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Barium compounds (soluble)

MAK Value Documentation, supplement – Translation of the German version from 2010

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Keywords:

barium, toxicity, heart, kidney, MAK value, maximum workplace concentration, irritation, inhalation

MAK value (1966)	**0.5 mg/m³ I (inhalable fraction)**
Peak limitation (2009)	**Category II, excursion factor 8**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2009)	**Pregnancy Risk Group D**
Germ cell mutagenicity	–
BAT value	–

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Barium compounds

Substance	CAS number	Molecular formula	Molar mass [g/mol]	Solubility in water [g/l]
Barium acetate	543-80-6	$Ba(C_2H_3O_2)_2$	255.43	588 (0 °C)[a)]
Barium chloride	10361-37-2	$BaCl_2$	208.25	375 (20 °C)[a)]
Barium chloride dihydrate	10326-27-9	$BaCl_2 \times 2\ H_2O$	244.23	no data[c)]
Barium fluoride	7787-32-8	BaF_2	175.34	1.2 (25 °C)[b)]
Barium hydroxide	17194-00-2	$Ba(OH)_2$	171.38	no data[d)]
Barium hydroxide octahydrate	12230-71-6	$Ba(OH)_2 \times 8\ H_2O$	315.48	56 (15 °C)[d)] 39 (20 °C)[d)]
Barium nitrate	10022-31-8	$Ba(NO_3)_2$	261.38	87 (20 °C)[b)]
Barium oxide	1304-28-5	BaO	153.36	38 (20 °C)[a)]

values from [a)] US EPA (2005), [b)] WHO (1990), [c)] NTP (1994), [d)] ECB (2000)

1 Toxic Effects and Mode of Action

Soluble barium compounds are readily absorbed after inhalation exposure, but poorly after oral administration. The amount absorbed is excreted primarily with the faeces, but also with the urine.

The barium ion induces calcium-mediated processes and, like calcium, is incorporated into and accumulates in bone. In muscles, soluble barium compounds such as barium chloride first have a stimulating effect and then induce paralysis. After acute poisoning, they primarily cause cardiac arrhythmia in humans, dogs and guinea pigs. Barium chloride is nephrotoxic after repeated exposure.

Barium oxide and barium hydroxide are irritating to the skin and corrosive to the conjunctiva.

There are no data available for sensitizing effects induced by soluble barium compounds.

A one-generation study in rats found evidence of foetotoxic effects (reduced birth weights) after exposure to barium at the high dose of 200 mg/kg body weight and day. No studies for prenatal toxicity are available.

Negative results were obtained for the differential killing of bacillus subtilis by barium chloride in an in vitro test system. Barium chloride was not mutagenic in Salmonella mutagenicity tests. The incidences of sister chromatid exchanges or chromosomal aberrations were not increased by exposure to barium chloride. Positive results were obtained with barium chloride in $TK^{+/-}$ mutation assays using the mouse lymphoma cell line L5178Y only in the presence of a metabolic activation system and in some cases at concentrations in the cytotoxic range. No in vivo studies of genotoxicity are available.

In a 2-year study, barium acetate and barium chloride were not carcinogenic in rats and mice.

2 Mechanism of Action

Barium induces calcium-mediated processes in some cases: like calcium, barium leads to the release of neurotransmitters, including the release of acetylcholine from the motor nerve endings or from the sympathetic ganglion

or the release of noradrenaline from the sympathetic nerve endings or catecholamines from the adrenal medulla. However, the mechanism of transmitter release initiated by barium differs from that of calcium. Calcium induces the release of transmitters only after the nerve membrane has been depolarized by a nerve impulse, while barium induces the release of the transmitters without prior depolarization. Whereas the effects of calcium are only temporary and the membrane is ultimately repolarized, the effects of barium are permanent (WHO 1990). For this reason, barium first has a stimulating effect on muscles and then induces paralysis (see Sections 4.1 and 5.1).

In addition, the barium ion is a chemical antagonist of the potassium ion. As the ions of barium and potassium are fairly similar in radius, barium ions can occupy the efflux channels of potassium ions. They remain in the channel 10 000 to 100 000 times longer than potassium ions, inhibiting the passage of potassium to the outside of the cell and leading to a reduction in the extracellular concentration of potassium. In the myocardium, potassium deficiency leads to arrhythmia (Jaritz 2004).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Barium and its soluble compounds are absorbed after inhalation exposure and oral routes of administration (WHO 1990). After inhalation exposure of Syrian hamsters to labelled **barium chloride** ($^{133}BaCl_2$), 61% of the amount deposited on the nasal mucosa was absorbed within 4 hours. After oral administration, 11% of the substance was absorbed (WHO 1990). Age has an influence on the absorption of barium. After oral exposure to labelled **barium chloride**, 14 to 18-day-old rats absorbed 85% of the administered amount, while 22-day-old animals absorbed 63%. Only 7% was absorbed by 6 to 8-week-old and 60 to 70-week-old animals. Hungry rats absorbed more barium chloride (20%) than animals that had been fed (7%) (WHO 1990). When labelled **barium chloride** was given by gavage after a 12-hour fast, 32% of the administered amount was found in the stomach and 11% in the intestines after 4 hours (WHO 1990). In male weanling rats given oral doses of **barium chloride** ($^{133}BaCl_2$), the highest concentrations were found in the blood and soft tissues 30 minutes after exposure. The substance was found in the submaxillary salivary glands, adrenal glands, kidneys and gastric mucosa (WHO 1990).

