The MAK Collection for Occupational Health and Safety

Barium sulfate (respirable fraction)

MAK Value Documentation, addendum – Translation of the German version from 2017

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Keywords: barium sulfate; MAK value; maximum workplace concentration; lung; mechanism of action; general limit value for dust, respirable fraction; peak limitation; developmental toxicity; carcinogenicity; analogy

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Barium sulfate / (barium(2+);sulfate)

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated barium sulfate [7727-43-7]. Barium sulfate is a biopersistent granular dust. Therefore, the respirable fraction of barium sulfate dust has been classified in Carcinogen Category 4 and a MAK value of 0.3 mg/m³ × material density was established for the respirable fraction in analogy to the other biopersistent granular dusts. This classification is based on animal data that showed increased tumor incidences in rats exposed to biopersistent granular dusts in the high dose range. These tumors are regarded to be a consequence of the inflammatory mechanism of action, for which thresholds can be defined. Direct genotoxic effects appear to be of subordinate relevance for the carcinogenicity of biopersistent granular dusts. In analogy to biopersistent granular dusts the Peak Limitation Category II was established for barium sulfate with an excursion factor of 8. Since barium sulfate is not systemically distributed and accumulates only locally in the lungs, no developmental effects due to this dust are expected to occur at the MAK value of 0.3 mg/m³ × material density (respirable, R-fraction). Barium sulfate has accordingly been classified in Pregnancy Risk Group C. Barium sulfate is not designated with either "Sa" or "Sh" or "H".

Keywords

barium sulfate; baryte; heavy spar; blanc fixe; mechanism of action; toxicokinetics; metabolism; 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

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Barium sulfate (respirable fraction)

[7727-43-7]

Supplement 2017

MAK value (2016)	**0.3 mg/m³ R × material density[1)]**
Peak limitation (2016)	**Category II, excursion factor 8**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity (2016)	**Category 4**
Prenatal toxicity (2016)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
Chemical name	barium sulfate baryte (heavy spar, natural $BaSO_4$) blanc fixe (synthetic $BaSO_4$)
Molar mass	233.43 g/mol
Density at 20 °C	4.5 g/cm³
Solubility at 18 °C	2.2 mg/l water; soluble in hot, concentrated sulfuric acid, as a result of the formation of hydrogen sulfate; 0.09% in physiological saline (pH = 7.4) (Cullen et al. 1999)
Solubility product	1.5×10^{-9} mol²/l²

Since the first documentation from 1999 (documentation "Bariumsulfat" 1999, available in German only) and the supplement on prenatal toxicity from 2009 (documentation "Bariumsulfat" 2009, available in German only) the threshold limit value for the respirable fraction of biopersistent granular dusts (documentation

1) The effect of barium sulfate is based on the effect of biopersistent granular dusts. The MAK value of 0.3 mg/m³ for the respirable fraction applies to a material density of 1 g/cm³.

"General threshold limit value for dust (R fraction) (Biopersistent granular dusts)" 2012) has been lowered. Barium sulfate has been examined as to whether it is a biopersistent granular dust.

General information

Barium sulfate is produced from the natural mineral baryte. It is used in the production of petroleum and natural gas, in fillers, putty, modelling clay, coatings, paints, fireworks, and as an X-ray contrast agent in medicine. Barium sulfate in powder form is white (Seroka 2015), with particles of a median diameter of 0.8 to 50 µm (baryte) or < 0.1 to 10 µm (blanc fixe) (determined using the laser diffraction method) (Römpp 2015). Barium sulfate is poorly soluble and is regarded as biopersistent because only 0.09% dissolves in physiological saline solution (pH = 7.4) within 35 days (Cullen et al. 1999).

1 Toxic Effects and Mode of Action

Barium sulfate ($BaSO_4$) particles are taken up by inhalation and ingestion. Dermal absorption of the substance is not known. $BaSO_4$ particles are chemically inert (documentation "Bariumsulfat" 1999, available in German only).

They are poorly soluble dusts which, like the biopersistent granular dusts, have general particle effects. Like other inhaled poorly soluble dusts the particles can accumulate in the lungs and in the lymph nodes and impair the clearance function in the lungs (documentation "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)" 2012).

Genotoxic effects of barium sulfate are not known.

As barium sulfate particles represent poorly soluble biopersistent granular dusts, it is to be expected that tumour formation is particle-related as a result of the overloading of lung clearance.

It is known that high long-term exposure to barium sulfate dust leads to baritosis (non-fibrotic pneumokoniosis) in humans.

