Danish Ministry of the Environment
Environmental Protection Agency

Barium, inorganic water-soluble compounds

Evaluation of health hazards and proposal of health based quality criteria for soil and drinking water

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Title:

Barium, inorganic water-soluble compounds. Evaluation of health hazards and proposal of health based quality criteria for soil and drinking water

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Content

Preface

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to inorganic water-soluble barium compounds and a proposal of health based quality criteria for soil and drinking water. This resulted in 2006 in the present report, which was prepared by Elsa Nielsen and Ole Ladefoged, Department of Toxicology and Risk Assessment, Danish Institute for Food and Veterinary Research, i.e. the present Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The report has been subjected to review and discussion and has been endorsed by a steering committee consisting of representatives from the following Danish authorities:

The Danish Nature Agency,
The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences),
The Danish Veterinary and Food Administration,
The National Board of Health, Denmark,
Danish Regions, (former Amternes Videncenter for Jordforurening)
The Danish Environmental Protection Agency.

The Danish Environmental Protection Agency
Copenhagen, December 2013.

1 General description

This evaluation will only cover water-soluble inorganic barium salts in relation to an estimation of health based quality criteria in soil and drinking water.

1.1 Identity

Compound:	1) Barium chloride 2) Barium nitrate
Molecular formula:	1) $BaCl_2$ 2) $Ba(NO_3)_2$
Molecular weight:	1) 208.25 2) 261.38
CAS-no.:	1) 10361-37-2 2) 10022-31-8
Synonyms:	-

1.2 Physical / chemical properties

Description:	1) Crystals or granules or powder (dihydrate), bitter salty taste. 2) Crystals or crystalline powder.
Purity:	-
Melting point:	1) 962 °C 2) 592 °C
Boiling point:	1) 1560 °C 2) decomposes
Density:	1) 3.856 g/ml 2) 3.24 g/ml
Solubility:	1) Water: 375 g/l (26 °C) 2) Water: 87 g/l (20 °C).
Stability:	-
Incompatibilities:	-
References:	Merck Index (1996), WHO (1996), Beliles (1994), WHO (1990), CICAD (2001).

1.3 Production and use

The two most prevalent naturally occurring barium ores are barite (90-98% barium sulphate) and witherite (barium carbonate). Barite ore is the raw material from which nearly all other barium compounds are derived. (WHO 1990, CICAD 2001).

Barium and its compounds are used extensively by man and is an essential component of a vast number of manufacturing processes.
Barite is used as a weighting agent for oil and gas well drilling muds; it is also used as a filler in a range of industrial coatings, as a dense filler in some plastics and rubber products, in brake linings, and in some sealants and adhesives.
Barium compounds are used in cement, speciality arc welding, glass industries, electronics, roentgenography, cosmetics, pharmaceuticals, inks, and paints. Barium compounds (e.g., barium metaborate, barium polysulphide, and barium fluorosilicate) have also been used as insecticides and rodenticides.
(WHO 1990, CICAD 2001).

In Denmark, barium sulphate is used in ground-water drillings, which may result in an increased level of barium in the water shortly after the drilling (MST 2000).

1.4 Environmental occurrence

Barium is the 16th most abundant non-gaseous element of the Earth's crust, constituting about 0.04% of it. Barium does not exist in nature in the elemental form but occurs as the divalent cation in combination with other elements. The two most prevalent naturally occurring barium ores are barite (barium sulphate) and witherite (barium carbonate). (WHO 1990, CICAD 2001, Beliles 1994, Reeves 1986).

Anthropogenic sources of barium are primarily industrial. Emissions may result from mining, refining, or processing of barium minerals and manufacture of barium products. (CICAD 2001).

1.4.1 Air

Barium is released to the atmosphere during the burning of coal, fossil fuels, and waste. It is generally present in air in particulate form. The levels of barium in air are not well documented; in general, higher concentrations have been observed in areas where metal smelting occurred. (WHO 1990, CICAD 2001).

In the USA, ambient barium concentration ranged from 0.0015 to 0.95 µg/m^3 (US-EPA 1984 - quoted from WHO 1996 and from WHO 1990).
The dust fall has been found to contain an average of 137 mg Ba/g dust (US-EPA 1974 - quoted from WHO 1990 and from CICAD 2001).

1.4.2 Water

Barium in water comes primarily from natural sources. The acetate, nitrate, and halides are soluble in water, but the carbonate, chromate, fluoride, phosphate, and sulphate are quite insoluble; the solubility of barium compounds increases as the pH level decreases. (WHO 1996).

The concentration of barium ions in natural aquatic systems is limited by the presence of naturally occurring anions and possible also by adsorption of these ions onto metal oxides and hydroxides (Hem 1959 - quoted from WHO 1996).

In Denmark, more than 1000 measurements of the barium concentration in ground water have been reported; the reported values are in the range of 1 to 500 µg/l with 10% of the values being greater than 162 µg/l (MST 2000).

The median value for barium in Danish ground water has been reported to be 65 µg/l with a 90 percentile of 159 µg/l (Grundvandsovervågningen 2000).

1.4.3 Soil

In the Earth's crust, the barium concentration is 400 to 500 mg/kg. The background level of barium in soils is considered to range from 100 to 3000 mg/kg with an average of 500 mg/kg (Brooks 1978 - quoted from WHO 1990).

No Danish data are available.

1.4.4 Foodstuffs

Most foods contain less than 0.002 mg Ba/g (Gormican 1970 - quoted from WHO 1996).

Some cereal products and nuts may contain high levels, e.g. bran flakes (0.0039 mg Ba/g), pecans (0.0067 mg Ba/g), and Brazil nuts (up to 4 mg Ba/g) (Mertz 1986 - quoted from WHO 1996).

1.5 Environmental fate

1.5.1 Air

Barium sulphate and carbonate are the forms of barium most likely to occur in particulate matter in the air, although the presence of other insoluble compounds cannot be excluded. The residence time of barium in the atmosphere may be several days, depending on the particle size. Most of the particles are larger than 10 µm in size and rapidly settle back to earth. Particles can be removed from the atmosphere by rainout or washout wet deposition. (WHO 1990).

1.5.2 Water

Soluble barium and suspended particulates can be transported great distances in rivers. In the absence of any removal mechanisms, the residence time of barium in aquatic systems could be several hundred years. For most water samples, the barium ion concentrations are controlled by the amount of sulphate ion in the water. Unless it is removed by precipitation, exchange with soil, or other processes, barium in surface waters ultimately reaches the ocean. (WHO 1990).

1.5.3 Soil

Barium is present in the soil through the natural process of soil formation, which includes the breakdown of parent rocks by weathering. When soluble barium-containing minerals weather and come into contact with solutions containing sulphates, barium sulphate is deposited in available geological faults. If there is insufficient sulphate to combine with barium, the soil material formed is partially saturated with barium. Barium replaces other cations in the soil particles by ion exchange. Barium in soils would not be expected to be very mobile because of the formation of water-insoluble salts and its inability to form soluble complexes with humic and fulvic materials. Under acid conditions, some of the water-insoluble barium compounds may become soluble and move into ground water. (WHO 1990).

1.5.4 Bioaccumulation

Despite relatively high concentrations of barium in soils, only a limited amount accumulates in plants. Barium is actively taken up by legumes, grain stalks, forage plants, red ash leaves, and the black walnut, hickory, and Brazil nut trees. (WHO 1990).

A bioconcentration factor (BCF) for soil to plants of 0.4 has been estimated based on samples of a variety of plant species (mean barium concentration of 29.8 mg/kg) that were taken from a site in which the mean concentration of barium in the soil was 104.2 mg/kg.
Based on the ratio of barium concentration in the soil to whole-body barium concentration, BCFs of 0.2 for terrestrial insects, 0.02 for white-footed mice, and 0.02 for hispid cotton rats have been estimated. Based on dissolved barium concentrations in surface water of 0.07 mg/l and whole-body barium concentrations of 2.1 mg/kg in fish, a BCF of 129 l/kg has been estimated.
Field data were collected during a single summer sampling event, and the authors advised caution in extrapolating the results to terrestrial systems in general.
(Hope et al. 1996 – quoted from CICAD 2001).

1.6 Human exposure

The most important route of exposure to barium appears to be ingestion of barium through drinking water and food (WHO 1990).

A number of different estimates of the dietary intake for adults have been reported. The long-term mean dietary barium intake for adults has been found to be 0.75 mg/day (range 0.44-1.8 mg Ba/day), including food and fluids (ICRP 1974 – quoted from WHO 1996, WHO 1990, CICAD 2001).
Schroeder et al. (1972 – quoted from CICAD 2001) estimated a total of 1.33 mg/day, including food, water, and air (0.001 mg) intake.

According to WHO (1996), the mean daily intake of barium from food, water, and air is estimated to be slightly more than 1 mg Ba/day with food being the primary source for the non-occupationally exposed population; in areas where barium levels in water are high, drinking water may contribute significantly to the total intake of barium.

In Denmark, the latest reported median value of the concentration of barium in the ground water is 65 µg Ba/l (Grundvandsovervågningen 2000). If an average daily

water consumption of 2 litres for adults and a similar concentration in drinking water of barium as in ground water are assumed, the daily intake of barium from drinking water is approximately 130 µg Ba/day corresponding to 2 µg/kg b.w./day assuming an adult body weight of 70 kg.