Shortly (no other details) after inhalation exposure of dogs to **barium chloride** ($^{140}BaCl_2$), increased concentrations of barium were found in the upper respiratory tract, in the stomach and small intestines (30% of the amount administered), in the lungs and tracheobronchiolar tissue (6%) and also in various internal organs (64%) (WHO 1990). Like calcium, **barium** is incorporated into the bones of rats and mice (WHO 1990). Intravenously injected **barium chloride** ($^{133}BaCl_2$) was detected primarily in the bones, cartilage and tissues containing melanin. In foetuses, the radioactivity was detected primarily in the growth zones of the bones (WHO 1990). After inhalation exposure of dogs to labelled **barium chloride**, the radioactivity was found primarily in the bones (WHO 1990). Twenty-four hours after rats were given oral doses of labelled **barium chloride**, the highest concentrations were found in the heart, followed by the eyes, kidneys, liver and blood (WHO 1990). In a drinking water study, young adult rats were given **barium chloride** (0, 10, 50 or 250 mg barium/l) with the drinking water for 4, 8 or 13 weeks. The highest concentrations of barium were determined in the bones. The barium concentrations in the liver, skeletal muscles, heart and bones were dependent on the level of the administered dose, not on the duration of exposure. Therefore, the steady state is reached in the bones of rats after 4 weeks. No differences were found in the concentrations of barium determined in male and female animals (Tardiff et al. 1980). A carcinogenicity study (see also Sections 5.2.2 and 5.2.7) examined barium levels in the plasma and the femurs of rats given **barium chloride** dihydrate with the drinking water for 15 months. The barium concentrations in plasma were significantly increased in male rats given daily doses of barium of 30 mg/kg body weight and day and above and in female rats given doses of 15 mg/kg body weight and day and above (males: 0 mg/kg body weight: 0.9 mg barium/l plasma, 15 mg/kg body weight: 1.0 mg barium/l, 30 mg/kg body weight: 1.25 mg barium/l, 60 mg/kg body weight: 1.6 mg barium/l; females: 0 mg/kg body weight: 0.74 mg barium/l plasma, 15 mg/kg body weight: 0.99 mg barium/l, 35 mg/kg body weight: 0.97 mg barium/l,

75 mg/kg body weight: 1.43 mg barium/l). The barium concentrations determined in the femurs of males given barium doses of 60 mg/kg body weight and day and of females given doses of 75 mg/kg body weight and day were about 400 times as high as the levels determined in control animals (NTP 1994).

The biological half-life of barium in the bones was estimated to be 100 days in mice and 90 to 120 days in rats (NTP 1994).

In rats given **barium chloride** ($^{133}BaCl_2$) by intraperitoneal injection, the labelled barium was excreted primarily with the faeces, but also with the urine. After the injection of **barium chloride**, more than 65% of the administered dose was excreted within 16 days (NTP 1994).

Welders used stick electrodes containing **barium** (8 persons) and self-shielded flux cored wires with and without an integrated exhaust system (5 persons in each case) for 1 week under conditions similar to actual working conditions. The welding fumes of the stick electrodes contained barium, 81% of which was soluble in water and 85% of which was soluble in acids. The welding fumes of the flux cored wires contained barium, 16% of which was soluble in water and 99% of which was soluble in acids. The median barium concentrations (acid-soluble) in air were 4.4 (0.1 to 22.7 mg/m³) and 2.0 mg/m³ (0.3 to 6.0 mg/m³), respectively, for the first two welding types and 0.3 mg/m³ (0.1 to 1.5 mg/m³) for welding with an integrated exhaust system. Over the course of the week, the median barium concentrations in the urine of the 3 exposure groups after the shift were about 45 to 90, 45 to 80 and 15 to 50 µg/g creatinine, respectively (normal: 2 to 12 µg/g creatinine). The barium concentrations in the plasma were less variable at 13 to 25, 11 to 16 and 2 to 4 µg barium/l, respectively (normal: 1 to 4 µg/l) (values determined from the figures). Slight accumulation was observed over the course of the week. The biological half-lives in the blood and urine were calculated to be 10 to 18 hours. The elimination curve displayed first-order kinetics (Zschiesche et al. 1992).

In a 60-year-old man who was given **barium chloride** ($^{133}BaCl_2$) intravenously, 20% of the administered substance was excreted with the urine and faeces within 24 hours, 70% within 3 days and 89.5% within 15 days. After 8 days, 9 times more barium chloride was excreted with the faeces than with the urine (NTP 1994). A half-life of between 24 and 72 hours can be estimated from this study.

Data from humans demonstrated that **barium** crosses the placental barrier and is transported in breast milk (WHO 1990).

3.2 Metabolism

There are no data available.

4 Effects in Humans

4.1 Single exposures

4.1.1 Inhalation

There are no data available.

4.1.2 Ingestion

The **barium** ion first has a stimulating effect in muscles and then induces paralysis. The initial symptoms of toxicity are nausea, vomiting, colic and diarrhoea followed by myocardial and general muscular stimulation with tingling in the extremities (WHO 1990).

In humans, the lethal dose for **barium chloride** was determined to be 11.4 mg/kg body weight (WHO 1990).

Acute renal failure occurred in a 52-year-old man who had ingested 13 g of **barium chloride**. Diarrhoea, abdominal pain, weakness in the legs and paralysis were observed. In the blood, the potassium and urea nitrogen levels were reduced and renal tubule cells and granular casts were determined in the urinary sediment. The patient recovered after undergoing intravenous treatment with magnesium sulfate, saline diuresis and potassium. This case report demonstrated that nephrotoxicity induced by barium chloride is caused by electrolyte imbalance and particularly by a potassium imbalance (NTP 1994).