Barium sulfate has no toxic effects on reproduction and no sensitizing effects (see documentation "Bariumsulfat" 1999, available in German only).

2 Mechanism of Action

See documentation "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)" 2012.

3 Toxicokinetics and Metabolism

In an inhalation study, 72 male Wistar rats (12 weeks old, 12 animals per examination) were exposed to 37.5 mg $BaSO_4/m^3$ (mass median aerodynamic particle diameter (MMAD) 4.3 ± 1.7 µm) for 7 hours a day, on 5 days a week, for 203 days, and to 75 mg $BaSO_4/m^3$ for 7 hours a day, on 5 days a week, for 119 days (inhalation of particles in whole animal exposure chambers). The lung load was about 10 mg after 119 days following exposure to 75 mg/m^3 and about 5 mg after 203 days following exposure to 37.5 mg/m^3. This corresponds to a load of 27 mg and 17 mg $BaSO_4$/g dry lung tissue, respectively. The authors interpreted the lung load data as showing that barium sulfate in the concentrations tested does not lead to an overloading of lung clearance. Examination of the lymph node load after exposure to barium sulfate dust showed translocation of the particles and confirmed that clearance from the lungs took place. The load increased after 70 days exposure to the higher $BaSO_4$ concentration and was significantly increased after 90 days exposure. In the bronchoalveolar lavage (BAL) fluid the mean neutrophil count (polymorphonuclear neutrophils (PMN)) was increased after 70 days exposure to the higher $BaSO_4$ concentration, reached a plateau after 90 days and remained significantly increased thereafter (percentage of these cells in the lavage 7% to 12%). The mean lymphocyte count in the BAL fluid of the exposed animals was likewise significantly increased (no other details). On the other hand, the mean alveolar macrophage count in the lavage fluid of the exposed animals did not change significantly in comparison with that of the control animals during the entire study period. Histopathological examination revealed an accumulation of pulmonary macrophages, which had phagocytized many of the dust particles, around the deposition sites such as the bifurcations of the terminal airways and the bronchioles. The authors reported that in some cases inflammatory cells, including fibroblasts, had accumulated in the interstitium and that also some particle-laden macrophages were found in the interstitium, which had led to the formation of microgranulomas. In most of the cases in which centro-acinar macrophage accumulation occurred, also type II cell hyperplasia was found. The authors reported that no fibrogenic effects were induced by the barium sulfate particles (Cullen et al. 1999, 2000).

Comparative kinetic investigations from earlier inhalation studies in rats with microscale barium sulfate and more recent studies with nanoscale barium sulfate demonstrate that the clearance of barium sulfate from the lungs is more rapid with decreasing particle size than the clearance mediated by macrophages. This finding is considered to be causally related to the higher dissolution kinetics of smaller particles in the lung tissue. A certain bioavailability is to be assumed depending on the particle size. For microscale dust particles this is of minor importance. The extent of bioavailability depends on the absorption capacity of Ba2+ binding sub-compartments or of the elimination kinetics of these ions (Pauluhn 2014).

4 Effects in Humans

Various publications report the accidental aspiration of barium sulfate used as a contrast agent, for example the fatal intoxication of a 61-year-old female patient who had undergone two CT examinations of the gastrointestinal tract with oral administration of barium sulfate as the contrast agent. Within a few hours non-specific neurological and cardiovascular manifestations occurred, which progressed rapidly and resulted in the death of the patient a few days later. Laboratory investigations revealed an increased barium concentration in the blood and cerebrospinal fluid. The authors suggested that the mechanism of intoxication was the result of progressive intravasation of barium due to stasis of the contrast agent related to intestinal obstruction (Pelissier-Alicot et al. 1999).

Another report describes the case of a woman who accidentally inhaled the contrast agent barium sulfate during an examination of the gastrointestinal tract. The X-ray of the chest revealed the presence of barium sulfate in the alveolar region. The woman suffered pronounced hypoxia and, after endotracheal intubation, artificial respiration was carried out for two weeks. Spontaneous breathing still required support two months after the accident (Shulan and Ali 2013).

Another study describes a case of accidental death. Five weeks before the exposure the 64-year-old patient was in poor health due to metastasizing stomach cancer and laparoscopic cholecystectomy. After oral administration of 100 ml barium sulfate as contrast agent she suddenly vomited and aspirated $BaSO_4$. She subsequently suffered from dyspnoea and bilateral aspiration pneumonia, which, after 35 hours, resulted in acute lung failure (ARDS, *adult respiratory distress syndrome*). Forensic autopsy confirmed the extensive aspiration-related inflammation of the right lobe of the lungs. Histological examination revealed polarized rhombic crystalline accumulations within the alveolar region with granulocytic infiltration and hyaline membrane formation. In addition, barium sulfate particles were found contained in macrophages (Buschmann et al. 2011).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

There are no new data available.