Based on a barium concentration in air in the USA, ranging from 0.0015 to 0.95 $\mu g/m^3$, the estimated respiratory intake for an adult male is in the range of 0.03 to 22 µg/day (US-EPA 1984 - quoted from WHO 1996).

2 Toxicokinetics

2.1 Absorption and distribution

2.1.1 Inhalation

No quantitative data on the deposition and absorption of barium compounds through inhalation in humans are available (EPA 1999, WHO 1990).

Animal studies provide evidence that barium compounds, including poorly water-soluble compounds such as the sulphate, are absorbed from the respiratory tract. Differences in water solubility account for differences in respiratory tract clearance rates for barium compounds. (EPA 1999, WHO 1990, Reeves 1986).

Soluble forms of barium are readily absorbed from all segments of the respiratory tract (Reeves 1986). Nasal absorption of barium chloride in Syrian hamsters was approximately 60% at four hours after exposure (Reeves 1986, WHO 1990).

2.1.2 Oral intake

In a mass balance study of one man consuming a single dose of 179.2 mg barium in 92 g of Brazil nuts, it was estimated that at least 91% of the dose was absorbed (Lisk et al. 1988 - quoted from EPA 1999).

Based on urinary elimination, it has been reported that 2 males fed controlled diets for 80 weeks absorbed between 2 and 6% of the barium content in their diet (Tipton et al. 1969 – quoted from WHO 1990).

A wide range of absorption efficiencies (0.7 to 85%) has been reported in animal studies. The large variation may be due in part to differences in study duration, species, age, and fasting status of the animals. The presence of food in the gastrointestinal tract appears to decrease barium absorption as well as the presence of sulphate in food, which results in the precipitation of barium sulphate. Soluble barium salts are most readily absorbed, although insoluble compounds may also be absorbed to some extent. Studies indicate that soluble barium is absorbed to the extent of less than 10% in adults, but more in the young. (EPA 1999, WHO 1990, WHO 1996).

2.1.3 Dermal contact

Barium salts are not likely to be absorbed systemically to any great extent (ATSDR 1992).

2.1.4 Distribution

The barium content in humans has been estimated to be in the range of 16 to 22 mg barium (Seiler et al. 1988, National Research Council Canada 1982 - both quoted from HSDB 1998).

The highest concentrations of barium in the body are found in the bone with approximately 90% of the total body burden being found in the bone. In the bone, barium is primarily deposited in areas of active bone growth. The uptake of barium into the bone appears to be rapid. The remainder of the barium in the body is found in soft tissues, i.e., aorta, brain, heart, kidney, spleen, pancreas, and lung (WHO 1990, EPA 1999, Reeves 1986).

Normal levels for barium in various organs of unexposed persons have been published by Schroeder et al. (1972 – quoted from Reeves 1986). The total amount in the skeleton of a 70-kg American adults was estimated at 2 µg/g or about 90% of the total body barium. Other organs with measurable levels included the eye (330 ng/g), lungs (160 ng/g), connective tissue (125 ng/g), skin (50 ng/g), and adipose tissue (35 ng/g). Normal human blood contained 0.08 to 0.4 mg Ba/l with most or all in the plasma fraction.

Based on autopsy data, barium levels in human bone are relatively constant and do not appear to increase with age, ranging from an average value of 7.0 ppm in bone at age 3 months to an average of 8.5 ppm at age 33 to 74 years (Sowden & Stitch 1957 - quoted from WHO 1990).

Barium has been reported to cross the placental barrier in humans (National Research Council 1977 - quoted from WHO 1996).

2.2 Elimination

Barium is excreted in the urine and faeces following oral, inhalation, and parenteral exposure, the rates varying with the route of administration. In both humans and animals, the faeces is the primary route of excretion accounting for about 90% following oral intake (WHO 1990, EPA 1999).

In healthy humans in a state of barium equilibrium (virtually all intake occurring by mouth) approximately 91% of the total output was found in the faeces, 6% in sweat, and 3% in urine (Schroeder et al. 1972 - quoted from WHO 1990 and from Reeves 1986).

The pattern of total excretion in humans fitted a three-component exponential function with biological half-times of 3.6, 34.2, and 1033 days, respectively (Rundo 1967 - quoted from EPA 1999 and from Reeves 1986).

An estimate of the biological half-life for barium in the rat is 90 to 120 days (WHO 1990).

2.3 Mode of action

The barium ion is essentially a muscle poison causing first stimulation and then paralysis. It is a physiological antagonist of potassium, and it appears that the symptoms of barium poisoning are attributable to barium induced hypokalaemia (abnormally low potassium concentration in the blood). The effect is probably due to a transfer of potassium from extracellular to intracellular compartments rather than to urinary or gastrointestinal losses. This imbalance between cells and intercellular fluids results from blockage by barium of the K^+-channel of the Na-K pump in the cell membranes, thereby blocking the potassium efflux from the cells. (Reeves 1986).

Barium possesses chemical and physiological properties that allow it to compete with and replace calcium in processes mediated normally by calcium, particularly those relating to the release of adrenal catecholamines and neurotransmitters, such as acetylcholine and noradrenaline. Barium mimics the action of calcium and can evoke the release of acetylcholine from the neuromuscular junction and from the sympathetic ganglia, of noradrenaline from the sympathetic nerve terminals, and catecholamines from the adrenal medulla. However, the mode of release of neurotransmitter by barium is distinct from that by calcium and is thus unsuitable as a normal physiological mediator. Barium can also affect calcium metabolism by blocking its efflux from cells. (WHO 1990).

3 Human toxicity

Barium is not considered to be an essential element for human nutrition (WHO 1996).

3.1 Single dose toxicity

3.1.1 Inhalation

No data regarding effects following inhalation of soluble barium compounds have been found.

3.1.2 Oral intake

There have been several reports of barium poisoning due to accidental or suicidal ingestion of barium chloride or barium carbonate, or due to the diagnostic use of barium sulphate in gastrointestinal tract studies (WHO 1990).

There are three stages of barium poisoning: a) acute gastroenteritis; b) loss of deep reflexes with onset of muscular paralysis; and c) progressive muscular paralysis. The muscular paralysis seems to be related to severe hypokalaemia. These three stages need not be present in each patient for barium poisoning to be suspected. In most cases, recovery is rapid and uneventful. (WHO 1990).

The symptoms usually begin with the gastrointestinal muscles and acute barium poisoning manifests itself rapidly after ingestion of a toxic dose with nausea, vomiting, colic, and diarrhoea. Skeleto-muscular and cardiac symptoms follow with myocardial and general muscular stimulation and tingling of the extremities. Severe cases of poisoning progress to loss of tendon reflexes, heart fibrillation, and general paralysis including the respiratory muscles, leading to death. (Reeves 1986, WHO 1990, WHO 1996).
Depending on the dose and solubility of the barium salt, death may occur in a few hours or a few days (WHO 1996).

It has been estimated that the oral lethal dose of soluble barium compounds in untreated cases is 3 to 4 g (43-57 mg Ba/kg b.w. assuming an adult body weight of 70 kg) and the threshold for an oral toxic dose is 0.2 to 0.5 g (3 - 7 mg Ba/kg b.w.). The figures apply to the portion absorbed from the gastro-intestinal tract as prompt administration of a soluble sulphate causes precipitation of barium sulphate in the gastro-intestinal tract and thus stops absorption. (Reeves 1986).

3.1.3 Dermal contact

No data regarding effects following dermal contact to soluble barium compounds have been found.

3.2 Repeated dose toxicity

3.2.1 Inhalation

No data regarding effects following inhalation of soluble barium compounds have been found.

3.2.2 Oral intake

Repeated exposures to barium chloride in table salt are believed to have caused recurrent outbreaks of “pa-ping” disease (a transient paralysis resembling familial periodic paralysis) in China; recovery was usually rapid (WHO 1996).

Eleven healthy men completed a 10 week dose-response protocol in which diet was strictly controlled; however, the barium content of the diet was unknown, but the barium content of a typical American hospital diet has been measured and found to be about 0.75 mg/day, which was considered to be a small amount relative to the amount ingested in the drinking water during the study periods (7.5 and 15 mg/day, respectively, for the 5-ppm and 10-ppm periods). Also other aspects of the subjects’ lifestyle known to affect cardiac risk factors were controlled. The barium content (administered as barium chloride) of the drinking water (1.5 l/day) varied from 0 (first 2 weeks) to 5 ppm (0.11 mg Ba/kg b.w./day) (next four weeks), and to 10 ppm (0.21 mg Ba/kg b.w./day) (last four weeks). (Wones et al. 1990).
There were no changes in the following measured parameters: morning or evening systolic or diastolic blood pressures, plasma cholesterol, lipoproteins, or apolipoproteins levels, serum potassium or glucose levels, or urine catecholamine levels. There were no arrhythmias related to barium exposure detected on continuous electrocardiographic monitoring. A trend was seen toward increased total serum calcium levels with exposure to barium, which was judged to be of borderline statistical significance (no data given) and of doubtful clinical significance. The authors concluded that drinking water barium levels of 5 and 10 ppm did not appear to affect any of the known modifiable cardiovascular risk factors.

In two studies by Brenniman et al. (1979, 1981), the association between barium levels in the drinking water and death rates for all cardiovascular diseases (the 1979-study) and the association between barium levels and elevated blood pressure (the 1981-study) were studied in communities with high or low barium levels in the drinking water.

