duration of employment was six months. In all, 5054 workers fulfilled the criteria for inclusion in the study. The average worker was white (81%), male (90%), 31 years of age (SD ± 9 years) at the beginning of the study and 60 years of age (SD ± 15 years) at the end of the study. The workers were observed for an average of 29 years (SD ± 15 years). This amounts to a total of 145,151 person years. The aim of the study was to investigate the mortality of the exposed workers in comparison with that of the average American population. In the cohort 1475 deaths occurred. Standardized mortality ratios (SMRs) were calculated according to sex and ethnic origin. The SMR for all causes of death over the whole cohort was 0.81 (95% CI = 0.77–0.85). The SMRs for cancer in the respiratory tract and for the respiratory organs were, with one exception, lower than expected: with a total of only 3 deaths at one of the three factories, the SMR for cancer in respiratory organs apart from the larynx and lungs was 2.49 (95% CI = 0.62–6.46). The authors concluded that overall there was no positive association between the occupational exposure and deaths caused by cancer, non-malignant respiratory diseases or heart disease (Ellis et al. 2010; Warheit et al. 2016).

In 2012, this research group published a mortality study carried out at the same plant. The workers were exposed to titanium dioxide or titanium tetrachloride. The reference value was the number of deaths company-wide. The study period included the years 1935 to 2006, the cohort comprised 3607 workers, the majority of whom were male and white. Monitoring of the exposure began in 1975. At this point in time, the workers were on average 29 years of age, and at the end of the observations 56 years of age. This totalled 91,835 person years. Death certificates were available for 818 of the total 833 deaths. Also in this study, increased risks could not be found for all causes of death, all types of cancer, lung cancer, non-malignant respiratory diseases or heart disease. The SMRs for all of these causes of death were < 1 compared with that for the American general population. The authors explained this by, among other factors, the healthy worker effect. Compared with that for all workers at the company, there was a statistically significant increase in the mortality ratio for all causes of death (SMR = 1.23; 95% CI = 1.15–1.32), all cases of cancer (SMR = 1.17; 95% CI = 1.02–1.33), and lung cancer (SMR = 1.35; 95% CI = 1.07–1.66) (Ellis et al. 2012; Warheit et al. 2016).

4.3 Local effects on skin and mucous membranes

There are no new data available.

4.4 Allergenic effects

Despite the widespread use of titanium dioxide, there are to date no findings of allergic contact dermatitis in humans caused by topical exposure to the substance. Nevertheless, commercially available 0.1% preparations of titanium dioxide in petrolatum are used in patch tests to diagnose possible sensitization to titanium. Sporadic reactions that were evaluated as "positive" by the investigators are found above all in individual patients or in collectives with suspected allergic intolerance (to dental implants) (review in e.g. Fage et al. 2016; Wood and Warshaw 2015). In view of the low solubility of titanium dioxide it is unclear to what extent such reactions are really the result of

sensitization to "titanium", in particular as there are no data available as regards concurrent positive reactions to soluble titanium salts.

4.5 Reproductive and developmental toxicity

There are no new data available.

4.6 Genotoxicity

There are no new data available.

4.7 Carcinogenicity

There are no new data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

There are no new data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In a study, titanium dioxide in the form of nanoparticles (pyrogenic titanium dioxides, 20% rutile, 80% anatase) with an average diameter of 21 nm and fine particles (Bayertitan T, 99.5% rutile) with an average diameter of 0.3 µm were administered via inhalation to female rats at the age of 10 weeks. Exposure was for 6 hours a day on 21 consecutive days. The control group inhaled pure air, the group treated with nanoparticles inhaled 25 mg/m^3 and the group with fine particles 45 mg/m^3. As regards the surface areas, the two groups were therefore exposed to a similar extent. After a recovery period of 3, 28 or 90 days, the animals were sacrificed. After 3 days, multifocal white foci of 0.5 to 2 mm in size were found in the lungs of the rats, which were described by the authors as pigment deposits. In some lungs, in addition acute multifocal alveolar emphysema was observed. After a longer recovery period these findings were no longer present. Also alveolar infiltrates with particle-laden macrophages were observed in the lungs. In the bronchoalveolar lavage fluid (BALF) only β-glucuronidase was reduced after 3 days, the other parameters did not differ from the findings in the control group. The observed effects occurred in both treated groups. No differences could be found between exposure to nanoparticles or fine particles (Eydner et al. 2012).

Titanium dioxide particles with an average diameter of 1 µm were administered as a suspension in DEP (diethyl phthalate) or in PBS (phosphate-buffered saline) via the nose to pregnant mice and females that were not pregnant (50 µg/mouse) to investigate the effects of "inert" substances during gestation (Lamoureux et al. 2010). The animals were sacrificed 48 hours after exposure and the gene expression was analysed by means of PCR array. A number of upregulated genes responsible for inflammatory reactions were identified in the lungs of the pregnant animals.

