Danish Ministry of the Environment
Environmental Protection Agency

Beryllium, inorganic and soluble salts

Evaluation of health hazards and proposal of a health based quality criterion for drinking water

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Title:

Beryllium, inorganic and soluble salts.
Evaluation of health hazards by exposure and proposal of a health based quality criterion for drinking water

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Content

Preface

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to Beryllium, inorganic and soluble salts, and a proposal of a health based quality criterion for drinking water. This resulted in 2009 in the present report, which was prepared by Elsa Nielsen, Krestine Greve, Ole Ladefoged and John Christian Larsen, 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,
The Danish Environmental Protection Agency

The Danish Environmental Protection Agency
Copenhagen, December 2013.

1 General description

Beryllium is a naturally occurring alkaline earth metal. It exists in the oxidation states 0 and +2 and belongs to group IIA of the periodic table together with magnesium and calcium. Chemically it is very similar to aluminium, which like beryllium has a high charge-to-radius ratio (accounts for the amphoteric nature of the ion and the strong tendency of the compounds to hydrolyze). Beryllium is highly reactive and exists only under normal environmental conditions associated with other elements.

Two radionuclides, ^{7}Be and ^{10}Be, are formed in the atmosphere by the interaction of cosmic-ray particles. The radioactive half-life of ^{7}Be and ^{10}Be is 53.29 days and 1.51×10^{6} years, respectively.

In this evaluation only soluble inorganic and non-radioactive beryllium (^{9}Be) salts are considered in relation to an estimation of a health based quality criterion in drinking water.

This evaluation is based on reviews and evaluations published by ATSDR (2002), WHO (1990) and US-EPA (IRIS 2008).

In this evaluation, the term "beryllium" is used in a generic sense and refers to the beryllium content of the various beryllium salts mentioned in this document. For the purpose of comparison, concentrations and dose levels of the various beryllium salts are expressed in terms of beryllium equivalents (Be) whenever possible.

1.1 Identity and physical / chemical properties

The identity of selected inorganic soluble beryllium salts is presented in Table 1.1 and physico-chemical properties are presented in Table 1.2.

1.2 Production and use

There are more than 40 minerals with beryllium as the main constituent. The two important beryllium minerals of commercial interest are beryl ($Be_3Al_2(SiO_3)_6$) and bertrandite ($Be_4Si_2O_7(OH)_2$), which contain up to 4 and 1% beryllium, respectively. After mining, the beryllium minerals are milled to beryllium hydroxide. Beryllium hydroxide is the starting material for the production of beryllium metal, alloys and compounds (US Bureau of Mines 1985ab, 1982 – quoted from WHO 1990).

Beryllium nitrate is used as a hardening agent for mantles on gas lanterns. Beryllium phosphate has no commercial uses (ATSDR 2002).

In Denmark, the main fields of use of beryllium are in metal and electronic components, oil and gas industry, dental alloy, sport equipment and x-ray equipment. The estimated total annual consumption of beryllium is 5 tonnes/year (MST 2003).

Table 1.1 Identity of selected inorganic soluble beryllium salts (Weast 1985, ChemFinder, ChemIDplus Advanced, ATSDR 2002, HSDB 2007)

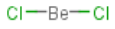
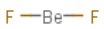
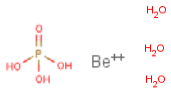
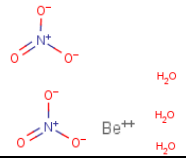
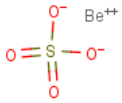
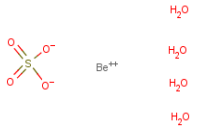
	Beryllium chloride	Beryllium fluoride	Beryllium phosphate, trihydrate	Beryllium nitrate trihydrate	Beryllium sulfate	Beryllium sulfate, tetrahydrate
Molecular formula	$BeCl_2$	BeF_2	BeH_3PO_4 $3H_2O$	$Be(NO3)_2$ $3H_2O$	BeH_2SO_4	BeH_2SO_4 $4H_2O$
Structural formula						
Molecular weight	79.93	47.01	271.03	187.07	105,07	177.13
CAS-no	7787-47-5	7787-49-7	35089-00-0	7787-55-5	13510-49-1	7787-56-6
Synonyms	-	Beryllium difluoride	Berylium orthophosphate	Beryllium dinitrate	-	

Table 1.2 Physico-chemical properties of selected inorganic soluble beryllium salts (Weast 1985, ChemFinder, ChemIDplus Advanced, ATSDR 2004, HSDB 2003)

	Beryllium chloride	Beryllium fluoride	Beryllium phosphate, trihydrate	Beryllium nitrate trihydrate	Beryllium sulfate	Beryllium sulfate, tetrahydrate
Description	White to faintly yellow crystalline mass	Colourless mass/white solid	White solid	White to slightly yellow crystal	Colourless crystalline solid	Colourless crystalline solid
Melting point °C	399°C	555°C	-H_2O at 100°C	60°C	Decomposes at 550°C	-$2H_2O$ at 100°C -$4H_2O$ at 400°C
Boiling point °C	482°C	1160°C	-	142°C	-	-
Density g/ml	1.90	1.99 at 25°C	-	1.56 at 20°C	2.44	1.713
Solubility in water	Very soluble	Very soluble	Soluble	Very soluble	Insoluble in cold water, converted to tetrahydrate in hot water	425 g/l
Odour threshold	-	Odourless	-	Odourless	Odourless	-
Taste threshold	Sweetish taste 0.003 mol/l	-	-	-	-	-

1.3 Environmental occurrence and fate

Beryllium is the 44th most abundant element in the earth's crust, with an average content of about 2-5 mg/kg (Drury et al. 1978, Griffitts and Skilleter 1990, Kram et al. 1998, Mason and Moore 1982, Reeves 1989 – quoted from ATSDR 2002).