In a 45-year-old man who ingested a large quantity of **barium** (no other details) with suicidal intent, general muscle weakness and hypokalaemia developed within a few hours. The patient had difficulty swallowing and suffered respiratory failure that required artificial respiration. Renal insufficiency developed, which the patient recovered from only after undergoing haemodialysis for three weeks. In addition, disorders of the extrapyramidal system were induced, which were accompanied by muscle tone and movement disorders. Contraction of the oesophageal sphincter occurred, which caused severe difficulties in swallowing that only subsided after 3 months. Magnetic resonance tomography revealed changes in the basal ganglion and in the thalamus that could not be interpreted. The patient was given artificial respiration for 3 months. After a year he was still very weak, but able to carry out purposeful movements (Fogliani et al. 1993).

In 2 persons who had taken **barium chloride** with suicidal intent, gastroenteritis, loss of consciousness, cardiac arrhythmia and hypokalaemia were reported (NTP 1994).

4.1.3 Dermal absorption

Accidental exposure of a 62-year-old man to melted **barium chloride** caused corrosion of the skin, vomiting, an abnormal electrocardiogram and reduced potassium levels in plasma (ATSDR 2007). Scalding with a **barium chloride** solution induced impairment of the heart function in one person (no other details) and death by cardiac arrest in another (NTP 1994).

4.1.4 Other routes of absorption

A woman developed epithelial dysplasia 48 hours after applying 1.25 mM of a **barium chloride** solution to the squamous cells of the cervix uteri (Ayre 1966).

4.2 Repeated exposure

4.2.1 Inhalation

Healthy welders who had worked with stick electrodes containing barium (8 persons), self-shielded flux cored wires (5 persons) or welding guns with an integrated fume exhaust system (5 persons) for about 3.2 hours a day, on 5 days, were exposed to median barium concentrations of 4.4 (0.1 to 22.7), 2.0 (0.3 to 6.0) and 0.3 (0.1 to 1.5) mg/m^3, respectively (see Section 3.1). The potassium levels were determined prior to exposure; the median concentrations were 3.7 to 4.2 mmol/l plasma. During the week of exposure, the medians ranged from 3.4 to 4.1 mmol/l; the lowest values were found in the group exposed to the lowest concentrations of barium. The differences were not significant. No unusual findings were determined in the clinical and neurological examinations, the electrocardiogram (ECG), the determination of plasma electrolytes and in the activities of the tubular renal enzymes *N*-acetyl-β-D-glucosaminidase and alanine aminopeptidase. Cardiac arrhythmia and circulatory disturbances were observed in 1 person from the high exposure group on one day and the welding operations using stick electrodes were discontinued after 1 hour. These symptoms had been present for some time, but did not occur again during the remaining 2 days of exposure. Therefore, they were probably not related to exposure (Zschiesche et al. 1992). According to a report submitted to the TLV Committee, an internal occupational exposure limit for barium of 0.5 mg/m^3 was employed with satisfactory results for the control of exposure to **barium nitrate** (no other details; ACGIH 2001).

4.2.2 Ingestion

Eleven healthy male volunteers between 27 and 61 years of age and without pre-existing diabetes, high blood pressure or cardiovascular complaints were given 1.5 litres of distilled drinking water purified with activated carbon for the first 2 weeks. Barium (as **barium chloride**) was added to the drinking water at levels of 5 mg per litre from weeks 3 to 6 and 10 mg per litre from weeks 7 to 10. Over the entire study period, blood and urine samples were taken and the blood pressure was determined in the mornings and evenings. Electrocardiograms and 24-hour electrocardiographic monitoring were carried out on 2 successive days at the end of each study period. Overall, no changes in blood pressure or total cholesterol, triglycerides, high and low-density lipoproteins, potassium concentrations, glucose levels and protein levels in the blood or metanephrines, the degradation products of catecholamines, in the urine were determined. Cardiac arrhythmia was not found. An increase in the number of premature atrial contractions was observed; this increase was not statistically significant and was not considered to be clinically relevant by the authors. The calcium levels in serum were slightly increased, but the authors considered the increase too slight to be relevant as a risk factor for possible cardiovascular disorders (Wones et al. 1990). It was concluded that effects are not induced by the uptake of barium at a level of 1.5 mg/day (assuming 10% absorption, as determined in rats).

A number of epidemiological studies investigated the relationship between **barium** levels in drinking water and mortality resulting from cardiovascular diseases. Some of the studies established a questionable negative correlation, while others reported a high correlation. Follow-up studies did not determine any differences in blood pressure, heart and kidney disorders (NTP 1994).

There are no human data available for effects on the skin and mucosa, sensitizing effects, reproductive toxicity, genotoxicity and carcinogenicity.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

In 5 anaesthetized guinea pigs, exposure to **barium chloride** aerosols (0.06 mg barium/m^3 and minute) for up to 60 minutes induced bronchoconstriction, increased blood pressure and cardiac arrhythmia. **Barium fluoride** caused the same effects (Hicks et al. 1986). However, as the reported concentration levels are probably calculated from the amount of liquid fed into the ventilation system and as the substances were administered directly via the ventilation system without a pre-separator, the aerosol may have adhered to the surfaces of the supply tubes and then flowed directly into the trachea in liquid form. A liquid of this kind containing barium chloride may then have caused the bronchoconstriction. This route of administration cannot be regarded as inhalation exposure.

5.1.2 Oral administration

The acute oral toxicity induced by soluble barium compounds is shown in Table 1.

Tab. 1 Acute toxicity of soluble barium compounds after oral administration

Substance	Species	LD_{50} [mg/kg body weight]	LD_{50} [mg barium/kg body weight]	References
barium chloride	rat	118–277	78–183	ATSDR 2007; NTP 1994; WHO 1990
	rat	409–419	270–276	Borzelleca et al. 1988
	mouse	430	284	NTP 1994
barium fluoride	rat	250	165	WHO 1990

In male and female Sprague Dawley rats given single oral **barium chloride** doses of 300 mg/kg body weight (198 mg barium/kg body weight), mortality, reduced body weights and relative liver weights, increased relative kidney weights and the accumulation of fluid in the trachea, changes in liver colour and inflammation in the small and large intestines were found (Borzelleca et al. 1988).