Titanium dioxide with an average particle size of 1.5 µm (GSD 1.8) was administered to rats by intratracheal instillation. Doses of 2 mg in a physiological solution were given to 25 male rats at the age of 10 weeks. After treatment, 5 animals were killed after 3 days, 1 week, 1 month, 3 months or 6 months. Examination of the BALF revealed a significant ($p < 0.05$) increase in granulocytes up to 3 days after exposure compared with the number in the controls. The other parameters investigated were not different from those in the control group (Ogami et al. 2009).

In a study, as a negative control, groups of 32 rats were given intratracheal doses of 1, 5 or 10 mg of titanium dioxide with an average diameter of 1 µm. After 24 hours, 3 days, 7 days or 6 months the animals were sacrificed. In the high dose group, biochemical analysis revealed increased total protein values and on day 3 increased LDH activity. Histopathological examination revealed mild to moderate macrophage and neutrophil pneumonitis at the middle and high dose. Slight cardiomyopathy was observed in all dose groups. Pulmonary lesions were seen in the animals 3 and 7 days after the exposure. These were manifest as severe macrophage and neutrophil alveolitis or pneumonitis. After 6 months, titanium dioxide particles were still found in the alveolar macrophages (Wilfong et al. 2011).

In a study, various nanomaterials were administered to rats, including titanium dioxide with a target concentration of 0.5, 2 or 10 mg/m³. Primarily, the particles were 15 × 20 nm in size and were administered by inhalation on 5 consecutive days, for 6 hours a day. Concentration-dependent inflammatory reactions were observed in the lungs. Pigment-laden alveolar macrophages and mild diffuse histiocytosis were observed. In the BALF, neutrophils, monocytes, total protein, GGT (gamma-glutamyl transferase) and ALP (alkaline phosphatase) were increased. Apart from a slight increase in the BALF parameters, the effects were reversible during the 3-week recovery period (Landsiedel et al. 2014).

5.2.2 Oral administration

There are no new data available.

5.2.3 Dermal application

There are no new data available.

5.3 Local effects on skin and mucous membranes

There are no new data available.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

Apart from the optimization test with unchanged titanium dioxide described in the supplement from 2009 (Hartwig 2014 a), there are only studies with nanoscale titanium dioxide available for the sensitizing effects of the substance.

In a local lymph node assay (LLNA) with BALB/c mice, preparations with 2.5%, 5% and 10% titanium dioxide in acetone/olive oil (4:1) led to only a slight increase in lymphocyte proliferation of a maximum of about 30% that was not concentration-dependent; a three-fold increase in lymphocyte stimulation was therefore not reached. In a mouse ear swelling test, the induction treatment with the same preparations likewise did not cause sensitization, determined by means of the slight swelling of the ear obtained after provocation with a 10% preparation (Auttachoat et al. 2014).

Investigations with silanized or otherwise coated or modified titanium dioxide in two maximization tests and a Buehler test likewise yielded negative results (SCCNFP 2000; SCCS 2013). The investigations are, however, not used for the evaluation of unchanged titanium dioxide, nor are the investigations carried out in the LLNA and Buehler test with “ultrafine” or nanoscale and evidently also coated varieties of titanium dioxide described in the ECHA registration dossier (ECHA 2018) for titanium dioxide.

5.4.2 Sensitizing effects on the airways

There are no new data available.

5.5 Reproductive and developmental toxicity

There are no new data available.

5.6 Genotoxicity

5.6.1 In vitro

In a re-evaluation of the carcinogenic effects of titanium dioxide in June 2016, the ECHA published a CLH report. Numerous in vitro studies were reviewed, but did not yield any reliable evidence of a genotoxic effect (ECHA 2016).

5.6.2 In vivo

There are no new data available.

5.7 Carcinogenicity

See the supplement from 2009 (Hartwig 2014 a).

In the CLH report (ECHA 2016) re-evaluating the carcinogenic effects of titanium dioxide, reference is made above all to earlier studies. Merely two more recent studies, which are referred to as "supportive data", are described in the following.

In a study, six-week-old female Hras 128 transgenic rats were given titanium dioxide in the form of nanoparticles via intratracheal instillation. The average diameter of the particles was 20 nm. These rats, like the wildtype, are susceptible to developing lung tumours, but have a much higher susceptibility for mammary tumours. Initially, to induce carcinogenesis 33 animals were exposed for two weeks via the drinking water to *N*-bis(2-hydroxypropyl)nitrosamine (DHPN), 9 other animals were given untreated drinking water. The animals were then divided into 4 groups. Exposure to DHPN alone, DHPN followed by 250 µg/ml TiO_2, DHPN followed by 500 µg/ml TiO_2 and 500 µg/ml TiO_2 alone. The solutions were administered to the animals every 2 weeks up to week 16 in amounts of 0.5 ml via intratracheal instillation. The total dose of TiO_2 at the end of the experiment was 0, 0.875, 1.75 and 1.75 mg/rat. In the animals treated with titanium dioxide there was an increase in DHPN-induced hyperplasia of the alveolar cells of the lungs and an increase in mammary adenocarcinomas. Alveolar lesions were only found with previous treatment with DHPN; without DHPN, merely mild inflammatory lesions were observed. The authors explained this by the low carcinogenic potential or short exposure duration. Although the titanium dioxide was instilled into the lungs, small amounts were found also in other organs (Xu et al. 2010).