The natural average contents of beryllium in fossil fuels are 1.8-2.2 mg/kg (dry weight) in coal and up to 100 µg/ l in oil. Ber
not degrade in the environment (WHO 1990).

Levels of beryllium in selected emissions and waste products measured in Denmark in the autumn of 2001 are listed in Table 1.3 (MST 2003).

Table 1.3. Levels of beryllium in selected emissions and waste products (from MST 2003).

Emission / waste type	Concentration (dw = dry weight)
Compost	
Compost from household waste	330 µg/kg dw
Compost fromgarden waste	270 µg/kg dw
Landfill leachate	
Landfill 1	<0.03 µg/l
Landfill 2	<0.03 µg/l
Stack gas from MSW (muncipal solid waste) incineration	
MSW incenerator 1, semi-dry gas cleaning	<2.6 µg/m^3
MSW incinerator 2, wet gas cleaning	<0.2 µg/m^3
MSW (muncipal solid waste) gas cleaning residuals	
Landfill leachate, semi-dry gas cleaning	<0.03 µg/l
Landfill leachate, wet gas cleaning	<0.03 µg/l
Wastewater and sludge from municipal WWTP (wastewater treatment plant)	
WWTP 1, effluent	<0.03 µg/l
WWTP 2, effluent	<0.03 µg/l
WWTP 1, sludge	400 µg/kg dw
WWTP 2, sludge	252 µg/kg dw
Road run off rentention basins,sediment	
Motorway 1	780 µg/kg dw
Motorway 2	780 µg/kg dw

1.3.1 Air

Beryllium is naturally released into the atmosphere by windblown dusts and volcanic particles. Anthropogenic sources of beryllium released to the atmosphere include combustion of coal and fuel oil (approximately 93% of the total beryllium emission), incineration of municipal solid waste, production, use and recycling of beryllium alloys and chemicals. Atmospheric beryllium particles return to earth through wet and dry deposition. The residence time in air is dependant upon particle size (ATSDR 2002).

The atmospheric mean concentrations of beryllium that have been measured at rural sites in the US ranged from 0.03 to 0.06 ng/m^3. Annual average atmospheric concentrations in urban air in the US, with levels exceeding 0.1 ng/m^3, range from 0.1 to 6.7 ng/m^3 (US-EPA 1987; Ross et al. 1977 – quoted from WHO 1990).

1.3.2 Water

Beryllium is released to surface water and groundwater by the naturally weathering of rocks and soils and from the deposition of windblown dusts and volcanic particles (US-EPA 1980 – quoted from ATSDR 2002).

Anthropogenic sources of beryllium released into water include wastewater effluents from the industry and from the deposition of atmospheric combustion particles (ATSDR 2002).

Levels of beryllium in Danish wastewater effluents are presented in Table 1.3.

In the US, dissolved beryllium was detected in groundwater at 262 of 4177 sites (6.6%) with an average concentration of 13.0 ± 50.3 µg/l. Total beryllium was detected at 30 of 334 sites (9.0%) with an average concentration of 1.7 ± 1.8 µg/l (US-EPA 2000a – quoted from ATSDR 2002).

In the Netherlands, the average concentration of beryllium in 266 tap water samples were <0.1 µg/l (range <0.1-0.2 µg/l) (Fonds et al. 1987 – quoted from ATSDR 2002).

Geological studies show concentrations ranging from <0.005-2.7 µg/l (median 0.01 µg/l) across Europe (WHO 2007).

In Denmark, beryllium was found in 90 of 313 groundwater samples across the country. The concentrations ranged from 0.002 (detection limit) to 2.2 µg/l with an average concentration of 0.15 µg/l and a median of 0.02 µg/l. The concentrations of sixteen of these samples (located in the counties of Sønderjylland, Ribe or Ringkøbing) were above 0.2 µg/l (GEUS 2006).

1.3.3 Soil

Beryllium is naturally present in soil. Atmospheric beryllium oxide particles return to earth through wet and dry deposition. Within the environmental pH range of 4-8, beryllium is strongly adsorbed by sedimentary minerals and thus prevented from release to ground water (WHO 1990).

Disposal of coal fly ash and municipal solid waste incinerator ash in landfills and land application of sewage sludge may increase the concentration of beryllium in soil (Stadnichenko 1961 – quoted from ATSDR 2002).

Typical transformation processes for beryllium in soil include precipitation, complexation and anion exchange. Factors affecting the transformation of beryllium in soils and sediments include pH, ionic strength, concentration and distribution of species, composition of the mineral matrix, organic matter, biological organisms and temperature (ATSDR 2002).

In Florida and California the average concentrations of beryllium in soil were 0.46 and 1.14 mg/kg, respectively (Chen et al. 1999 – quoted from ATSDR 2002).

Beryllium concentrations in ammonia, nitrate and phosphorus fertilizers used in agriculture have been repoted to be in the range from <0.2 to 13.5 mg/kg (Raven and Loeppert 1997 – quoted from ATSDR 2002).

1.3.4 Foodstuffs

Beryllium is believed not to biomagnify to any extent within food chains. Most plants take up beryllium from the soil in small amounts, and very little is translocated from the roots to other plant parts (WHO 1990).

The median concentration of beryllium in 38 foods from around the world was 22.5 µg/kg fresh weight (excluding kidney beans) (range <0.1-2200 µg/kg fresh weight). The highest concentrations were reported for kidney beans (2200 µg/kg fresh weight), crisp bread (112 µg/kg fresh weight), garden peas (109 µg/kg fresh weight), parsley (77 µg/kg fresh weight) and pears (65 µg/kg fresh weight). The average concentration of beryllium in fruit and fruit juices was 13.0 µg/l (range from < the detection limit to 74.9 µg/l) (ATSDR 2002).

In the US, reported beryllium concentrations in fish and mussels ranged from < the detection limit to 6 µg/kg (Nicola et al. 1987, Byrne and DeLeon 1986, Caspar and Yess 1996, Allen et al. 2001 – quoted from ATSDR 2002).