5.1.3 Dermal application

There are no data available.

5.1.4 Subcutaneous, intravenous and intraperitoneal injection

The acute toxicity induced by soluble barium compounds after parenteral administration is shown in Table 2. Oral absorption is poor, as is demonstrated by the higher level of toxicity after parenteral administration in comparison with the oral LD_{50}.

Tab. 2 Acute toxicity of soluble barium compounds after subcutaneous, intravenous and intraperitoneal exposure (WHO 1990)

Substance	Species	Administration	LD_{50} [mg/kg body weight]	LD_{50} [mg barium/kg body weight]
barium acetate	mouse	intravenous	35	19
barium chloride	rat	subcutaneous	178	117
	mouse	intraperitoneal	54	36
	mouse	intravenous	12–18	8–19
barium oxide	mouse	subcutaneous	50	45
barium nitrate	mouse	intravenous	8.5–30	4.5–16

In rabbits, the subcutaneous injection of an aqueous **barium chloride** solution at a dose level of 5 mg/kg body weight (3.3 mg barium/kg body weight) led to death within 2 to 2.5 hours (ACGIH 2001).

In 3 to 5 guinea pigs, intravenous injection of **barium chloride** doses of 0, 4, 8 or 12 mg/kg body weight (0, 2.6, 5.3 or 7.9 mg barium/kg body weight) or **barium fluoride** doses of 0, 4.2 or 8.4 mg/kg body weight (0, 3.3 or 6.6 mg barium/kg body weight) induced bronchoconstriction, an increase in blood pressure and cardiac arrhythmia (Hicks et al. 1986).

Cardiovascular toxicity (no other details) and bradycardia were observed in pigs (no other details) exposed to **barium chloride** by intravenous infusion for 20 minutes at a dose level of 1.7 mg/kg body weight (1.1 mg barium/kg body weight) and minute (total doses: 34 mg barium chloride/kg body weight; 22.4 mg barium/kg body weight) (WHO 1990).

In dogs given **barium chloride** by intravenous infusion at dose levels of 0.2 to 2.0 µmol/kg body weight and minute (0.04 to 0.4 mg barium chloride/kg body weight and minute; 0.0027 to 0.27 mg barium/kg body weight and minute) for 10 to 100 minutes, cardiac stimulation was observed with arrhythmia, diarrhoea, twitching in the skeletal muscles, hypokalaemia, high blood pressure and stimulation of the smooth arterial muscles (WHO 1990).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

Drinking water studies with repeated oral administration of **barium chloride** or **barium acetate** are shown in Tables 3 and 4. The kidneys were found to be the target organ.

The effects on blood pressure, adrenal gland weights and heart function reported in the studies of Perry et al. (1983, 1985), Tardiff et al. (1980) and Kopp et al. (1985) after exposure to very low doses of barium were not confirmed by an NTP study with much higher doses. The feed given to the animals in these studies contained very little calcium; the calcium content was below the daily required dose. Therefore, the effects may have been induced by calcium deficiency (WHO 2001). Nephrotoxicity was observed in a number of studies. The relative kidney weights of rats were increased in a 15-month study with exposure to barium doses of 45 mg/kg body weight and day and above and in a 13-week study with exposure to barium doses of 65 mg/kg body weight and day and above (NTP 1994). However, in the 15-month study, the absolute kidney weights of male rats were reduced at the same dose levels. The NTP does not regard the changes in kidney weights to be biologically relevant (NTP 1994). In a 2-year study, the incidence of nephropathy was significantly increased in mice after exposure to barium at a dose level of 200 mg/kg body weight and day (NTP 1994). In the kidneys, ultrastructural changes in the glomeruli with basal membrane thickening and epithelial changes were observed by electron microscope in male rats given barium at a dose level of 50 mg/kg body weight and day for 16 weeks (McCauley et al. 1985). Thymus weights were significantly reduced in female rats given barium at a dose of 121 mg/kg body weight and day. Following exposure to barium at 136 mg/kg body weight and day, bent posture and renal tubule degeneration were observed in female and male rats. Lymphocyte depletion was found in the spleen, thymus and lymph nodes in animals that died early (Dietz et al. 1992).

In mice given **barium chloride** dihydrate for 13 weeks, the relative and absolute liver weights were reduced after exposure to barium doses of 100 mg/kg body weight and day and above. Mortality was observed at barium doses of 450 mg/kg body weight and day and above (Dietz et al. 1992; NTP 1994).

In animal studies, the primary effect induced by barium was renal damage. Hypokalaemia was observed in the 15-day study only in male rats given barium at a dose level of 110 mg/kg body weight and day, but not in the 13-week study with exposure to barium up to the highest dose tested of 200 mg/kg body weight and day. No studies were carried out in mice (NTP 1994). After exposure of rats to barium for 13 weeks up to the high dose of 200 mg/kg body weight and day, no changes in heart rate or systolic arterial pressure were observed and no unusual findings were determined in the ECG (NTP 1994).

In summary: A significant increase in notable effects was not found in the 2-year study in mice after exposure to barium at dose levels up to 75 mg/kg body weight and day; the same was reported at the interim analysis after 15 months. In rats exposed over the same length of time and at the same dose levels, changes in both the relative and absolute organ weights did not occur at the same time. However, a significant reduction in body weights was determined in female animals. The NOAEL (no observed adverse effect level) for barium was 45 mg/kg body weight and day in rats.