In another study, groups of 5 or 15 rats were treated with titanium dioxide with a diameter of < 5 µm via intratracheal instillation. Each animal was exposed to 0.5 mg. Also in this case, some animals were pretreated with DHPN. The animals were sacrificed after 30 weeks. In all the animals that were pretreated with DHPN, hyperplasia, adenomas and adenocarcinomas of the lung were observed. Without pretreatment there were no effects on the lungs (Yokohira et al. 2009). The study has methodological shortcomings and does not conform to the test guidelines (ECHA 2016).

Male rats (n = 62) were given intraperitoneal injections of titanium dioxide microparticles (anatase) in doses of 16 g/kg body weight in 5 ml saline. The particles were spherical with an average diameter of 0.14 µm ± 0.3. The animals were investigated after 3, 6 or 18 months. Histological examination revealed at all time points particle-laden mononuclear phagocytic cells, and deposits in the liver and parenchyma of the lungs, phagocytized by alveolar macrophages and Kupffer cells. The particles induced the increased formation of reactive oxygen in alveolar macrophages (Olmedo et al. 2011).

5.8 Other effects

To investigate the effects of titanium dioxide on the production of interleukin IL-1β, particles of different size and form were tested in vitro in macrophage-like human THP-1 cells. Anatase particles of 10 nm, < 25 nm and < 50 µm in size and rutile particles of 10 nm, 30–40 nm and < 5 µm in size were used. In each case 1.5×10^4 cells were treated with titanium dioxide concentrations of 20, 100 or 500 µg/ml, sometimes with LPS (lipopolysaccharide), an activator of the cells used. The concentrations of IL-1β and tumour necrosis factor (TNF)α were determined by ELISA. The characteristics of the particles had severe effects on the production of IL-1β. Especially smaller anatase and larger rutile particles caused higher IL-1β levels (Morishige et al. 2010).

Alveolar macrophages of the rat (NR8383) were treated in vitro with fine (250 nm) and ultrafine (25 nm) titanium dioxide particles. Both types were rapidly taken up by the macrophages. Only the ultrafine particles, however, caused the increased release of extracellular ROS (reactive oxygen species), the expression of haem oxygenase 1 mRNA and the production of TNF-α (Scherbart et al. 2011).

6 Manifesto (MAK value/classification)

The critical effect is the effect of biopersistent granular TiO_2 particles on the lungs.

Carcinogenicity. In 2009, titanium dioxide was initially classified in Carcinogen Category 3A, because at the time a MAK value could not be established.

Titanium dioxide dust is poorly soluble and after inhalation, exposure has effects on the lungs resulting from the general particle effect of granular dusts.

Titanium dioxide induced lung tumours in rats both after inhalation and after intratracheal instillation. The available epidemiological studies yielded no reliable evidence of an increased risk of lung cancer after long-term exposure to fine titanium dioxide dust (Hartwig 2014 a). No new studies are available.

Inflammation in the alveolar and bronchial region, which is accompanied by the release of reactive oxygen species, is mainly responsible for the carcinogenic effects of titanium dioxide in the rat. For this reason, the respirable fraction of titanium dioxide dust is classified in Carcinogen Category 4 in analogy to other biopersistent granular dusts.

MAK value. In analogy to other biopersistent granular dusts, the general threshold limit value for dust of 0.3 mg/m³ × material density applies for the respirable fraction of titanium dioxide.

Peak limitation. The critical effect is the effect of biopersistent granular particles on the lungs. Like other biopersistent granular dusts, titanium dioxide dust (respirable fraction) is therefore classified in Peak Limitation Category II. As the clearance half-life for biopersistent granular dusts is about 400 days, an excursion factor of 8 has been established.

Prenatal toxicity. There are no studies available of the developmental toxicity of titanium dioxide. As titanium dioxide is a poorly soluble dust, prenatal toxicity is not expected if the MAK value of 0.3 mg/m³ × material density for the respirable fraction is observed. The substance is therefore classified in Pregnancy Risk Group C in analogy to the other biopersistent granular dusts.

Germ cell mutagenicity. The available data for genotoxicity did not yield evidence of germ cell mutagenicity caused by titanium dioxide dust. In analogy to other biopersistent granular dusts, the substance is therefore not classified in a category for germ cell mutagenicity.

Absorption through the skin. Dermal absorption of titanium dioxide is not known. In analogy to other biopersistent granular dusts, the substance is not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no clinical findings in humans and no positive results from animal studies for sensitizing effects of titanium dioxide on the skin. There is likewise no evidence of sensitizing effects of titanium dioxide on the airways. Titanium dioxide is therefore not designated with either "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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