In the US, an average concentrations of beryllium in bottled water of <0.1 µg/l has been reported (Vaessen and Szteke 2000 – quoted from ATSDR 2002).

1.4 Bioaccumulation

Beryllium does not bioconcentrate in aquatic organisms. A measured BCF (bioconcentration factor) of 19 has been reported for beryllium in bluegill fish and a BCF of 100 has been reported for freshwater and marine plants, vertebrates, and fish (US-EPA 1980, Callahan et al. 1979 – quoted from ATSDR 2002).

No evidence of bioaccumulation of beryllium in the food chain of humans has been located in the literature (Fishbein 1981 – quoted from ATSDR 2002).

1.5 Human exposure

A relatively small number of workers worldwide are potentially exposed to high levels of beryllium, mainly in the refining and machining of the metal and in production of beryllium-containing products. A growing number of workers are potentially exposed to lower levels of beryllium in the aircraft, aerospace, electronics and nuclear industries (IARC 1997).

The general population is exposed to trace amounts of beryllium by inhalation of air and ingestion of drinking water and food. Individuals may be exposed to high levels of beryllium from implanted dental prostheses (US-EPA 1987, ATSDR 2002).

The highest concentration of beryllium released from base metal alloy used as dental crowns measured in an artificial oral environment was 8 µg/day per crown (Tai et al. 1992 – quoted from ATSDR 2002).

In the US, the estimated daily intake of beryllium from food was 0.12 µg. This estimate was based on an arbitrary value for beryllium content of a total diet sample of 0.1 ng/g food and a daily consumption of 1200 g of food (US-EPA 1987). In a study examining the trace element concentrations of food samples via hospital diets in Japan, the average daily intake of beryllium was determined to be 84.4 µg/day (Muto et al. 1994 – quoted from ATSDR 2002).

In a Japanese study the daily dietary intake of beryllium were estimated to be 5 µg, based on the 24-hour total food duplicate method and using composition tables for foods in Japan. However as the number of food items was insufficient, the results should be taken as semi-quantitative (Shimbo et al. 1996).

Other investigators have reported the total daily intake of beryllium to be in the range of 5-100 µg/day (Emsley 1998, Tsalev and Zaprianov 1984, Vaessen and Szteke 2000 – quoted from ATSDR 2002).

Using the average value for the concentration of beryllium in Danish ground water of 0.15 µg/l, and a consumption rate of 0.03 l/kg bw/day (median value for children 1-10 years old), the intake of beryllium from drinking water would be 0.005 µg/kg bw/day (assuming no dilution of groundwater). For an adult, assuming an average consumption rate of 1.4 l/day, the daily exposure to beryllium from drinking water would be 0.2 µg/day (about 0.003 µg/kg bw/day assuming an adult body weight of 70 kg).
Using the highest reported concentration of beryllium in Danish ground water of 2.2 µg/l, and a consumption rate of 0.08 l/kg bw/day (95th percentile for children 1-10 years old), the intake from drinking water would be 0.18 µg/kg bw/day (assuming no dilution of groundwater). For an adult, assuming a 90th percentile consumption rate of 2.3 litre/day, the daily exposure to beryllium from drinking water would be 5.1 µg/day (about 0.07 µg/kg bw/day).

Using the highest average atmospheric concentrations of beryllium measured in urban air in the US of 0.0067 µg/m^3 (WHO 1990) and assuming the inhalation rate as 0.5 m^3/kg bw/day (for children 1-5 years old), the inhalation exposure of beryllium will be 0.003 µg/kg bw/day. For an adult, assuming an average inhalation rate as 13 m^3/day or a high inhalation rate as 20 m^3/day, the daily inhalation exposure to beryllium from ambient air would be about 0.09 µg/day (average, about 0.001 µg/kg bw/day assuming an adult body weight of 70 kg) or about 0.13 µg/day (high, about 0.002 µg/kg bw/day).

2 Toxicokinetics

2.1 Absorption, distribution and excretion

2.1.1 Inhalation

Beryllium compounds are absorbed through the lungs of human and animal; however, no information on the rate and the extent of absorption has been located. Several studies in animals show that beryllium is widely distributed to the organs of animals following pulmonary absorption. (ATSDR 2002).

2.1.2 Oral intake

No data regarding absorption, distribution or excretion in humans after oral exposure to beryllium has been located.

In animals, oral administered trace amounts of radioactive beryllium chloride, absorption of ingested beryllium were below 1% in pigs, rats, mice, monkeys, dogs and cows (Hyslop et al., 1943, Crowley et al., 1949, Furchner et al., 1973, Mullen et al., 1972 – quoted from WHO 1990).

In mice, dogs and monkeys, exposed to radioactive beryllium chloride by gavage, most of the radiolabel was excreted in the faeces. In rats, the greatest amount (other than that in the gastrointestinal tract) was detected in the bone, followed by viscera, pelt, and muscle (Furchner et al. 1973 – quoted from ATSDR 2002).

In rats, exposed to 0.6 or 6.6 µg Be/day (as beryllium sulphate) in the drinking water, 60-91% of the ingested beryllium was eliminated with the faeces. The author assumed that the remainder was absorbed from the stomach, at the pH of which the $BeSO_4$ is in the ionized form. At the alkaline pH of the intestine, beryllium precipitates as the phosphate. However, according to WHO, on subtracting the measured beryllium content of the gastrointestinal tract from the total body burden plus the urinary beryllium, it is evident that only 0.06-1.5% of the total intake must have been absorbed from the gastrointestinal tract into the blood and distributed to the tissues or excreted by the kidneys (Reeves 1965 – quoted from WHO 1990).