Tab. 3 Effects of soluble barium compounds after repeated oral administration in rats

Species, strain, number per group	Exposure	Findings	References
Barium chloride			
rat, Sprague Dawley, 10 ♂, 10 ♀	**10 days**, 0, 100, 145, 209 or 300 mg barium chloride/kg body weight and day (0, 66, 96, 138 or 198 mg barium/kg body weight and day) gavage	**66 mg/kg body weight**: blood urea nitrogen ↓ (♀); **198 mg/kg body weight**: mortality ↑ (♀); blood urea nitrogen ↓ (♂), ovary weights ↓, ovary:brain ratio ↓	Borzelleca et al. 1988

Tab. 3 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, F344/N, 5 ♂, 5 ♀	**15 days**, 0, 125, 250, 500, 1000 or 2000 mg barium chloride dihydrate/l drinking water (0, 10, 15, 35, 60 or 110 mg barium/kg body weight and day)	**60 mg/kg body weight**: NOAEL; **110 mg/kg body weight**: drinking water consumption ↓ (16%), serum: K^+ ↓ (♂)	NTP 1994
rat, no data, 30 ♂, 30 ♀	**4, 8 or 13 weeks**, 0, 10, 50 or 250 mg barium/l drinking water (young animals: ♂: 0, 2.8, 12.9 or 64.2 mg/kg body weight and day; ♀: 0, 2.7, 14.5 or 68.3 mg/kg body weight and day; old animals: ♂: 0, 1.5, 6.3 or 27.5 mg/kg body weight and day; ♀: 0, 1.9, 6.9 or 35.5 mg/kg body weight and day), in addition 6.6 ± 0.5 µg barium/kg feed (0.5 µg/kg body weight and day)	**1.9 mg/kg body weight and above**: relative adrenal gland weights ↓ (♀) after treatment for 13 weeks; **6.3 mg/kg body weight and above**: relative adrenal gland weights ↓ (♂) after treatment for 8 weeks, but not after 13 weeks; **27.5/35.5 mg/kg body weight**: drinking water consumption ↓, relative adrenal gland weights ↓ (♀) after treatment for 13 weeks, no unusual findings for body weights, or in the biochemical or haematological examination or the gross pathological examination of the liver, kidneys, spleen, heart, brain, muscles, femur or adrenal glands	Tardiff et al. 1980
rat, F344/N, 10 ♂, 10 ♀	**13 weeks**, 0, 125, 500, 1000, 2000 or 4000 mg barium chloride dihydrate/l drinking water (♂: 0, 10, 30, 65, 110 or 200 mg barium/kg body weight and day, ♀: 0, 10, 35, 65, 115 or 180 mg barium/kg body weight and day)	**35 mg/kg body weight and above**: drinking water consumption ↓; **65 mg/kg body weight**: significant ↑ in relative kidney weights (♀), serum: phosphor levels significantly ↑ (♀), possibly an artefact as suggested by the authors, K^+ concentration significantly ↑ (♀), NOAEL; **110/115 mg/kg body weight**: serum: phosphor levels significantly ↑ (♂), possibly an artefact as suggested by the authors, K^+ concentration significantly ↑ (♀), relative and absolute kidney weights significantly ↑ (♀); **180/200 mg/kg body weight**: mortality: 3 (♂), 1 (♀), body weight gains ↓, drinking water consumption ↓, absolute and relative liver weights ↓, relative and absolute kidney weights ↑, absolute heart weights ↓ (♂), relative testis weights ↓, absolute thymus weights ↓ (♀), kidneys: tubular dilation and changes to the tubular epithelium, lymphocyte depletion in the spleen, thymus and lymph nodes in the animals that died early, no effects on heart rate, systolic arterial pressure or ECG after 45 and 90 days, serum: Na^+ and Ca^{2+} concentrations unchanged, K^+ concentration significantly ↑ in ♀ only at 65 and 115 mg/kg body weight, according to the NTP, the NOAEL is 110 mg/body weight and day, as the effects at lower doses were not biologically relevant	Dietz et al. 1992; NTP 1994
rat, Sprague Dawley, 6 ♂	**16 weeks**, 0, 1, 10, 100 or 1000 mg barium/l drinking water (about 0, 0.05, 0.5, 5 or 50 mg/kg body weight and day)	**5 mg/kg body weight**: no data whether examination by electron microscopy was performed also at this dose; **50 mg/kg body weight**: kidneys: ultrastructural changes in the glomeruli with basal membrane thickening and epithelial changes, examination by electron microscopy	McCauley et al. 1985
rat, Sprague Dawley, 10–12 ♂ (no other data)	**20 weeks**, 0 or 250 mg barium/l drinking water (about 0 or 12.5 mg/kg body weight and day)	**12.5 mg/kg body weight**: NOAEL; weekly determinations: large fluctuations in systolic arterial pressure, no substance-related trend	McCauley et al. 1985
rat, Sprague Dawley, 12 ♂	**36 weeks**, 0, 1, 10, 100 or 250 mg barium/l drinking water (about 0, 0.05, 0.5, 5 or 12.5 mg/kg body weight and day)	**12.5 mg/kg body weight**: NOAEL, no unusual histopathological findings, no cardiovascular effects	McCauley et al. 1985