The first study (Brenniman et al. 1979) was a retrospective study, for the years 1971 to 1975, of the association between age- and sex-adjusted cardiovascular death rates and barium levels in the drinking water in 16 communities in the USA. Comparisons of death rates were made between communities that had high barium levels (2 to 10 mg Ba/l) and communities with low barium level (less than 0.2 mg Ba/l). Of those death rates which were higher in the high barium communities, a significant difference was found for male and female deaths combined for “all cardiovascular diseases”, “heart disease (arteriosclerosis)”, and “all causes” (“all causes” are not further explained). When males and females were analysed separately, a significant difference was found only for male deaths from “all cardiovascular diseases”, and for female deaths from “all causes”. According to the authors, deaths rates were adjusted and as many as possible of the demographic and socio-economic status characteristics were controlled; however, additional factors associated with death, other than barium, were considered of concern and there were many uncontrollable factors that could have had a decided impact on the

results in this mortality study. Among these factors was a population change in the high and low barium communities with a considerable increase of the population in two communities in the high barium group whereas the low barium group had a more stable population. Another confounding factor was that many of the individuals in the high barium group who died from cardiovascular diseases lived in the communities less than 10 years and thus, death attributed to cardiovascular disease in these people probably was not highly associated with barium ingestion. Furthermore, since there appears to be a relationship between softened water and cardiovascular diseases (National Academy of Sciences 1977 - quoted from Brenniman et al. 1979), the home water softener presented a confounding factor that was not controlled in the study.

As a follow-up to the 1979-study, a cross-sectional study, for the years 1976-1977, of the association between intake of elevated barium levels in drinking water and elevated blood pressure was conducted (Brenniman et al. 1981). One community (1175 males and females participated) had high barium levels (mean of 7.3 mg Ba/l corresponding to 0.21 mg Ba/kg b.w./day assuming water ingestion of 2 l/day and 70 kg body weight) and one community (1203 males and females participated) had low barium levels (mean of 0.1 mg Ba/l corresponding to 0.003 mg Ba/kg b.w./day); all other drinking water constituents were nearly identical between the two communities. No significant differences ($p>0.05$) were found in blood pressures between the high and low barium communities. Adjustment for duration of exposure, home water softeners, and high blood pressure medication did not alter the findings. Thus, the data from this study indicate that elevated levels of barium in the drinking water do not significantly elevate blood pressure levels in adult males or females. (Brenniman et al. 1981)

3.2.3 Dermal contact

No data regarding effects following dermal contact to soluble barium compounds have been found.

3.3 Toxicity to reproduction

The possible correlation between the level of barium in the drinking water and human congenital malformations has been discussed in two studies. No association was found in one study (Schroeder & Kraemer 1974 - quoted from WHO 1990). In the other study, a negative association between the concentration of barium in drinking water and the presence of malformations in the central nervous system was reported (Morton et al. 1976 - quoted from WHO 1990). According to WHO (1990), the data do not allow any firm conclusions to be drawn.

3.4 Mutagenic and genotoxic effects

No data have been found.

3.5 Carcinogenic effects

No data regarding carcinogenic effects following exposure to soluble barium compounds have been found.

4 Animal toxicity

4.1 Single dose toxicity

4.1.1 Inhalation

No data regarding effects following inhalation of soluble barium compounds have been found.

4.1.2 Oral intake

For barium chloride, an oral LD_{50}-value of 118 mg /kg b.w. has been reported for rats. The lowest lethal oral doses of barium chloride reported were 70 mg/kg b.w. in mice, 90 mg/kg b.w. in dogs, 170 mg/kg b.w. in rabbits, and 76 mg/kg b.w. in guinea-pigs. (WHO 1990).

An oral LD_{50}-value for barium nitrate in rats has been reported to be 355 mg /kg b.w. (WHO 1990).

4.1.3 Dermal contact

No data regarding effects following dermal contact to soluble barium compounds have been found.

4.2 Irritation

4.2.1 Skin irritation

In rabbits, barium nitrate has been reported to cause mild skin irritation (24 hours of exposure) (WHO 1990, EPA 1999).

4.2.2 Eye irritation

In rabbits, barium nitrate has been reported to cause severe eye irritation (24 hours of exposure) (WHO 1990, EPA 1999).

4.3 Sensitisation

No data regarding sensitisation following exposure to soluble barium compounds have been found.

4.4 Repeated dose toxicity

4.4.1 Inhalation

No data regarding effects following inhalation of soluble barium compounds have been found.

4.4.2 Oral intake

4.4.2.1 Rats

Barium chloride was administered by gavage (30, 100, or 300 mg/kg b.w. for 1 day, or 100, 145, 209, or 300 mg/kg b.w. for 10 days) to male and female Sprague-Dawley rats. (Borzelleca et al. 1988 - quoted from WHO 1990).
In the one-day exposure study, decreased body weight and liver/brain weight ratios, and increased kidney weight were found at 300 mg/kg.
In animals exposed for 10 days, decreased survival rate of high-dose females. Reductions in ovary/brain ratios and blood urea nitrogen (BUN) levels were also reported at the high-dose level. No other effects were reported.

Charles River rats (30 animals of each sex per group) were exposed to 0, 10, 50, or 250 mg Ba/l as barium chloride in the drinking water for 4, 8, or 13 weeks (equal to 0, 1.5/1.9, 6.3/6.9, or 27.5/35.5 mg/kg b.w./day in males and females, respectively, after 13 weeks). The animals were fed a commercial diet containing barium at an average concentration of 6.6 $\pm$ 0.5 µg/kg of feed (equal to approximately 0.5 µg Ba/kg b.w./day). (Tardiff et al. 1980).
No adverse effects related to barium ingestion were observed in food consumption, clinical signs, body weights, haematological parameters (haemoglobin, haematocrit, red cell count, leukocyte count, prothrombin time, and fibrinogen), serum enzyme activities (SGOT, SGPT, and BUN), serum ions (sodium, potassium, and calcium), gross pathology, and histopathology of major tissues (liver, kidney, spleen, heart, brain, muscle, femur, and adrenal glands). Water consumption was slightly depressed (no further details) in the high-dose group. A slight decrease (not dose-related) was observed in the relative weight of adrenals of treated versus control animals. Increasing concentrations of barium in the drinking water, but not duration of exposure, produced related increases in barium concentrations in liver, skeletal muscles, heart, and bone, with the highest concentrations observed in bone (7.9/10.3 (controls), 16.2/12.8 (low-dose), 50.5/50.5 (mid-dose), and 214/226 µg Ba/kg (high-dose) in males and females, respectively).

In a 13-week NTP-study, F344/N rats (10 animals of each sex per group) were given barium chloride dihydrate in the drinking water at concentrations of 0, 125, 500, 1000, 2000, or 4000 mg/l (equal to 0, 10/10, 30/35, 65/65, 110/115, or 200/180 mg Ba/kg b.w./day for males and females, respectively). Neurobehavioural (at days 0, 45, and 90) and cardiovascular assessments were conducted as part of this subchronic study. (NTP 1994).
Three males and on female of the high-dose group died. The final mean body weights and mean body weight gains were significantly lower in high-dose animals; drinking water consumption was also lower but not significant. Significantly increases in the absolute and relative kidney weights were observed in females at the two highest dose levels and in relative kidney weights of high-dose males. Kidney lesions (minimal to mild, focal to multifocal dilatation of the proximal convoluted tubules in the outer medulla and the renal cortex) occurred in 3/10 males and 3/10 females at the highest dose level. Minimal to mild atrophy of

the spleen and/or thymus was observed the high-dose rats that died during the study. No other histological changes were observed.
A slight but significant decrease in undifferentiated motor activity was observed in high-dose rats at day 90 of the study; a marginal decrease in this parameter was observed at day 90 in all other exposed groups except in 1000 ppm females. No significant or dose-related changes were observed in other neurobehavioural end-points (thermal sensitivity judged by a tail flick latency test, startle-response to acoustic and air-puff stimuli, forelimb or hind limb grip strength, or hind limb foot splay).
Cardiovascular studies revealed no barium-associated differences in heart rate, systolic blood pressure, or electrocardiogram.
Based on the increased absolute and relative kidney weight in female rats from 2000 ppm, a subchronic NOAEL of 1000 ppm (65 mg Ba/kg b.w./day for both sexes) can be determined with a NOAEL of 2000 ppm (110/115 mg Ba/kg b.w./day for males and females, respectively) for histological lesions in the kidneys.