In rats, exposed to 0.019 or 0.190 mg Be/kg/day (as beryllium sulphate) in drinking water for 24 weeks, the urinary excretion accounted for 0.5% of the total dose of the beryllium sulphate. The percent absorption, determined as the percentage of the dose that could be recovered from the total body load and excreta, was 0.9% in the 0.019 mg Be/kg/day group and 0.2% in the 0.190 mg Be/kg/day group (Reeves 1965 – quoted from ATSDR 2002).

In rats, dietary exposed to 0.3, 2.8 or 31 mg Be/kg/day (as beryllium sulphate) for 2 years, the beryllium accumulation in the bones was proportional to the administered dose. Excretion occurred mainly via the faeces (Morgareidge et al. 1975 – quoted from ATSADR 2002).

In hamsters, exposed to beryllium sulphate, beryllium oxide or beryllium metal in the diet for 3-12 months, beryllium was found in the liver, large intestine, small

intestine, kidneys, lungs, stomach, and spleen (Watanabe et al. 1985 - quoted from ATSDR 2002)

In mice, exposed to a radioactive dose of beryllium chloride by gavage, the radioactivity was greatest in the liver followed by the kidney, mesenteric lymph nodes, lungs, blood and carcass, 3 hours after exposure (LeFevre and Joel 1986 – quoted from ATSDR 2002).

2.1.3 Dermal contact

No data regarding distribution or excretion in humans or animals after dermal exposure to beryllium has been located.

Tail skin of rats was exposed to an aqueous solution of beryllium chloride. Only small amounts of the applied beryllium were absorbed through the skin (Petzow and Zorn 1974 – quoted from ATSDR 2002).

2.2 Transfer through placenta and breast milk

A study of human colostrum, maternal and umbilical cord sera, provides evidence that beryllium is transferred across the placenta and excreted via breast milk. The levels of beryllium in umbelical cord serum and in colostrum were higher than in maternal serum (Krachler et al. 1999a – quoted from ATSDR 2002).

In mice, intravenously administered 0.1 mg Be/kg bw (as radioactive beryllium chloride) on gestational day 14, the placental permeability for beryllium was slight. The concentrations of beryllium in the placenta and in the remaining organs of the females were one order of magnitude higher than those in the foetuses (Bencko et al. 1979a – quoted from WHO 1990).

In cows, the transfer of ingested radioactive beryllium chloride (3.1 mCi) to the milk was low. Less than 0.002% of the administered activity was secreted in the milk of the cows (Mullen et al. 1972 – quoted from WHO 1990).

2.3 Mode of action

Beryllium effects on bone tissue (rickets) are likely due to impaired gastrointestinal phosphate absorption rather than a direct effect of beryllium on the bone tissue. Following ingestion of beryllium carbonate, the beryllium in the gut binds to soluble phosphorus compounds and forms an insoluble beryllium phosphate. The rickets are a result of the decreased phosphorus levels (ATSDR 2002).

Results of several studies indicate that beryllium can affect DNA synthesis, probably by direct interacting with DNA polymerases (Witschi 1970, Luke et al. 1975, Sirover & Loeb 1976 – quoted from WHO 1990).

In several studies beryllium has been shown to inhibit various enzymes of the phosphate metabolism that may be the biochemical basis for many of the toxic and carcinogenic actions of beryllium (Thomas & Aldridge 1966, Cummings et al. 1982, Thomas & Aldridge 1966, Mukhina, 1967, Witschi & Marchand 1971 – quoted from WHO 1990).

3 Human toxicity

3.1 Single dose toxicity

Single dose toxicity following inhalation is addressed in Section 3.4.1.

No data regarding single dose toxicity following oral intake or dermal contact have been located.

3.2 Irritation

3.2.1 Skin irritation

Dermatitis has been observed in workers as a result of occupational dermal contact with beryllium fluoride, ground metallic beryllium, or water drippings from overhead pipes coated with dust of various compounds (Curtis 1951 – quoted from ATSDR 2002).

3.2.2 Eye irritation

No data have been located.

3.2.3 Respiratory irritation

Irritation of the nasal and pharyngeal mucous membranes, sore nose and throat has been reported in a number of cases of acute beryllium disease (see section 3.4.1) among workers exposed to beryllium sulphate, beryllium oxide, beryllium fluoride, and beryllium oxyfluoride (Van Ordstrand et al. 1945 – quoted from ATSDR 2002).

3.3 Sensitisation

Chronic beryllium disease (CBD) is an immunological disease that can result from inhalation exposure to beryllium compounds (see section3.4).

Employees of a beryllium machining plant were screened with the BeLPT (beryllium lymphocyte proliferation test) biennially, and new employees were screened within 3 months of hire. Of 235 employees screened from 1995 to 1997, a total of 15 (6.4%) had confirmed abnormal BeLPT results indicating beryllium sensitization; nine of these employees were diagnosed with chronic beryllium disease. Four of the 15 cases were diagnosed within 3 months of first exposure. When 187 of the 235 employees participated in biennial screening in 1997 to 1999, seven more had developed beryllium sensitization or chronic beryllium disease, increasing the overall rate to 9.4% (22 of 235) (Newman et al. 2001).

No data regarding sensitisation following oral intake and no relevant data following dermal contact have been located.

3.4 Repeated dose toxicity

3.4.1 Inhalation

Most data regarding adverse effects in humans after inhalation exposure to beryllium compounds are studies of occupational exposure. Two types of non-neoplastic respiratory disease can result from inhalation exposure to beryllium, acute beryllium diseases and chronic beryllium disease. The duration of exposure does not necessarily govern the type of disease. Low-level exposure of a few hours has been reported to produce a chronic beryllium disease similar to that following years of exposure. Similarly, brief but massive, or prolonged but less intensive, exposure to beryllium may cause the acute disease (ATSDR 2002, WHO 1990).

Acute beryllium disease (ABD) is a fulminating inflammatory reaction of the entire respiratory tract and is usually associated with exposure to high concentrations of soluble beryllium compounds. The respiratory tract symptoms range from a mild inflammation of the nasal mucous membranes and pharynx to tracheobronchitis and to severe chemical pneumonitis, depending on the degree, duration, and type of exposure (ATSDR 2002, WHO 1990).