Tab. 3 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 12 ♀	**46 weeks**, 0 or 250 mg barium/l drinking water (about 0 or 12.5 mg/kg body weight and day)	**12.5 mg/kg body weight**: NOAEL, no unusual histopathological findings, no cardiovascular effects	McCauley et al. 1985
rat, Sprague Dawley, 10 ♂	**68 weeks**, 0, 1, 10 or 100 mg barium/l drinking water (about 0, 0.05, 0.5 or 5 mg/kg body weight and day)	**5 mg/kg body weight**: NOAEL, no unusual histopathological findings in 34 types of tissue, feed and water consumption and body weights unchanged	McCauley et al. 1985
rat, Long Evans, 13 ♀	**1, 2, 4, 8, 12, 16 months,** 0, 1, 10 or 100 mg barium/l drinking water (about 0, 0.05, 0.5 or 5 mg/kg body weight and day)	**0.05 mg/kg body weight**: NOAEL; **about 0.5 mg/kg body weight and above**: indirect systolic pressure significantly ↑ after 8 months (animals were heated to 39 °C for 10 minutes before determinations were taken), Ca^{2+} levels in kidneys ↓, K^+ levels in the aorta ↑; **about 5 mg/kg body weight**: indirect systolic pressure significantly ↑ after 1 month, cardiac contractility and conduction ↓, ATP levels in the heart ↓, phosphocreatine ↓, ADP ↑, K^+ and Mg^{2+} levels in serum ↑, kidney weights ↑ only after 4 months, no changes in body weight gains, no other symptoms of toxicity, after 16 months, examination of the myocardium: impairment of contractility, hypersensitivity of the cardiovascular system to sodium pentobarbital, disturbances in energy metabolism, excitability of the cardiac conduction system ↓ ⟶ symptoms of functional cardiomyopathy, effects probably caused by insufficient amount of calcium in the feed	Kopp et al. 1985; Perry et al. 1983, 1985
rat, F344/N, 10 ♂, 10 ♀	**15 months**, 0, 500, 1250 or 2500 mg barium chloride dihydrate/l drinking water (♂: 0, 15, 30 or 60 mg barium/kg body weight and day, ♀: 0, 15, 45 or 75 mg barium/kg body weight and day)	**15 mg/kg body weight and above**: absolute liver weights ↓ (♀) not dose-dependent; **30/45 mg/kg body weight and above**: absolute heart weights ↓ (♂), absolute kidney weights ↓ (♂), relative kidney weights ↑; **60/75 mg/kg body weight**: body weights ↓, Ba concentration in the femur about 400 times higher, Ca^{2+} concentration in the lower part of the femur significantly ↓, no increased incidences of neoplastic or non-neoplastic changes, phosphorus concentrations in serum unchanged, potassium concentration not determined, changes only in relative or absolute organ weights; this is difficult to interpret in conjunction with the decreasing body weights and increasing doses	NTP 1994
rat, F344/N, 50 ♂, 50 ♀	**104 weeks** (♂), **105 weeks** (♀), 0, 500, 1250 or 2500 mg barium chloride dihydrate/l drinking water (♂: 0, 15, 30 or 60 mg barium/kg body weight and day, ♀: 0, 15, 45 or 75 mg barium/kg body weight and day)	**30/45 mg/kg body weight**: NOAEL; **60/75 mg/kg body weight**: body weights ↓ (5% ♂, 11% ♀), drinking water consumption 11%–33% ↓, no increased incidences of neoplastic or non-neoplastic changes, no other details relating to organ toxicity, no determination of organ weights	NTP 1994
Barium acetate			
rat, Long Evans, 52 ♂, 52 ♀	**lifetime** 0 or 5 mg/l drinking water (about 0 or 0.25 mg barium/kg body weight and day)	**0.25 mg/kg body weight**: body weight gains significantly ↑ after 150 days (♀), proteinuria (♂), serum glucose, cholesterol and uric acid: no unusual findings	Schroeder and Mitchener 1975 a

Tab. 4 Effects of soluble barium compounds after repeated oral administration in mice

Species, strain, number per group	Exposure	Findings	References
Barium chloride			
mouse, B6C3F1, 5 ♂, 5 ♀	**15 days**, 0, 40, 80, 173, 346 or 692 mg barium chloride dihydrate/l drinking water (♂: 0, 5, 10, 20, 40 or 70 mg barium/kg body weight and day, ♀: 0, 5, 10, 15, 40 or 85 mg barium/kg body weight and day)	**40 mg/kg body weight**: NOAEL; **70 mg/kg body weight**: relative liver weights ↑ (♂); **85 mg/kg body weight**: absolute liver weights ↑ (♀)	NTP 1994
mouse, B6C3F1, 10 ♂, 10 ♀	**13 weeks**, 0, 125, 500, 1000, 2000 or 4000 mg barium chloride dihydrate/l drinking water (♂: 0, 15, 55, 100, 205 or 450 mg barium/kg body weight and day, ♀: 0, 15, 60, 110, 200 or 495 mg barium/kg body weight and day)	**15 mg/kg body weight**: mortality: 1 animal (♂), absolute testis weights ↓; **100/110 mg/kg body weight and above**: relative and absolute liver weights ↓; **200 mg/kg body weight**: absolute thymus weights ↓ (♀); **450/495 mg/kg body weight**: mortality: 6 ♂, 7 ♀, body weight gains ↓, drinking water consumption ↓ (♂), absolute adrenal gland weights ↓ (♂), relative brain weights ↑, absolute heart weights ↑ (♂), ↓ (♀), absolute and relative thymus weights ↓ (♂), relative kidney weights ↑ (♀), relative lung weights ↑ (♀), debilitation, bent posture, motor activity ↓, nephropathy in the form of tubular dilation and pale eosinophilic finely granular casts and refractile crystals in the tubules or collapsed tubules with closely packed epithelial cells with a scant amount of basophilic stained cytoplasm, a renal capsule with irregular depressions was found over the collapsed or atrophic tubules, in the case of more severe nephrosis: fibrous connective tissue between tubules, lymphocyte depletion in the spleen, thymus and lymph nodes of animals that died early; according to the NTP, the NOAEL is 200 mg/kg body weight	Dietz et al. 1992; NTP 1994
mouse, B6C3F1, 6–10 ♂, 6–10 ♀	**15 months**, 0, 500, 1250 or 2500 mg barium chloride dihydrate/l drinking water (♂: 0, 30, 75 or 160 mg barium/kg body weight and day, ♀: 0, 40, 90 or 200 mg barium/kg body weight and day)	**75/90 mg/kg body weight**: NOAEL; **160/200 mg/kg body weight**: absolute brain weights ↓ (♂), absolute and relative spleen weights ↓ (♀), lymphocyte depletion in the spleen	NTP 1994
mouse, B6C3F1, 50 ♂, 50 ♀	**103 weeks** (♂), **104 weeks** (♀), 0, 500, 1250 or 2500 mg barium chloride dihydrate/l drinking water (♂: 0, 30, 75 or 160 mg barium/kg body weight and day, ♀: 0, 40, 90 or 200 mg barium/kg body weight and day)	**40 mg/kg body weight**: nephropathy: 2/53 ♀ (control 0/50); **75/90 mg/kg body weight**: nephropathy: 2/48 ♂ (controls 1/50), 1/50 ♀, NOAEL; **160/200 mg/kg body weight**: mortality, body weight gains ↓ (9% ♂, 12% ♀), drinking water consumption ↓, nephropathy: 19/50 ♂, 37/54 ♀, no increase in tumour incidences	NTP 1994
Barium acetate			
mouse, Swiss, 42 ♂, 36 ♀	**lifetime** 0 or 5 mg barium chloride/l drinking water (about 0 or 0.25 mg barium/kg body weight and day)	**0.25 mg/kg body weight**: NOAEL, no gross pathological or microscopic organ changes	Schroeder and Mitchener 1975 b