In a series of studies, McCauley et al. (1985 - quoted from WHO 1990 and from EPA 1999) investigated the histological and cardiovascular effects on rats (Sprague-Dawley, 6-10 animals per group in the various studies) exposed to barium chloride in drinking water for various durations and fed Purina rat chow (contributing a significant barium intake) or Tekland rat chow (insignificant barium intake).
In the histology studies, rats were fed the Purina diet containing 12 ppm barium and exposed to barium in three different drinking water exposure regimens (various concentrations for 36, 48, or 68 weeks). The authors stated, according to EPA, that rats receiving 10 mg/l barium in the drinking water ingested 1.5 mg Ba/kg b.w./day from water and 1 mg Ba/kg b.w./day from the Purina diet. This barium intake was used to estimate total barium intake for the other exposure levels (1, 1.15, 2.5, 16, and 38.5 mg Ba/kg b.w./day for the 0, 1, 10, 100, and 250 mg/l concentrations for all exposure regimens). Histological evaluations of an extensive number of tissues did not reveal barium-related lesions. No alterations in haematocrit levels were observed. A NOAEL for histological lesion of 250 mg/l (38.5 mg Ba/kg b.w./day) can be considered.
In an electrocardiographic study, no significant alterations were observed following exposure of up to 250 mg Ba/l in the drinking water for 5 months. A NOAEL for electrocardiographic parameters of 250 mg/l (38.5 mg Ba/kg b.w./day) can be considered.
In blood pressure studies, normotensive rats received up to 100 mg Ba/l (15 mg Ba/kg b.w./day) in drinking water or in 0.9% sodium chloride solution as drinking water for 16 weeks and unilaterally nephrectomised rats received up to 1000 mg Ba/l (150 mg Ba/kg b.w./day) in the drinking water or in 0.9% sodium chloride solution as drinking water for 16 weeks. The rats in this study were fed the Tekland diet (0.5 µg Ba/kg b.w./day). All of the exposure groups showed fluctuations of blood pressure but no hypertension; the transient changes in blood pressure were, according to WHO, not considered to be dose- or duration-related. A NOAEL of 1000 mg/l (150 mg Ba/kg b.w./day) can be considered for hypertension. Electron microscopic examinations of kidneys in all the rats in the blood pressure studies demonstrated no histopathological changes in arteriolar vessel walls or in tubules of the nephrons. Structural changes in glomeruli were observed at the highest concentration (150 mg Ba/kg b.w./day), which was administered to unilaterally nephrectomised rats only. A NOAEL of 100 mg/l (15 mg Ba/kg b.w./day) can be considered for ultrastructural changes in the glomeruli with the LOAEL being 1000 mg/l (150 mg Ba/kg b.w./day).

Female Long-Evans rats (13 treated rats per duration and 21 control rats per duration) received 0, 1, 10, or 100 mg Ba/l (barium chloride) in the drinking water for 1, 4, or 16 months. The drinking water was fortified with five essential metals (molybdenum, cobalt, copper, manganese, and zinc). All animals received a diet with low trace metal content. (Perry et al. 1983, 1985 - quoted from EPA 1999 and from WHO 1990).
According to WHO (1990), average daily doses of 0, 0.051, 0.51, or 5.1 mg Ba/kg b.w./day were calculated based on water consumption data. According to EPA (1999), the cumulative intake from drinking water and diet was reported by the authors as 16, 28, 134, and 1198 mg Ba/rat for the 0, 1, 10, and 100 ppm groups at 16 months (termination). Based upon these cumulative intakes, EPA calculated estimated doses from water plus diet of 0.098, 0.17, 0.82, and 7.4 mg Ba/kg b.w./day, respectively. Systolic blood pressures were measured at 1, 2, 4, 8, 12, and 16 months. After 8 months of exposure to 10 ppm, mean systolic blood pressure had increased by 6 mm Hg and continued to be significantly elevated through 16 months. Significant increases in mean systolic blood pressure were evident at 100 ppm starting at 1 month and continuing through 16 months. At the highest dose level, there was a decrease at 16 months in cardiac ATP, phosphocreatine, and phosphorylation potential, an increase in ADP levels, and depressed rates of cardiac contraction and electrical excitability. A significant increase in barium levels was observed in the hearts of rats exposed to 100 ppm; no other changes in barium levels or organ weights were reported. The NOAEL for hypertension in rats maintained on low-mineral-content diets was, according to EPA, 1 ppm (0.17 mg Ba/kg b.w./day). For neoplastic findings, see 4.5.2.1.

In a 2-year NTP-study, F344/N rats (60 animals of each sex per group) were given barium chloride dihydrate in the drinking water at concentrations of 0, 500, 1250, or 2500 mg/l (equal to 0, 15/15, 30/45, or 60/75 mg Ba/kg b.w./day for males and females, respectively) (NTP 1994).
No significant increases in mortality were found. Water consumption was decreased in a dose-related manner; at 2500 ppm consumption was 22% and 25% lower than controls in the males and females, respectively. Final mean body weights were slightly lower in male rats receiving 2500 ppm (5% lower than controls) and in female rats receiving 1250 ppm or 2500 ppm (6% or 11% lower, respectively). At the 15-month interim evaluation, the plasma barium levels were significantly increased in males receiving 1250 and 2500 ppm and in all exposed groups of females and barium levels in all portions of femoral bone were approximately 400 times greater in high-dose animals than in controls. A significant increase in relative kidney weights was observed in high-dose females at the 15-month interim evaluation, but no kidney lesions. At the end of the study, there were no increased incidences of non-neoplastic lesions in any organs or tissues that could be attributed to barium chloride dihydrate. Based on the increased relative kidney weight in female rats from 2500 ppm, a chronic NOAEL of 1250 ppm (45 mg Ba/kg b.w./day for both sexes) with a NOAEL of 2500 ppm (60/75 mg Ba/kg b.w./day for males and females, respectively) for histological lesions. For neoplastic findings, see 4.5.2.1.

Long-Evans rats (52 animals of each sex per group) were exposed to 0 or 5 mg Ba/l (barium acetate, 0.61/0.67 mg Ba/kg b.w./day for males and females, respectively, according to EPA 1999) in the drinking water from weaning to natural death. The diet was characterised as a “low metal” diet, but the barium content was not reported. The incidence of proteinuria in males was significantly higher than in controls. Histopathology of heart, lung, kidney, liver, and spleen did not reveal alterations. According to EPA (1999), a LOAEL of 0.61 mg Ba/kg b.w./day can be identified for renal glomerular damage evidenced as proteinuria in male rats. For neoplastic findings, see 4.5.2.1. (Schroeder & Mitchener 1975).

4.4.2.2 Mice

In a 13-week NTP-study, $B6C3F_1$ mice (10 animals of each sex per group) were given barium chloride dihydrate in the drinking water at concentrations of 0, 125, 500, 1000, 2000, or 4000 mg/l (equal to 0, 15/15, 55/60, 100/110, 205/200, or 450/495 mg Ba/kg b.w./day for males and females, respectively) (NTP 1994).
Six males and seven females at 4000 ppm and one male at 125 ppm died during the study. Final mean body weights were significantly decreased (>30%) in animals receiving 4000 ppm and water consumption by high-dose males was 18% lower than that of controls. The forelimb grip strength of high-dose females was significantly lower than that of the controls at 90 days due to debilitation. The absolute and/or relative liver weights of mice exposed at concentrations from 1000 ppm and the absolute and relative thymus weights of high-dose mice were significantly decreased. Nephropathy (mild to moderate, multifocal to diffuse tubule dilatation, regeneration, and atrophy with sporadic birefringent crystals in the lumens of the atrophic tubules) was observed in 10 male and 9 female mice in the high-dose group and grossly, the kidneys were pale and had roughened surfaces. Atrophy of the thymus (necrosis or moderate to marked depletion of thymic lymphocytes) and spleen (diminution of the haematopoietic elements of the red pulp and depletion of lymphocytes in the peri-arteriolar lymphoid sheath) was observed in the majority of early death male and female mice at the high-dose level. Based on the nephropathy and decreased survival observed at 4000 ppm, a subchronic NOAEL of 2000 ppm (205/200 mg Ba/kg b.w./day for males and females, respectively) can be considered.

In the 2-year NTP-study, $B6C3F_1$ mice (60 animals of each sex per group) were given barium chloride dihydrate in the drinking water at concentrations of 0, 500, 1250, or 2500 mg/l (equal to 0, 30/40, 75/90, or 160/200 mg Ba/kg b.w./day for males and females, respectively) (NTP 1994).
Survival at 2500 ppm was significantly lower than that of the controls, which, according to NTP, was attributed to chemical-related renal lesions. Final mean body weights were lower in animals receiving 2500 ppm (9 and 12% for males and females, respectively) than that of controls. At the 15-month interim evaluation, the plasma barium levels were significantly increased in all exposed groups of mice. At the end of the study, there were increased incidences of nephropathy (male: 1/50, 0/50, 2/48, 19/50; female: 0/50, 2/53, 1/50, 37/54); the incidences were significantly increased in the high-dose group only. According to NTP, the nephropathy was morphologically distinct from the spontaneous degenerative lesions that are commonly observed in aging $B6C3F_1$ mice. Based on the nephropathy and decreased survival observed at 2500 ppm, a chronic NOAEL of 1250 ppm (75/90 mg Ba/kg b.w./day for males and females, respectively) can be considered. For neoplastic findings, see 4.5.2.2.

Charles River CD mice (36-54 animals of each sex per group) were exposed to 0 or 5 mg Ba/l (barium acetate, 1.18/1.20 mg Ba/kg b.w./day for males and females, respectively, according to EPA 1999) in the drinking water for their lifetimes. The diet was characterised as a “low metal” diet, but the barium content was not reported. Histopathology of heart, lung, kidney, liver, and spleen did not reveal alterations. For neoplastic findings, see 4.5.2.2. (Schroeder & Mitchener 1975).

4.4.3 Dermal contact

No data regarding effects following dermal contact to soluble barium compounds have been found.

4.5 Toxicity to reproduction

4.5.1 Inhalation

No data regarding toxicity to reproduction following inhalation of soluble barium compounds have been found.