Chronic beryllium disease (CBD), also referred to as berylliosis or chronic berylliosis, is an inflammatory lung disease characterized by the formation of granulomas with varying degrees of interstitial fibrosis. As CBS is an immune response to beryllium, it is only observed in individuals who are sensitized to beryllium. The symptoms associated with chronic beryllium disease include chest pain, cough, and/or dyspnea with relatively mild exertion (ATSDR 2002, WHO 1990).

3.4.2 Oral intake

No data have been located.

3.4.3 Dermal contact

No relevant data have been located.

3.5 Toxicity to reproduction

No data have been located.

3.6 Mutagenic and genotoxic effects

No data have been located.

3.7 Carcinogenic effects

3.7.1 Inhalation

A number of epidemiology studies have been conducted to assess the carcinogenic potential of beryllium following inhalation exposure. Increased incidences of lung cancer deaths were reported in retrospective cohort mortality studies of workers at beryllium extraction, processing, and fabrication facilities. Increased lung cancer mortality was also seen in entrants to the Beryllium Case Registry. No

correlation between the incidence of lung cancer deaths and exposure has been established because historical exposure levels were not reported. A positive association between length of latency and lung cancer deaths was found, with the highest cancer risks among workers with a latency of at least 25 years (ATSDR 2002).

Further details on cancer risk from inhalation exposure to beryllium can be found in ATSDR 2002.

3.7.2 Oral intake

No human studies investigating the carcinogenicity of ingested beryllium were located and US-EPA concluded that the human carcinogenic potential of ingested beryllium cannot be determined (ATSDR 2002).

3.7.3 Dermal contact

No data have been located.

4 Animal toxicity

4.1 Single dose toxicity

4.1.1 Inhalation

No relevant data have been located.

4.1.2 Oral intake

Oral LD_{50}-values in animals vary according to the species and the compound, see Table 4.1.

Signs of acute toxicity, observed in LD_{50} studies, were respiratory disorders, spasms, hypoglycaemic shock and respiratory paralysis. Hypoglycaemia was attributable to liver necrosis caused by beryllium (Kimmerle, 1966 – quoted from WHO 1990).

Table 4.1.2. Oral LD_{50} values of beryllium compounds.

Compound/ species	LD_{50} Mg Be/kg bw	Reference
Beryllium chloride		
Rat	9.8	Venugopal and Luckey (1978 in WHO 1990)
Rat	200	Kimmerle (1966 in WHO 1990)
Beryllium fluoride		
Mouse	19.1	Kimmerle (1966 in WHO 1990)
Beryllium phosphate		
Rat	6.5	Venugopal and Luckey (1978 in WHO 1990)
Beryllium sulphate		
Mouse	6.95	Venugopal and Luckey (1978 in WHO 1990)
Mouse	140	Ashby et al. (1990 in ATSDR 2002)
Rat	7.02	Venugopal and Luckey (1978 in WHO 1990)
Rat	120	Lanchow University (1978 in ATSDR 2002)

4.1.3 Dermal contact

No data have been located.

4.2 Irritation

No data have been located.

4.3 Sensitisation

In C3H mice, the application of beryllium sulphate to the dorsal side of the ear for 3 consecutive days per week for 2 weeks, generated beryllium-specific sensitisation that was documented by peripheral blood and LN beryllium lymphocyte proliferation tests (BeLPT) and by changes in LN T-cell activation markers, increased expression of CD44, and decreased CD62L (Tinkle et al. 2003).

4.4 Repeated dose toxicity

The toxicity of beryllium compounds following repeated exposure have been extensively studied in a number of animal species using inhalation (rat, mouse, rabbit, guinea pig, hamster, dog, cat, monkey), oral (rat, mouse, dog) and dermal (guinea pig) routes, in studies with durations ranging from 7 days to 172 weeks. Inhalation and dermal repeated dose studies are only briefly described in each of its sections. Further details of beryllium toxicity following inhalation or dermal application can be found in ATSDR (2002).

4.4.1 Inhalation

Following inhalation, toxicity has been observed in rats at exposure concentrations from 0.006 mg Be/m^3 (inflammation and fibrosis of the lung, and lung cancer – beryllium oxide for 6-18 months, lowest concentration in the study, Vorwald and Reeves 1959), in mice from 2 mg Be/m^3 (4/38 died – beryllium sulphate for 51 days, Stokinger et al. 1950), in rabbits from 0.04 mg Be/m^3 (atelectasis – beryllium sulphate for 51-100 days, Stokinger et al. 1950), in guinea pigs from 0.43 mg Be/m^3 (2/34 died – beryllium sulphate for 51-100 days, Stokinger 1950), in dogs from 0.04 mg Be/m^3 (emphysema, decreased arterial oxygen, macrocytic anaemia, increased serum albumin and globulin, and body weight loss – beryllium sulphate for 51-100 days, Stokinger 1950), in cats from 0.04 mg Be/m^3 (emphysema and severe weight loss – beryllium sulphate for 51-100 days, Stokinger 1950), in hamsters from 0.21 mg Be/m^3 (granulomas in the lung and increased mortality – beryllium oxide for 6-17 months, Wagner et al. 1969), in monkeys from 0.035 mg Be/m^3 (cancer – beryllium sulphate for 63weeks, Vorwald 1968) and in pigs from 2 mg Be/m^3 (28% weight loss – beryllium sulphate for 63weeks, Stokinger 1950). (All references quoted from ATSDR 1999).

4.4.2 Oral intake

The oral studies on beryllium compounds included in ATSDR (2002), WHO (1990) and IRIS (2008) are summarised in Table 4.4.2 and supplementary information on the studies is given in the text. The NOAELs and LOAELs presented in this section are those stated in the reviews and criteria documents.