5.2.3 Dermal application

There are no data available.

5.2.4 Subcutaneous injection

Effects on the central nervous system were observed (no other details) in rabbits given **barium chloride** doses of 0, 2, 5 or 10 mg/kg body weight and day (0, 1.3, 3.3 or 6.6 mg barium/kg body weight and day) for 98 or 193 days (ACGIH 2001).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Barium hydroxide and **barium oxide** are highly alkaline in aqueous solution and cause irritation of the skin (ACGIH 2001).

5.3.2 Eyes

Barium hydroxide and **barium oxide** are corrosive to the conjunctiva (ACGIH 2001).

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

Reduced ovary weights and a decreased ovary:brain ratio were observed in rats given **barium chloride** (198 mg barium/kg body weight) by gavage for 10 days (Borzelleca et al. 1988). However, other studies did not report effects on the reproductive organs of male or female rats and mice after exposure to barium chloride dihydrate for 13 to 104 weeks at concentrations up to 2500 mg/l drinking water (60 to 200 mg barium/kg body weight and day) (McCauley et al. 1985; NTP 1994).

In a one-generation study, groups of 20 male rats and 20 male mice were given **barium chloride** dihydrate in the drinking water for 60 days and then mated with female animals that had been given drinking water containing barium chloride dihydrate for 30 days. Rats were exposed to barium chloride dihydrate concentrations of 0, 1000, 2000 or 4000 mg/l drinking water (0, 65, 112 or 190 mg barium/kg body weight and day; mean values from the data for barium chloride doses in male and female animals) and mice to 0, 500, 1000 or 2000 mg/l drinking water (0, 58, 105 or 203 mg barium/kg body weight and day; mean values from the data for barium chloride doses in male and female animals). The percentage of pregnant animals was lower in the control groups (mice: 55% and rats: 40%) than in the groups of treated animals (mice: 55% to 70% and rats: 65%). The decreases in litter sizes were not statistically significant in any of the dose groups. The testis and epididymis weights of male rats and mice were not affected by exposure to barium chloride dihydrate. No changes were observed in the sperm stored in the epididymis as regards number, motility and morphology. No unusual gross-pathological findings were determined in the vagina, cervix, oviducts and ovaries of the females (Dietz et al. 1992).

5.5.2 Developmental toxicity

There are no studies of prenatal developmental toxicity.

After the injection of 20 mg of **barium chloride** into the yolk sac of chicken embryos, defects were observed in the toes only when barium was injected on day 8 of development. Developmental toxicity was not induced when barium was injected on day 4 of development (WHO 1990).

In the one-generation study in rats and mice described in Section 5.5.1, the litter size was slightly decreased and the birth weights of the offspring were significantly decreased in rats of the high dose group (190 mg barium/kg body weight and day). The body weight gains in the offspring were not affected up to postnatal day 5. On postnatal day 5, the differences in the body weights of the offspring of rats of the high dose group and those of the control group were no longer statistically significant. No postnatal effects were determined in the offspring of mice (Dietz et al. 1992). The NOAEL derived from this study for the developmental toxicity of barium in rats was 112 mg/kg body weight and day.

5.6 Genotoxicity

Barium chloride yielded negative results in tests that investigated the differential killing of bacillus subtilis (rec assay) (WHO 1990).

Barium chloride, barium chloride dihydrate and **barium nitrate** were not mutagenic in the Salmonella typhimurium strains TA97, TA98, TA100, TA1535 or TA1537 both with and without a metabolic activation system (Monaco et al. 1990, 1991; NTP 1994).

Barium chloride dihydrate did not induce an increased incidence of sister chromatid exchange or chromosomal aberrations in CHO cells (a cell line derived from Chinese hamster ovary) either with or without metabolic activation (NTP 1994).