4.5.2 Oral intake

Single-generation reproductive toxicity studies have been performed in rats and mice. Male and female F344/N rats and B6C3F1 mice (20 animals of each sex per group) were exposed to barium chloride dihydrate in the drinking water for 60 days (males) or 30 days (females) at concentrations of 0, 1000, 2000, or 4000 mg/l for rats or at concentrations of 0, 500, 1000, or 2000 mg/l for mice. Doses were not reported in the study, but EPA (1999) estimated doses of 0, 65/65, 110/115, and 200/180 mg Ba/kg b.w./day for males and females rats, respectively, and of 0, 55/60, 100/110, and 205/200 mg Ba/kg b.w./day for males and females mice, respectively, based on dosages from the respective subchronic studies (NTP 1994), see 4.2.2.1 and 4.2.2.1, respectively. (Dietz et al. 1992).
In rats, the pregnancy rates ranged from 40% in the controls to 65% in the 4000 ppm group and did not appear to be adversely affected by barium exposure. No significant alterations in gestation length, pup survival, or the occurrence of external abnormalities were observed. Marginal reductions (not statistically significant) in the number of implants per pregnant dam and live litter size at birth and day 5 were observed in the 4000 ppm group. A significant decrease in live pup weight at birth was observed in the 4000 ppm group (5.2 g vs. 5.7 g in control group), but no significant alterations were observed at 5 days of age.
In mice, low pregnancy rates were also observed, the rates ranged from 55% in controls to 55-70% in the barium exposed groups. No alterations in maternal weight gain, average length of gestation, pup survival, or pup weights were observed. A significant decrease in average litter size was seen on day 0 and 5 at 1000 ppm but not at 2000 ppm. No external anomalies were observed in any of the offspring.
No alterations in epididymal sperm counts, sperm motility, sperm morphology, testicular or epididymal weights, or vaginal cytology were observed in either species.

4.5.3 Dermal contact

No data regarding toxicity to reproduction following dermal contact to soluble barium compounds have been found.

4.6 Mutagenic and genotoxic effects

4.6.1 *In vitro* studies

Negative results have been reported for barium chloride in Ames tests with *Salmonella typhimurium* strains TA1535, TA1538, TA1537, TA97, TA98, and TA100 with or without metabolic activation (NTP 1994; Monaco et al. 1990, 1991 - quoted from EPA 1999), rec assays with *Bacillus subtilis* strains H17 and H45 (Nishioka 1975, Kanematsu et al. 1980 - both quoted from EPA 1999), and a microscreen assay with *Escherichia coli* with metabolic activation (Rossman et al. 1991 - quoted from EPA 1999).

A negative result has also been reported for barium nitrate in the rec assay using *Bacillus subtilis* strains H17 and H45 (Kanematsu et al. 1980 - quoted from EPA 1999).

Barium chloride (dihydrate) induced gene mutations (weak response compared to the positive control methyl methanesulphonate) in L5178Y mouse lymphoma cells at concentrations of 250 µg/ml and above in the presence of metabolic activation (Arochlor 1254-induced male Fischer 344 rat liver S9); without S9, no increase in the number of mutant colonies was observed (NTP 1994).

In cytogenetic tests with cultured Chinese hamster ovary cells, barium chloride (dihydrate) did not induce sister chromatid exchanges or chromosomal aberrations with or without metabolic activation (Arochlor 1254-induced male Sprague-Dawley rat liver S9); no cell cycle delay was observed at any of the concentrations tested in either assay (50 – 5000 µg/ml) (NTP 1994).

Neither barium acetate nor barium chloride decreased the fidelity of DNA synthesis in avian myeloblastosis virus polymerase (Sirover & Loeb 1976 - quoted from EPA 1999 and from WHO 1990).

4.6.2 *In vivo* studies

No data have been found.

4.7 Carcinogenic effects

4.7.1 Inhalation

No data regarding carcinogenic effects following inhalation of soluble barium compounds have been found.

4.7.2 Oral intake

4.7.2.1 Rats

In the 2-year NTP-study in F344/N rats (60 animals of each sex per group) given barium chloride dihydrate in the drinking water at concentrations of 0, 500, 1250, or 2500 mg/l (equal to 0, 15/15, 30/45, or 60/75 mg Ba/kg b.w./day for males and females, respectively), there were no increased incidences of neoplasms that could be attributed to barium chloride dihydrate. Dose-related decreased incidences of adrenal medulla phaeochromocytomas and mononuclear cell leukaemia in male

rats and of mammary gland neoplasms in female rats were observed. For non-neoplastic findings, see 4.2.2.1. (NTP 1994).

In the histology studies by McCauley et al. (1985 - quoted from WHO 1990 and from EPA 1999), no significant increases in the incidence of neoplasms were observed in the barium-exposed rats (250 mg Ba/l as barium chloride in the drinking water for up to 68 weeks). For non-neoplastic findings, see 4.2.2.1.

No significant increases in the number of gross tumours were observed in Long-Evans rats exposed to 5 mg Ba/l (barium acetate, 0.61/0.67 mg Ba/kg b.w./day for males and females, respectively, according to EPA 1999) in the drinking water from weaning to natural death. For non-neoplastic findings, see 4.2.2.1. (Schroeder & Mitchener 1975 - quoted from EPA 1999 and from WHO 1990).

4.7.2.2 Mice

In the 2-year NTP-study in $B6C3F_1$ mice (60 animals of each sex per group) given barium chloride dihydrate in the drinking water at concentrations of 0, 500, 1250, or 2500 mg/l (equal to 0, 30/40, 75/90, or 160/200 mg Ba/kg b.w./day for males and females, respectively), there were no increased incidences of neoplasms that could be attributed to barium chloride dihydrate. The incidences of several neoplasms were significantly lower in high-dose animals than in the controls; this finding was attributed to the marked reduction in survival in the barium-exposed animals. For non-neoplastic findings, see 4.2.2.2. (NTP 1994).

The incidences of lymphoma leukaemia and lung tumours were not different from the incidences in the controls in Charles River CD mice exposed to 5 mg Ba/l (barium acetate, 1.18/1.20 mg Ba/kg b.w./day for males and females, respectively) in the drinking water for their lifetimes. For non-neoplastic findings, see 4.2.2.2. (Schroeder & Mitchener 1975 - quoted from EPA 1999 and from WHO 1990).

4.7.3 Dermal contact

No data regarding carcinogenic effects following dermal contact to soluble barium compounds have been found.

5 Regulations

5.1 Ambient air

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5.2 Drinking water

Denmark:	700 µg Ba/l (MM 2001)
WHO:	700 µg Ba/l (WHO 1996). Rationale: The NOAEL of 7.3 mg Ba/l from the most sensitive epidemiological study (Brenniman et al. 1981) conducted and an uncertainty factor of 10 to account for intraspecies variation.

5.3 Soil

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5.4 Occupational Exposure Limits

Denmark:	0.5 mg Ba/m^3 (soluble barium compounds) (At 2005).
ACGIH:	0.5 mg Ba/m^3 (soluble barium compounds). Rationale: 1) the lack of definitive data upon which to base a TLV and 2) the satisfactory results while employing an internal limit for barium nitrate at a national laboratory. 10 mg Ba/m^3 (barium sulphate). Rationale: barium sulphate is identified as a low to essentially non-toxic dust, but high dust levels have caused a benign pneumoconiosis (baritosis). (ACGIH 1991).

5.5 Classification

Barium compounds (except barium sulphate, compounds of 1-azo-2-hydroxynaphthalenylarylsulphonic acid, and barium compounds listed) are classified for acute toxic effects (Xn;R20/22 - harmful by inhalation and if swallowed).
Barium chloride and barium dichloride are classified for acute toxic effects (Xn;R20 - harmful by inhalation, T;R25 - toxic if swallowed).
Barium carbonate is classified for acute toxic effects (Xn;R22 - harmful if swallowed).
(MM 2002).

5.6 IARC

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5.7 US-EPA

5.7.1 Oral reference dose (RfD)

0.07 mg/kg b.w./day (EPA 1999).

The RfD is based on the no-effect levels identified in the Wones et al. (1990) and Brenniman & Levy (1984) human studies. The lack of adverse effect levels in the human studies precluded deriving an RfD using a benchmark concentration analysis approach. An uncertainty factor of 3 accounts for some database deficiencies and potential differences between adults and children. No modifying factor is proposed. (EPA 1999).

5.7.2 Carcinogenicity

D; not classifiable as to human carcinogenicity (EPA 1999).

The design of the rat and mouse NTP (1994) studies was adequate to assess carcinogenicity. Although adequate chronic oral exposure studies in rats and mice have not demonstrated carcinogenic effects, the lack of adequate inhalation studies precludes assessing the carcinogenic potential of inhaled barium. Barium is considered not likely to be carcinogenic to humans following oral exposure; its carcinogenic potential cannot be determined following inhalation exposure. (EPA 1999).

6 Summary and evaluation

6.1 Description

Barium does not exist in nature in the elemental form but occurs as the divalent cation in combination with other elements.

6.2 Environment

Barium and its compounds are naturally present in the earth's crust and constitutes about 0.04% of the Earth's crust. The two most prevalent naturally occurring barium ores are barite (barium sulphate) and witherite (barium carbonate).

Barium is released to the atmosphere during the burning of coal, fossil fuels, and waste. It is generally present in air in particulate form and barium sulphate and carbonate are the forms of barium most likely to occur in the particulate matter. The residence time of barium in the atmosphere may be several days, depending on the particle size. Particles can be removed from the atmosphere by rainout or wash-out wet deposition. The levels of barium in air are not well documented; in the USA, ambient barium concentrations ranging from 0.0015 to 0.95 µg/m^3 have been reported. No Danish data are available.