Rat, 40 days, beryllium nitrate (Goel et al. 1980 - in ATSDR 2002)
Test dose level was 2 mg Be/kg bw in the diet, every 3 days. According to ATSDR, the lung effects may result from aspiration of the beryllium nitrate particulates into the lungs during feeding.

Table 4.4.2. Animal repeated dose toxicity studies on beryllium, oral administration

Species/strain	Duration/ Dose levels/ Chemical form	Effects (mg/kg bw/day)	NOAEL[1)] (mg/kg bw/day)	LOAEL[1)] (mg/kg bw/day)	Reference
Rat (Wistar)	13-42 days 0, 345 mg Be/kg/day $BeCO_3$+Be(OH) in diet	Rickets.		345 (Musc/skel)	Jacobson (1933 - in ATSDR 2002)
Rat (NS)	21-22 days 0, 70 mg Be/kg/day $BeC0_3$ in diet	70: Rickets, severe. ↓ Serum phosphate levels and alkaline phosphatase activity.		70 (Musc/skel) 70 (Metab)	Kay and Skill (1934 - in ATSDR 2002)
Rat (Wistar)	4 weeks 0, 70, 480 mg Be/kg/day $BeC0_3$ in diet	480: ↓ Body weight gain (18%). 70: ↓ Serum phosphate levels and alkaline phosphatase activity.		480 (Bw) 480 (Metab)	Matsumoto et al. (1991 - in ATSDR 2002)
Rat, young (NS)	24-28 days 0, 1250 - 2000 mg/kg food $BeC0_3$ in diet	Rickets (due to intestinal precipitation of beryllium phosphate and concomitant phosphorus deprivation).		35 (Musc/skel)	Guyatt et al. (1933 – in ATSDR 2002 and WHO 1990)
Rats	Every 3 day for 40 days 0, 2 mg Be/kg bw every 3rd day. $Be(NO_3)_2$ in diet	2/3: Thickening of the alveolar epithelium with areas of necrosis.			Goel et al. (1980 - in ATSDR 2002)
Rat (Sprague-Dawley)	91 days 0, 0.7 mg Be/kg/day $BeS0_4$ in drinking water	0.7: No effect on body weight.	0.7 (bw)		Freundt and Ibrahim (1990 - in ATSDR 2002)
Rat (Wistar)	2 years 0, 0.3, 2.8, 31 mg/kg bw/day $BeS0_4$ in diet	No histopathological changes in lung, heart, aorta, stomach, small intestine, large intestine, bone marrow, muscle, liver, kidney, skin, spleen, lymph nodes, thymus, brain, nerve, spinal cord, adrenal, thyroid, pituitary or pancreas. No ocular effects and no effect on body weight gain. No changes in brain or liver weight. 31: ↑kidney weight, slightly.	31 (Resp, cardio, gastro, haemato, musclskel, hepatic, renal, endocr, ocular, bw)		Morgareidge et al. (1975 - in ATSDR 2002)
Rat (Long- Evans, weanling) 52/sex/group	2.3 years 0, 0.7 mg Be/kg bw/day $BeS0_4$ in drinking water (5 mg Be/l)	No histopathological changes in lung, liver or kidney. No histological cardiac effect. No effect on body weight gain, life span and survival. 0.7: Transient increases in serum cholesterol. Transient glucosuria (♀).	0.7 (Resp, cardio, hepatic, renal, bw, metab)		Schroeder and Mitchener (1975a - in ATSDR 2002, WHO 1990 and IRIS 2008)

Species/strain	Duration/ Dose levels/ Chemical form	Effects (mg/kg bw/day)	NOAEL[1)] (mg/kg bw/day)	LOAEL[1)] (mg/kg bw/day)	Reference
Mouse (Swiss) 54/sex/group	2.5 years 0, 1 mg Be/kg bw/day $BeSO_4$ in drinking water (5 mg Be/l)	No histopathological changes in lung, liver or kidney. No histological cardiac effect. No changes in serum cholesterol. No effect on body weight gain, life span and survival. 1: Slight effects on the body weight (♀).	1 (Resp, cardio, haemato, hepatic, renal, bw)		Schroeder and Mitchener (1975b - in ATSDR 2002, WHO 1990 and IRIS 2008)
Dog (Beagle)	33 weeks 0, 12 mg Be/kg/day $BeSO_4$ in diet	12: ↑ mortality		12 (imortality)	Morgareidge et al. (1976 - in ATSDR 2002)
Dog (Beagle, aged 8-12 month) 5/sex/group	143-172 weeks 0, 1, 5, 50 and 500 mg/kg Be in diet. The Be intakes were calculated to be: 0, 0.023, 0.12, 1.1, and 12.2 mg/kg bw/day for male dogs and 0.029, 0.15, 1.3, and 17.4 mg/kg bw/day for females (IRIS 2008). 0, 0.1, 1, 12 mg Be/kg bw/day for both sexes (ATSDR 2002). $BeSO_4$ $4H_2O$ in diet	No histopathological changes in lung, heart or aorta, in muscle tissue, liver, skin, spleen, lymph nodes, thymus, brain, nerve, spinal cord, kidney, adrenal, thyroid, pituitary, or pancreas. No ocular or bone effects. No alterations in organ weights. 500 mg/kg: Lassitude, weight loss, anorexia and visibly bloody faeces. Extensive ulcerative and inflammatory lesions observed in small intestine, stomach, and large intestine in 9 of 10 dogs. Erythroid hypoplasia of the bone marrow and slight decreases in erythrocyte counts, haemoglobin, and haematocrit levels. 50 mg/kg: No effect on body weight. No haematological, serum chemistry, or urinalysis alterations. Less severe, lesions in small intestine, stomach, and large intestine observed in 1 of 10 dogs. ↑ Mortality.	12 (Resp, cardio, musclskel, hepatic, renal, endocr, dermal, ocular) 1 (Gastro, haemato, bw)	12 (Gastro, hemato, bw)	Morgareidge et al. (1976 - in ATSDR 2002 and IRIS 2008)

↓: Reduced
↑: Increased
Bw = body weight
Cardio =cardiovascular
Endocr = endocrine
Gastro = gastrointestinal
Neuro = neurological
♀: Female
♂: Male
Haemato = haematological
Metab = metabolic
Skel = musculoskeletal
Immun = immunological
SD=Sprague-Dawley

1) The NOAELs and LOAELs presented in this section are those stated in ATSDR (2002).