Barium chloride dihydrate yielded positive results in $TK^{+/-}$ mutation assays using the mouse lymphoma cell line L5178Y only in the presence of S9 mix ($p < 0.05$). No differentiation was made between large and small colonies (NTP 1994). After exposure to barium chloride dihydrate concentrations of 0, 250, 500, 750 or 1000 µg/ml, the percentage of relative total growth of the cells in the first series of tests was 106%, 89%, 80%, 65% and 34%, respectively, and in the second series 100%, 51%, 22%, 13% and 10%, respectively. The mutation frequency was significantly increased at concentrations of 250 µg/ml and above in the first series of tests and at 500 µg/ml and above in the second series of tests. However, the mutation frequency was never doubled. It is unclear why barium chloride dihydrate was mutagenic only in the presence of S9 mix. It must be taken into account that the positive results in the second series of tests occurred only at toxic concentrations. In summary, because of the cytotoxicity, the results of this test can only be considered an indication that mutagenic effects are induced by barium chloride dihydrate.

As barium chloride did not induce genotoxic effects in CHO cells and there was only a suggestion of a mutagenic potential in mouse lymphoma cells, the overall findings are not sufficient to classify soluble barium compounds as genotoxic.

5.7 Carcinogenicity

The tumour incidence was not increased in groups of 52 male and 52 female Long Evans rats and 42 male and 36 female Swiss mice given **barium acetate** (0 or 5 mg barium/l drinking water) over their whole lifetime (see Section 5.2.2) (Schroeder and Mitchener 1975 a, b).

The tumour incidence was not increased in groups of 6 male Sprague Dawley rats given **barium chloride** with the drinking water for 68 weeks (0, 10, 100 or 250 mg barium/l drinking water, about 0, 0.5, 5.0 or 12.5 mg barium/kg body weight and day) (see Section 5.2.2) (McCauley et al. 1985).

Groups of 60 male and 60 female F344/N rats were given **barium chloride** dihydrate with the drinking water in concentrations of 0, 500, 1250 or 2500 mg/l (about 0, 15, 30, 60 mg barium/kg body weight and day in the males

and about 0, 15, 45 or 75 mg barium/kg body weight and day in the females). The incidences of neoplastic or non-neoplastic changes were not increased after 103 (males) and 104 weeks (females) (NTP 1994).

In addition, the tumour incidence was not increased in groups of 60 male and 60 female B6C3F1 mice given **barium chloride** dihydrate for 104 (males) and 105 weeks (females) at concentrations of 0, 500, 1250 or 2500 mg/l drinking water (males: 0, 30, 75 or 160 mg barium/kg body weight and day, females: 0, 40, 90 or 200 mg barium/kg body weight and day). The incidence of nephropathy was increased primarily in the high concentration group (see Section 5.2.2) (NTP 1994).

6 Manifesto (MAK value/classification)

MAK value and peak limitation. In 2-year and 15-month studies with oral exposure of rats and mice, a NOAEL of about 45 mg/kg body weight and day was derived for general toxic effects such as reduced body weights. However, of the three symptoms of barium poisoning typically induced in humans, nephrotoxicity, hypokalaemia and cardiac arrhythmia, only nephrotoxicity was observed in animal studies. For this reason, the NOAEL determined in animal studies may not offer humans protection from the critical effects. Human data of only limited validity have therefore been taken into account for the derivation of the MAK value: in a study of welders, no concentration-dependent effects on potassium levels and heart and kidney function were observed up to a median barium concentration of 4.4 mg/m^3 (Zschiesche et al. 1992). The test persons were exposed for only 5 days. As half-lives of 10 to 48 hours were determined for barium and the steady state of systemic exposure is achieved after about 5 half-lives, in the worst case, the steady state would be reached only after 2 weeks of exposure. Therefore, the NOAEC (no observed adverse effect concentration) of 4.4 mg/m^3 has to be halved in order to take into consideration potential accumulation. In addition, the length of daily exposure was only 3.2 instead of 8 hours. This has to be taken into account by conversion using Haber's law, which results in a threshold value of about 1 mg/m^3. However, as the number of persons tested was small and the statistical validity of the study is therefore limited, the previous MAK value for barium of 0.5 mg/m^3 has been retained. As barium has a long half-life in the body, short exposure peaks have very little effect on the barium concentration in the blood and soluble barium compounds have been assigned to Peak Limitation Category II with an excursion factor of 8. The highly alkaline compounds barium oxide and barium hydroxide are included in this classification on the basis of findings from the above described study. In this study, the barium oxide formed during welding operations and the barium hydroxide that in turn forms from this did not induce irritation in welders (Zschiesche et al. 1992). After subcutaneous injection, the acute toxicity induced in mice by barium oxide was similar to that induced by barium chloride (see Section 5.1.4). For this reason, the MAK value for barium of 0.5 mg/m^3 and the classification in Peak Limitation Category II with an excursion factor of 8 applies also to barium oxide and barium hydroxide.

Prenatal toxicity. In a one-generation study (Dietz et al. 1992), reduced offspring birth weights were observed only after exposure to the marked maternally toxic barium dose of 190 mg/kg body weight and day. However, as no studies of prenatal toxicity are available, soluble barium compounds have been classified in Pregnancy Risk Group D.

Carcinogenicity. Barium acetate and barium chloride dihydrate are not carcinogenic in rats and mice. Barium compounds (soluble) have not been classified in a carcinogen category.

Germ cell mutagenicity. Barium chloride dihydrate is not mutagenic in bacteria. Evidence of mutagenic effects was found in mammalian cells in only one of two test systems at concentration levels that were cytotoxic in some cases. No genotoxicity studies have been carried out in vivo. Therefore, soluble barium compounds have not been classified in a category for germ cell mutagens.

Sensitization. In the absence of relevant data, soluble barium compounds have not been designated with either "Sa" or "Sh" (for substances which cause sensitization of the airways or skin).

Absorption through the skin. Valid data relating to absorption through the skin are not available for soluble barium compounds. As model calculations cannot be carried out for the salts of soluble barium compounds, the substances have not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

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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