Barium in water comes primarily from natural sources. Soluble barium and suspended particulates can be transported great distances in rivers. In the absence of any removal mechanisms, the residence time of barium in aquatic systems could be several hundred years. In Denmark, the median value for barium in ground water has been reported to be 65 µg/l with a 90 percentile of 159 µg/l.

Barium is present in the soil through the natural process of soil formation, which includes the breakdown of parent rocks by weathering. Barium in soils would not be expected to be very mobile because of the formation of water-insoluble salts and its inability to form soluble complexes with humic and fulvic materials. Under acid conditions, some of the water-insoluble barium compounds may become soluble and move into ground water. The background level of barium in soils has been considered to range from 100 to 3000 mg/kg with an average of 500 mg/kg. No Danish data are available.

Despite relatively high concentrations of barium in soils, only a limited amount accumulates in plants. Barium is actively taken up by legumes, grain stalks, forage plants, red ash leaves, and the black walnut, hickory, and Brazil nut trees.
Most foods contain less than 0.002 mg Ba/g; some cereal products and nuts may contain higher levels.

6.3 Human exposure

The intake of barium is primarily from food, although drinking water may contribute significantly in areas with high barium levels in the water. According to WHO (1996), the mean daily intake of barium from food, water, and air is

estimated to be slightly more than 1 mg Ba/day with food being the primary source for the non-occupationally exposed population.

6.4 Toxicokinetics

Soluble barium compounds are absorbed following oral intake. Studies in experimental animals and limited human data indicate that soluble barium is absorbed to the extent of less than 10% in adults, but more in the young. Soluble forms of barium are readily absorbed from all segments of the respiratory tract and nasal absorption of barium chloride in Syrian hamsters has been reported to be approximately 60% at four hours after exposure. Barium salts are not likely to be absorbed systemically to any great extent following dermal contact.

Following absorption, barium accumulates in bone with approximately 90% of the total body burden being found in bone; the remainder of the barium in the body is found in soft tissues, i.e., aorta, brain, heart, kidney, spleen, pancreas, and lung. Barium has been reported to cross the placental barrier in humans.

Barium is excreted in the urine and faeces following oral, inhalation, and parenteral exposure, the rates varying with the route of administration. In both humans and animals, the faeces is the primary route of excretion accounting for about 90% following oral intake.

6.5 Mode of action

Barium stimulates all muscle, skeletal, smooth, and cardiac, irrespective of enervation. It produces strong vasoconstriction by direct stimulation of arterial muscle, violent stimulation of smooth muscle (peristalsis), and stimulation followed by paralysis of the central nervous system.

Barium is a physiological antagonist of potassium, and it appears that the symptoms of barium poisoning are attributable to barium induced hypokalaemia. Barium also possesses chemical and physiological properties that allow it to compete with and replace calcium in processes mediated normally by calcium, particularly those relating to the release of adrenal catecholamines and neurotransmitters, such as acetylcholine and noradrenaline.

6.6 Human toxicity

6.6.1 Single dose toxicity

Several reports of barium poisoning due to accidental or suicidal ingestion of barium have been reported. There are three stages of barium poisoning: a) acute gastroenteritis; b) loss of deep reflexes with onset of muscular paralysis; and c) progressive muscular paralysis; these three stages need not be present in each patient for barium poisoning to be suspected. The threshold for an oral toxic dose has been reported to be 0.2 to 0.5 g (3 - 7 mg Ba/kg b.w.) and the oral lethal dose of soluble barium compounds in untreated cases to be 3 to 4 g (43-57 mg Ba/kg b.w.).

No data regarding effects following inhalation or dermal contact to soluble barium compounds have been found.

6.6.2 Repeated dose toxicity

In a clinical study, 11 healthy men were exposed to barium (as barium chloride) in the drinking water (0 mg/l for 2 weeks; 5 mg/l for the next four weeks); and 10 mg/l for last four weeks). No consistent indication of any adverse cardio-vascular effects was found. The authors concluded that drinking water barium levels of up to 10 mg/l did not appear to affect any of the known modifiable cardiovascular risk factors.

The association between barium levels in the drinking water and death rates for all cardiovascular diseases (retrospective study) and the association between barium levels and elevated blood pressure (cross-sectional study, follow-up to the first study) have been studied in communities with high or low barium levels in the drinking water. In the retrospective study, age-adjusted mortality rates for cardiovascular diseases (combined), heart diseases (arteriosclerosis), and all causes for both sexes together were significantly higher in the elevated barium communities (2 to 10 mg Ba/l) compared with the low-barium communities (less than 0.2 mg Ba/l); however, the study did not control for several important variables. In the cross-sectional follow-up study, no significant differences were found in blood pressures between the high (mean of 7.3 mg Ba/l corresponding to 0.21 mg Ba/kg b.w./day) and low barium communities (mean of 0.1 mg Ba/l corresponding to 0.003 mg Ba/kg b.w./day).

No data regarding effects following inhalation or dermal contact to soluble barium compounds have been found.

6.6.3 Toxicity to reproduction

No adequate human data regarding toxicity to reproduction following exposure to soluble barium compounds have been found.

6.6.4 Mutagenic and genotoxic effects

No human data regarding mutagenic and genotoxic effects following exposure to soluble barium compounds have been found.

6.6.5 Carcinogenic effects

No human data regarding carcinogenic effects following exposure to soluble barium compounds have been found.

6.7 Animal toxicity

6.7.1 Single dose toxicity

Oral LD_{50}-values reported for barium chloride and barium nitrate in rats were 118 and 355 mg /kg b.w., respectively. The lowest lethal oral doses of barium chloride reported ranged from 70 mg/kg b.w. in mice to 170 mg/kg b.w. in rabbits.

No data regarding acute effects following inhalation or dermal contact to soluble barium compounds have been found.

6.7.2 Irritation

Barium nitrate has been reported to cause mild skin irritation and severe eye irritation in rabbits following 24 hours of exposure.

6.7.3 Sensitisation

No data regarding sensitisation following exposure to soluble barium compounds have been found.

6.7.4 Repeated dose toxicity

A decrease in the survival rate of female rats has been observed following oral administration (gavage) of barium chloride (300 mg/kg b.w./day) for 10 days; no adverse effects were observed in male rats at this dose level and no adverse effects in either sex at the lower dose levels (30 or 100 mg/kg b.w./day).

No adverse effects were observed in rats exposed to barium chloride at concentrations up to 250 mg Ba/l in the drinking water for 4, 8, or 13 weeks (equal to 27.5/35.5 mg/kg b.w./day in males and females, respectively, after 13 weeks). Increasing concentrations, but not duration of exposure, produced related increases in barium concentrations in liver, skeletal muscles, heart, and bone, with the highest concentrations observed in bone.

In a 13-week NTP-study, F344/N rats were given barium chloride dihydrate in the drinking water (concentrations of 0, 125, 500, 1000, 2000, or 4000 mg/l, equal to 0, 10/10, 30/35, 65/65, 110/115, or 200/180 mg Ba/kg b.w./day for males and females, respectively). Three males and on female of the high-dose group died. Additional effects in the high-dose group included decreased final mean body weights and mean body weight gains, lower water consumption, a slight but significant decrease in undifferentiated motor activity, increased absolute (females only) and relative kidney weights, kidney lesions, and minimal to mild atrophy of the spleen and/or thymus. Increased absolute and relative kidney weights were also observed in females receiving 2000 mg/l. No other histological changes and no changes in other neurobehavioural end-points were observed. Cardiovascular studies revealed no barium-associated differences. A subchronic NOAEL of 1000 mg/l (65 mg Ba/kg b.w./day for both sexes) can be determined for renal effects (increased absolute and relative kidney weight in female rats from 2000 mg/l) with a NOAEL of 2000 ppm (110/115 mg Ba/kg b.w./day for males and females, respectively) for histological lesions in the kidneys.

In a series of studies investigating the histological and cardiovascular effects on rats exposed to barium chloride in drinking water for various durations, no histopathological changes were observed in any of the tissues examined and no alterations in haematocrit levels at concentrations up to 250 mg Ba/l (38.5 mg Ba/kg b.w./day) for up to 68 weeks. No significant electrocardiographic alterations were observed following exposure of up to 250 mg Ba/l in the drinking water for 5 months. All of the exposure groups (up to 1000 mg Ba/l, 150 mg Ba/kg b.w./day) showed fluctuations of blood pressure but no hypertension and electron microscopic examinations of kidneys in all the rats demonstrated no histopathological changes in arteriolar vessel walls or in tubules of the nephrons; structural changes in glomeruli were observed at the highest concentration (150 mg

Ba/kg b.w./day, unilaterally nephrectomised rats only). A NOAEL of 15 mg Ba/kg b.w./day can be considered for ultrastructural changes in the kidneys, a NOAEL of 38.5 mg Ba/kg b.w./day for histological lesions and electrocardiographic parameters, and a NOAEL of 150 mg Ba/kg b.w./day for hypertension.

Rats given 10 or 100 mg Ba/l in their drinking water for 16 months experienced hypertension and at 100 mg Ba/l, analysis of myocardial function revealed significantly altered cardiac contractility and excitability, and myocardial metabolic disturbances. The NOAEL for hypertension was 1 mg Ba/l (0.17 mg Ba/kg b.w./day).