5.2 Subacute, subchronic and chronic toxicity

There are no new data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

There are no data available.

5.3.2 Eyes

In a study, 100 mg barium sulfate was instilled into the conjunctival sac of the right eye of 3 Himalayan rabbits (4.5 to 5.5 months old; 2.4 to 2.5 kg body weight). One hour after the instillation the eyes were rinsed with 20 ml aqueous (0.9%) sodium chloride solution. The left eye served as control. One hour after the instillation the conjunctiva in all animals was reddened. This hyperaemic reaction was reversible after 24 hours. The cornea and iris were not affected. Systemic intolerance reactions were not observed (ECHA 2015).

5.4 Allergenic effects

There are no studies with barium sulfate available. In a valid local lymph node assay barium chloride dihydrate did not have sensitizing effects up to concentrations of 25%. In this study, the application of 5%, 10% and 25% barium chloride resulted in stimulation indices of 1.3, 1.5 and 1.2, respectively. Thus, a tripling of the lymphocyte stimulation was not reached with any of the test concentrations (ECHA 2015).

5.5 Reproductive and developmental toxicity

There are no data available.

5.6 Genotoxicity

5.6.1 In vitro

In the comet assay, barium sulfate concentrations of 1, 100 and 1000 µg/ml did not induce DNA damage in human lymphocytes from 10 healthy donors after incubation for one hour (Braz et al. 2008). In another comet assay with fibroblasts (3T3-L1 cells) barium sulfate concentrations of 0, 10, 100 and 1000 µg/ml likewise did not cause DNA damage (Riberio et al. 2009).

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

See documentation "General threshold limit value for dust (R fraction) (Biopersistent granular dusts)" 2012.

5.8 Other Effects

In a cytotoxicity study, alveolar macrophages from rats and human lung epithelial cells (A549) were exposed to barium sulfate concentrations of 0, 25, 50, 100 and 200 µg/ml for 18 hours. Only at the highest concentration were slight effects observed in the LDH assay (cytotoxicity) and the MTT assay (metabolic activity) (Cullen et al. 1999).

6 Manifesto (MAK value/classification)

The critical effect of the poorly soluble barium sulfate is the non-specific particle effect.

MAK value. Barium sulfate dust is poorly soluble and affects the lungs after inhalation exposure as a result of the general particle effect of biopersistent granular dusts. For microscale barium sulfate dust particles there are no data available for substance-specific toxicity, which would preclude the application of the general threshold limit value for dusts. Therefore, the general threshold limit value for dusts of 0.3 mg/m^3 × material density applies for the respirable fraction of barium sulfate dust. The previous value for the inhalable fraction of 4 mg/m^3 has been retained because there are no data available for a re-assessment.

Peak limitation. The critical effect is the effect of biopersistent granular particles on the lungs. Barium sulfate dust, like other biopersistent granular dusts, is therefore classified in Peak Limitation Category II. As the clearance half-time of biopersistent granular dusts is about 400 days, an excursion factor of 8 has been established.

Prenatal toxicity. There are no studies available for the prenatal toxicity of barium sulfate. As barium sulfate is a poorly soluble dust, effects on development are not to be expected at the level of the MAK value of 0.3 mg/m^3 × material density for the respirable dust fraction. Like other biopersistent granular dusts, barium sulfate is therefore classified in Pregnancy Risk Group C.

Carcinogenicity. There are no epidemiological studies available. As barium sulfate is a poorly soluble biopersistent granular dust, the particle-related induction of tumours after inhalation exposure cannot be excluded in rats. Responsible for this is mainly inflammation in the alveolar or bronchiolar region, which is accompanied by the release of reactive oxygen species. Unlike with biopersistent granular dusts, there are no studies available for barium sulfate. The respirable fraction of the barium sulfate dust is classified in analogy to other biopersistent granular dusts in Carcinogen Category 4.

Germ cell mutagenicity. From the data available for the genotoxicity of barium sulfate, no germ cell mutagenicity is suspected. The substance is therefore not classified in one of the categories for germ cell mutagens.

Absorption through the skin. Dermal absorption of barium sulfate 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 and no animal experiments available for the sensitizing effects of the poorly soluble barium sulfate. The soluble barium chloride was not sensitizing to the skin in a valid local lymph node assay in the mouse, so that barium sulfate is not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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