Rat, 2.3 years, beryllium sulphate (Schroeder and Mitchener 1975a - in ATSDR 2002, WHO 1990, IRIS 2008).
According to ATSDR the test dose level was 0.7 mg Be/kg bw/day in drinking water. According to the authors the low bioavailability and, hence toxicity, of ingested beryllium in the form of beryllium sulphate in the drinking water, was confirmed. Neoplastic changes are addressed in section 4.7.2.

Dog 143-172 weeks, beryllium sulphate tetrahydrate (Morgareidge et al. 1976 – in ATSDR 2002, IRIS 2008)
Dogs were fed diets containing 0, 5, 50, or 500 ppm beryllium for 172 weeks. Because of overt signs of toxicity, the 500 ppm group was terminated at 33 weeks and a group of 5 male and 5 female dogs was added to the study and fed a diet containing 1 ppm beryllium. Duration of exposure for this group was 143 weeks. To calculate Be intake US-EPA (IRIS 2008) used estimated time-weighted average body weights and the reported average food intake of 300 g/day: 0.023, 0.12, 1.1, and 12.2 mg Be/kg bw/day for male dogs and 0.029, 0.15, 1.3, and 17.4 mg Be/kg bw/day for females. The intakes reported in ATSDR (2002) were calculated using an approach that was not further specified: 0, 0.1, 1, 12 mg Be/kg bw/day for both sexes.
Overt signs of toxicity observed in the 500 ppm group included lassitude, weight loss, anorexia, and visibly bloody faeces. In this group, a slight anaemia (slight decreases in erythrocyte count, haemoglobin, and haematocrit), more apparent in the females than in the males, was observed after 3 and 6 month of exposure; however, there were no alterations in the bone marrow and none of the animals was seriously affected (IRIS 2008). According to ATSDR, it is likely that the observed effects on the haematological system and the weight loss observed in this dose group were secondary to the severe gastrointestinal haemorrhages also observed in these animals (ATSDR 2002).
All animals in the 500 ppm group showed fairly extensive erosive (ulcerative) and inflammatory lesions in the gastrointestinal tract. These occurred predominantly in the small intestine and to a lesser extent in the stomach and large intestine, and were regarded by the authors as treatment related (IRIS 2008). According to US-EPA (IRIS 2008), this conclusion was also supported by an independent review of the study report (Goodman 1997), who concluded that the lesions were not considered to be related to some other cause such as intestinal worms. All of the animals with stomach or large intestinal lesions also had lesions in the small intestine except for one animal with stomach lesions only. This animal had stomach lesions that were very localized and not very severe. Lesions in the small intestine (4/5 males and 5/5 females) considered treatment related included: desquamation of the epithelium, oedema, fibrin thrombi, acute inflammation, subacute/chronic inflammation, necrosis and thinning/atrophy of the epithelium and ulceration. High-dose animals also showed moderate to marked erythroid hypoplasia of the bone marrow, which the authors also considered treatment related (Goodman 1997 – quoted from IRIS 2008).
Bile stasis and vasculitis in the liver and acute inflammation in the lymph nodes occurring in these animals were attributed to a likely systemic bacterial invasion through the damaged intestinal mucosa. A generalised low-grade septicaemia likely initiated the kidney damage.
In the 50 ppm group, one female dog died after 70 weeks of treatment. This animal showed gastrointestinal lesions, but less severe, occurring in the same locations and appearing to be the same types of lesions as those in dogs administered 500 ppm. The authors stated the cause of death of this animal appeared to be related to beryllium administration. Other animals in this treatment group survived until study termination and had no remarkable gross or microscopic findings.
A dose-response modelling of the data for small intestinal lesions in male and female dogs (0/10, 0/10, 0/10, 1/10, 9/10) was conducted by the US-EPA and a BMD_{10} (the lower 95% confidence limit on the dose from the maximum likelihood

estimate [MLE] of a 10% relative change) of 0.46 mg/kg/day (MLE = 1.4 mg/kg/day) was derived (US-EPA 1998, IRIS 2008).
Neoplastic changes are addressed in section 4.7.2.

4.4.3 Dermal contact

In guinea pigs, following 12 biweekly intradermal injections of 0.0005 µg beryllium sulphate, increased macrophage inhibition factor and T-cell activity was observed (Marx and Burrell 1973 – quoted from ATSDR 2002).

4.5 Toxicity to reproduction

4.5.1 Inhalation

No data have been located.

4.5.2 Oral intake

In rats, exposed for beryllium sulphate in the diet for 2 years, a significant decreased average absolute testes weight was observed at dose levels of 0.3 and 2.8 mg Be/kg/day, but not at 31 mg Be/kg/day. Histological examination of the testes, prostate, seminal vesicles and epididymides did not reveal any abnormalities. No decrease in ovary weight was observed in female rats. Furthermore, histological examination of the ovaries, uterus, and oviducts did not reveal any abnormalities (Morgareidge et al. 1975 – quoted from ATSDR 2002).
Non-reproductive effects are addressed in section 4.4.2.

In a chronic duration study (143-172 weeks), dogs exposed to 1 mg Be/kg/day (as beryllium sulphate in the diet) were allowed to mate and wean their pups. No significant alterations in the number of pregnancies, number of pups or number of live pups, pup body weights and pup survival were observed. Pups in the first litter were examined for gross and skeletal malformations. No significant alterations in the occurrence of gross or skeletal malformations were observed; however, stillborn or cannibalized pups dying within the first few postnatal days were not examined (Morgareidge et al. 1976 – quoted from ATSDR 2002).
Non-reproductive effects are addressed in section 4.4.2.