In the 2-year NTP-study, F344/N rats were given barium chloride dihydrate in the drinking water (concentrations of 0, 500, 1250, or 2500 mg/l, equal to 0, 15/15, 30/45, or 60/75 mg Ba/kg b.w./day for males and females, respectively). There was a dose related decrease in water consumption. At the 15-month interim evaluation, plasma barium levels were significantly increased (males at 1250 and 2500 ppm and all exposed groups of females), barium levels in femoral bone were approximately 400 times greater in high-dose animals than in controls, and a significant increase in relative kidney weights was observed in high-dose females. No increased incidences of non-neoplastic lesions were observed. A chronic NOAEL of 1250 mg/l (45 mg Ba/kg b.w./day for both sexes) can be determined for renal effects (increased relative kidney weight in female rats at 2500 mg/l) with a NOAEL of 2500 mg/l (60/75 mg Ba/kg b.w./day for males and females, respectively) for histological lesions in the kidneys.

No histopathological alterations were observed in tissues from Long-Evans rats exposed to 5 mg Ba/l (barium acetate, 0.61/0.67 mg Ba/kg b.w./day for males and females, respectively) in the drinking water from weaning to natural death. The incidence of proteinuria in males was significantly higher than in controls.

In a 13-week NTP-study, $B6C3F_1$ mice (10 animals of each sex per group) were given barium chloride dihydrate in the drinking water (concentrations of 0, 125, 500, 1000, 2000, or 4000 mg/l, equal to 0, 15/15, 55/60, 100/110, 205/200, or 450/495 mg Ba/kg b.w./day for males and females, respectively). Six males and seven females at 4000 ppm and one male at 125 ppm died during the study. Additional effects in the high-dose group included significantly decreased final mean body weights, lower water consumption by males, lower forelimb grip strength of females, significantly decreased absolute and/or relative liver weights and absolute and relative thymus weights, nephropathy in 10 male and 9 female mice, and atrophy of the thymus and spleen. Absolute and/or relative liver weights were also significantly decreased at 1000 and 2000 ppm. Based on the nephropathy and decreased survival observed at 4000 ppm, a subchronic NOAEL of 2000 ppm (205/200 mg Ba/kg b.w./day for males and females, respectively) can be considered.

In the 2-year NTP-study, $B6C3F_1$ mice were given barium chloride dihydrate in the drinking water (concentrations of 0, 500, 1250, or 2500 mg/l, equal to 0, 30/40, 75/90, or 160/200 mg Ba/kg b.w./day for males and females, respectively). Survival at 2500 ppm was significantly decreased. At the 15-month interim evaluation, the plasma barium levels were significantly increased in all exposed groups of mice. The incidence of nephropathy was significantly increased in the high-dose group. Based on the nephropathy and decreased survival observed at 2500 ppm, a chronic NOAEL of 1250 ppm (75/90 mg Ba/kg b.w./day for males and females, respectively) can be considered.

No histopathological alterations were observed in tissues from Charles River CD mice exposed to 5 mg Ba/l (barium acetate, 1.18/1.20 mg Ba/kg b.w./day for males and females, respectively, according to EPA 1999) in the drinking water for their lifetimes.

6.7.5 Toxicity to reproduction

Single-generation reproductive toxicity studies performed in rats and mice did not reveal any reproductive toxicity at doses of up to about 200 mg Ba/kg b.w./day when barium chloride was administered in the drinking water. Low pregnancy rates were observed in both exposed rats and mice, as well as in the control groups.

No data regarding toxicity to reproduction following inhalation or dermal contact to soluble barium compounds have been found.

6.7.6 Mutagenic and genotoxic effects

Negative results have been reported for barium chloride and barium nitrate for gene mutations in bacterial assays with or without metabolic activation.
Neither barium acetate nor barium chloride decreased the fidelity of DNA synthesis in avian myeloblastosis virus polymerase.
In mammalian cells, barium chloride did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without activation.
Barium chloride (dihydrate) induced gene mutations in L5178Y mouse lymphoma cells with metabolic activation but not in the absence of metabolic activation.

No *in vivo* studies have been found.

6.7.7 Carcinogenic effects

In the 2-year NTP-studies in F344/N rats and $B6C3F_1$ mice given barium chloride dihydrate in the drinking water (concentrations of 0, 500, 1250, or 2500 mg/l (equal to 0, 15/15, 30/45, or 60/75 mg Ba/kg b.w./day for male and female rats, respectively; and equal to 0, 30/40, 75/90, or 160/200 mg Ba/kg b.w./day for male and female mice, respectively), there were no increased incidences of neoplasms that could be attributed to barium chloride dihydrate.

No significant increases in the incidence of neoplasms were observed in Sprague-Dawley rats exposed (up to 250 mg Ba/l as barium chloride) in the drinking water for up to 68 weeks.

No significant increases in the number of gross tumours were observed in Long-Evans rats or Charles River CD mice exposed to 5 mg Ba/l (barium acetate) in the drinking water for their lifetime.

6.8 Evaluation

The available studies in experimental animals as well as limited human data indicate that soluble barium is absorbed following oral intake to the extent of less than 10% in adults, but may be higher in children. Soluble forms of barium are readily absorbed from all segments of the respiratory tract whereas absorption

following dermal contact is not considered to occur at any great extent. Following absorption, barium accumulates in bone with approximately 90% of the total body burden being found in bone. In both humans and animals, the faeces is the primary route of excretion accounting for about 90% following oral intake.

Soluble barium compounds are moderately to highly toxic in humans and experimental animals following oral intake of a single dose with a reported threshold for an oral toxic dose in humans of 0.2 to 0.5 g (3 - 7 mg Ba/kg b.w. for adults), an oral lethal dose of 3 to 4 g (43-57 mg Ba/kg b.w. for adults, in untreated cases). In experimental animals, oral LD_{50}-values for barium chloride and barium nitrate in rats of 118 and 355 mg /kg b.w., respectively have been reported with the lowest lethal oral doses of barium chloride being from 70 mg/kg b.w. in mice to 170 mg/kg b.w. in rabbits.
No data regarding acute effects following inhalation or dermal contact to soluble barium compounds have been found.

Barium nitrate has been reported to cause mild skin irritation and severe eye irritation in rabbits following 24 hours of exposure; no human data are available. No data regarding sensitisation following exposure to soluble barium compounds have been found. Thus, the available data are not adequate in order to evaluate the irritative and sensitisation potentials of soluble barium compounds.

Barium causes cardiovascular effects, including hypertension, in humans following acute ingestion of high doses. The association between barium levels in the drinking water and cardiovascular effects has been investigated in a clinical study and in two epidemiological studies (retrospective, cross-sectional follow-up to the retrospective study).
In the clinical study, no indication of any adverse cardio-vascular effects was found in 11 healthy men exposed to barium (as barium chloride) in the drinking water for 8 weeks at concentrations of up to 10 mg Ba/l (0.21 mg Ba/kg b.w./day).
In the retrospective study, age-adjusted mortality rates for cardiovascular diseases (combined), heart diseases (arteriosclerosis), and all causes for both sexes together were significantly higher in the population living in communities with elevated barium (2 to 10 mg Ba/l) compared with the population living in low-barium communities (less than 0.2 mg Ba/l); however, the study did not control for several important variables.
In the cross-sectional follow-up study, no significant differences were found in blood pressures between the high (mean of 7.3 mg Ba/l corresponding to 0.21 mg Ba/kg b.w./day) and low barium communities (mean of 0.1 mg Ba/l corresponding to 0.003 mg Ba/kg b.w./day).
Based on the clinical study and the cross-sectional follow-up study, a NOAEL for cardiovascular effects, including hypertension, of 0.21 mg Ba/kg b.w./day is considered for humans exposed to soluble barium compounds in the drinking water. A LOAEL cannot be determined based on the available human studies.
No data regarding effects following inhalation or dermal contact to soluble barium compounds have been found.

Additional evidence for the hypertensive effects of barium can be considered from drinking water studies in rats given diets low in trace minerals, calcium, and potassium; the NOAEL for hypertension in these studies (barium chloride in the drinking water for up to 16 months) was 1 mg Ba/l (0.17 mg Ba/kg b.w./day) with a LOAEL of 10 mg Ba/l (0.82 mg Ba/kg b.w./day)
Studies in which rats and mice were administered barium in drinking water and fed adequate diets indicate that renal effects are a more sensitive endpoint of barium toxicity in rats than is hypertension. Based on the 13-week and 2-year NTP-studies in rats and mice, a NOAEL of 45 mg Ba/kg b.w./day is considered for renal effects

(increased relative kidney weight) in rats and of 75 mg Ba/kg b.w./day for renal effects (nephropathy) in mice whereas a NOAEL of 150 mg Ba/kg b.w./day (highest dose level in the study) is considered for hypertension in rats. In one study, a NOAEL of 15 mg Ba/kg b.w./day has been reported for ultrastructural changes in the kidneys (glomeruli) of rats with a LOAEL of 150 mg Ba/kg b.w./day observed in unilaterally nephrectomised rats, the only group in the study receiving the high dose. The NOAEL for ultrastructural changes is lower than those observed for renal effects in the NTP-studies; however, detection of the glomerular effects requires, according to EPA (1999) electron microscopy, which was not performed in the NTP-studies on barium and which is not performed according to guideline studies in general. Furthermore, the applicability of data from renal toxicity studies in unilaterally nephrectomised rats to intact rats or humans is uncertain because removal of renal tissue may affect sensitivity of the remaining tissue to nephrotoxins (EPA 1999).
Overall, a NOAEL of 45 mg Ba/kg b.w./day is considered for renal effects in experimental animals based on increased relative kidney weight observed in female rats at the 15-month interim evaluation in the 2-year NTP-study at the next dose level (75 mg Ba/kg b.w./day); no histological lesions were observed in the kidneys at the NOAEL or LOAEL for increased relative kidney weight.
No data regarding effects following inhalation or dermal contact to soluble barium compounds have been found.

Data on the reproductive and developmental toxicity of soluble barium compounds are limited to a single-generation reproductive toxicity study in rats and mice, which did not reveal any reproductive toxicity at doses of up to about 200 mg Ba/kg b.w./day in the drinking water. However, the results should be interpreted cautiously because of the low pregnancy rates in both exposed and control rats and mice.

The data on the mutagenicity and genotoxicity of soluble barium compounds are limited to *in vitro* tests in bacteria and in mammalian cells. Most of these tests have yielded negative results. The only test yielding a positive result is a gene mutation test in L5178Y mouse lymphoma cells; the positive result, which was weak compared to the positive control methyl methanesulphonate, was only observed in the presence of metabolic activation and only at concentrations from 250 µg/ml. Overall, soluble barium compounds are considered to be without mutagenic and genotoxic properties.

Carcinogenicity studies have been performed in rats and mice exposed to barium chloride or barium acetate in the drinking water for lifetime. No carcinogenic effects were observed in any of the studies, including the NTP-studies. In fact, significant negative trends in the incidence of leukaemia, adrenal tumours, and mammary gland tumours were observed in the NTP-study in rats. The data are considered adequate in order to consider that soluble barium compounds are not likely to be carcinogenic to humans following oral exposure. The carcinogenic potential cannot be determined following inhalation exposure or dermal contact.

6.8.1 Critical effect and NOAEL

The available human data indicate that cardiovascular effects, inclusive hypertension, are the critical effects following oral exposure to soluble barium compounds. Additional evidence for the hypertensive effects of barium has been obtained in drinking water studies in rats given diets low in trace minerals, calcium, and potassium. Studies in which rats and mice were administered barium in drinking water and fed adequate diets indicate that renal effects may be a more

sensitive endpoint in rats than is hypertension. No data are available in humans for an evaluation of renal effects following exposure to soluble barium compounds.

No data regarding effects following inhalation or dermal contact to soluble barium compounds have been found.

A NOAEL for cardiovascular effects, including hypertension, of 0.21 mg Ba/kg b.w./day is considered for humans exposed to soluble barium compounds in the drinking water; a LOAEL cannot be determined based on the available human studies implicating that the NOAEL for cardiovascular effects in humans may be higher than 0.21 mg Ba/kg b.w./day.
A NOAEL of 150 mg Ba/kg b.w./day (highest dose level in the study) is considered for hypertension in rats; a LOAEL cannot be determined based on the available studies in experimental animals implicating that the NOAEL for hypertension in experimental animals may be higher than 150 mg Ba/kg b.w./day.
A chronic NOAEL of 45 mg Ba/kg b.w./day is considered for renal effects in experimental animals based on increased relative kidney weight observed in female rats at the next dose level (75 mg Ba/kg b.w./day); no histological lesions were observed in the kidneys at 75 mg Ba/g b.w./day (the highest dose level in the chronic study). A subchronic NOAEL of about 110 mg Ba/kg b.w./day is determined for histological lesions in the kidneys of rats with a subchronic LOAEL of about 180 mg Ba/kg b.w./day. In mice, a chronic NOAEL of about 75 mg Ba/kg b.w./day is determined for histological lesions in the kidneys with a chronic LOAEL of about 160 mg Ba/kg b.w./day.

For the purpose of estimating quality criteria in soil and drinking water, the NOAEL of 0.21 mg Ba/kg b.w./day for cardiovascular effects, inclusive hypertension, in humans will form the basis. This NOAEL is considered to take into account the possibility of barium-induced renal effects in humans although no data are available for an evaluation of renal effects following exposure to soluble barium compounds, but because the chronic and subchronic NOAELs for renal effects in experimental animals are more than 200 times higher than the NOAEL in humans for cardiovascular effects.

Additionally, soluble barium compounds are moderately to highly toxic in humans following oral intake of a single dose with a reported threshold for an oral toxic dose in humans of 0.2 to 0.5 g (3 - 7 mg Ba/kg b.w. for adults) and an oral lethal dose of 3 to 4 g (43-57 mg Ba/kg b.w. for adults, in untreated cases). The reported threshold for an oral toxic dose in humans of 200 mg will form the basis for the estimation of a quality criterion in soil for acute ingestion of a single high amount of soil.

7 TDI and quality criteria

7.1 TDI

The TDI is calculated based on a NOAEL of 0.21 mg Ba/kg b.w./day observed for cardiovascular effects, inclusive hypertension, in humans:

$$TDI = \frac{NOAEL}{UF_I * UF_{II} * UF_{III}} = \frac{0.21 \text{ mg Ba/kg b.w./day}}{1 * 10 * 1}$$

$$= 0.021 \text{ mg Ba/kg b.w./day}$$

The uncertainty factor UF_I is set to 1 as human data are used. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 1 because the NOAEL is derived from a well conducted clinical study and a well conducted epidemiological study, both evaluating the relevant route of exposure (oral).

7.2 Allocation

The general population is predominantly exposed to barium from food, although drinking water may contribute significantly in areas with high barium levels in the water. According to WHO (1996), the mean daily intake of barium from food, water, and air is estimated to be slightly more than 1 mg Ba/day with food being the primary source for the non-occupationally exposed population.

In Denmark, the latest reported median value of the concentration of barium in the ground water is 65 µg Ba/l (Grundvandsovervågningen 2000). If an average daily water consumption of 2 litres for adults and a similar concentration in drinking water of barium as in ground water are assumed, the daily intake of barium from drinking water is approximately 0.13 mg Ba/day for adults, which is about one-tenth of the total daily intake according to WHO (1996).

As food (and drinking water) is the predominant source of barium, only 10% of the TDI is allocated to ingestion of soil.

No allocation is suggested in relation to drinking water because the TDI is based on a NOAEL from drinking water studies in which the contribution of barium from food is considered as being low compared to the contribution of barium from the drinking water.

7.3 Quality criterion in soil

The quality criterion in soil QC_{soil} is calculated based on the TDI of 0.021 mg Ba/kg b.w. per day and assuming a daily ingestion of 0.2 g soil for a child weighing 10 kg (w_{child}):

$$QC_{soil} = \frac{TDI * X * w_{child}}{ingestion_{soil}} = \frac{0.021 \text{ mg Ba/kg day} * 0.1 * 10 \text{ kg}}{0.0002 \text{ kg/day}}$$

$$= 105 \text{ mg Ba/kg soil}$$

Additionally, soluble barium compounds are moderately to highly toxic in humans following oral intake of a single dose. Based on the reported threshold for an oral toxic dose in humans of 200 mg barium, a quality criterion for acute toxicity is calculated assuming that a child weighing 10 kg (w_{child}) occasionally might ingest up to 10 g of soil. The uncertainty factor UF_I is set to 1 as human data are used. The UF_{II} is set to 10 to protect the most sensitive individuals in the human population. The UF_{III} is set to 10 because a reported threshold for an oral toxic dose in humans is used, but for which some uncertainty exists; as there is a factor of 10 between the reported threshold and the reported oral lethal dose, a factor of 10 for UF_{III} as being sufficient.

$$QC_{soil} = \frac{threshold * w_{child}}{UF_{(I*II*III)} * ingestion_{soil}} = \frac{20 \text{ mg Ba/kg} * 10 \text{ kg}}{1 * 10 * 10 * 0.01 \text{ kg soil}}$$

$$= 200 \text{ mg/kg soil}$$

A quality criterion of 105 mg Ba/kg soil has been calculated based on children's ingestion of soil in small amount repeatedly. Furthermore, a quality criterion of 200 mg Ba/kg soil has been calculated for acute toxicity based on children's ingestion of a higher amount of soil occasionally. A quality criterion of 100 mg Ba/kg soil is proposed.

7.3.1 Quality criteria in soil

Quality criterion: 100 mg Ba/kg soil.

7.4 Quality criterion in drinking water

The quality criterion in drinking water QC_{dw} is calculated based on the TDI of 21 µg/kg b.w. per day and assuming a daily ingestion of 2 litres of drinking water for an adult weighing 70 kg (w_{adult}):

$$QC_{dw} = \frac{TDI * Y * w_{adult}}{ingestion_{dw}} = \frac{21\ \mu g\ Ba/kg\ day * 70\ kg}{2\ l/day}$$

$$= 735\ \mu g\ Ba/l$$

A quality criterion of 735 μg Ba/l has been calculated based on intake of drinking water. A guideline value of 700 μg Ba/l is proposed, which is the guideline value at present for barium (MM 2001).

7.4.1 Quality criterion in drinking water

700 μg Ba/l.

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Barium, inorganic water-soluble compounds

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to inorganic water-soluble barium compounds. This resulted in 2006 in the present report which includes health-based quality criteria for the mentioned barium compounds in soil and in drinking water.

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