4.5.3 Dermal contact

No data have been located.

4.5.4 Other routes

Effects on the behaviour (delayed response in head turning in a geotaxis test, acceleration in a straight-walking test, delayed bar-holding response, acceleration of bar holding) were observed in the offspring of mice, which had received 11 intraperitoneal injections of 140 ng Be/day (as $BeSO_4$) during pregnancy (Tsujii & Hoshishima 1979 - quoted from WHO 1990).

Effects of beryllium nitrate on early and late pregnancy were investigated in rats. When injected intravenously at a dose of 0.316 mg/kg bw on day 1 of pregnancy, implantation and late pregnancy phase were not affected; however, pups, which appeared to be normal when delivered, died after 2-3 days. When administered on

day 11 following mating, all the foetuses were resorbed. Administration of beryllium after the formation of the placenta, (after day 12) did not result in foetal resorption. (Mathur et al. 1987 – quoted from WHO 1990).

In male and female rats, intratracheally injected with 0.6 mg Be/kg (as radioactive beryllium oxide), no consistent effects on reproductive performance (determined by the average number of pregnancies per female, live pups per litter, dead pups per litter, live pups per female, lactation index, or average weight of live pups per female) were observed (Clary et al. 1975 – quoted form ATSDR 2002).

4.6 Mutagenic and genotoxic effects

4.6.1 *In vitro* studies

In vitro studies on mutagenicity and genotoxicity of beryllium compounds are summarised in Table 4.6.1.

4.6.2 *In vivo* studies

CBA mice were exposed by gavage to 117 and 71 mg Be/kg bw (as beryllium sulphate) corresponding to 80 and 50% of the LD50 values, respectively. The number of micronucleated polychromatic erythrocytes was not increased at 24, 48, and 72 hours after dosing (Ashby et al. 1990 – quoted from ATSDR 2002).

4.7 Carcinogenic effects

4.7.1 Inhalation

Lung cancer was observed in rats exposed to beryllium metal aerosols (410-980 mg/m^3 - Nickell-Brady et al. 1994), beryllium oxide (from 0.006 mg Be/m^3 - Vorwald and Reeves 1959) and beryllium sulphate (0.034 mg Be/m^3 - Reeves et al. 1967) and in monkeys exposed to beryllium sulphate (0.035 mg Be/m^3 - Vorwald 1968). In hamsters, exposed to 0.21 or 0.62 mg Be/m^3 (as bertrandite or beryl ore - Wagner et al. 1969), cancer incidence was not increased (all references quoted from ATSDR 2002).

4.7.2 Oral intake

Non-significant increases in the number of lung reticulum cell carcinomas were observed in male rats exposed to 0.3, 2.8 or 31 mg Be/kg bw/day (as beryllium sulphate) in the diet for 2 years (incidences: 10/50, 17/50, 16/50, and 5/50 in males and 5/50, 7/50, 7/50, and 5/50 in females at 0, 0.3, 2.8, and 31 mg Be/kg bw/day, respectively). No differences in the number of lung reticulum cell carcinoma bearing rats were observed in the beryllium-exposed rats compared to controls (12/50, 18/50, 16/50, and 13/50 for males and 8/50, 11/50, 7/50, and 8/50 for females at 0, 0.3, 2.8, and 31 mg Be/kg bw/day). (Morgareidge et al. 1975 – quoted from ATSDR 2002). Non-neoplastic effects are addressed in section 4.4.2.

Table 4.6.1 *In vitro* studies on mutagenicity and genotoxicity of beryllium compounds (From ATSDR 2002 and WHO 1990).

Test object	End point/ Test system	Compound	Results +/- activation	Reference
Salmonella typhimurium	Gene mutation/ Ames test	Beryllium sulphate	Negative/negative	Arlaukas et al. (1985), Ashby et al. (1990), Rosenkranz and Poirer (1979), Simmon et al. (1979), Simmon (1979a)
Salmonella typhimurium	Gene mutation/ Ames test	Beryllium nitrate	No data/negative	Arlauskas et al. (1985)
Bacillus subtilis	Gene mutation/ Forward mutation assay	Beryllium sulphate	No data/positive	Kanematsu et al. (1980)
Escherichia coli	Gene mutation/ Forward mutation assay	Beryllium chloride	No data/negative	Zakour and Glickman (1984)
Photobacterium fischeri	Gene mutation/ Reverse mutation assay	Beryllium chloride	No data/positive	Ulitzur and Barak (1988)
Saccharomyces cerevisiae	Gene mutation	Beryllium sulphate	No data/negative	Simmon (1979b)
Chinese hamster ovary K1-BH4 cell	Gene mutation	Beryllium sulphate	No data/positive	Hsie et al. (1979)
Chinese hamster V79 cells	Gene mutation	Beryllium chloride	No data/positive (2 and 3 M 6-fold enhanced induction)	Miyaki et al. (1981)
Chinese hamster ovary cell	Chromosomal aberration	Beryllium sulphate	No data/negative	Brooks et al. (1989)
Chinese hamster lung cells	Chromosomal aberration	Beryllium sulphate	Negative/negative	Ashby et al. (1990)
Syrian hamster cells	Chromosomal aberration	Beryllium sulphate	No data/positive (19% aberrations at 0.03 M compared with 1.5% in controls. Dose-related increase in SCE)	Larramendy et al. (1981)
Human lymphocytes	Chromosomal aberration	Beryllium sulphate	No data/positive (Clear clastogenic effect. Dose-related increase in SCE)	Larramendy et al. (1981)
Rat hepatocytes	DNA repair	Beryllium sulphate	No data/negative	Williams et al. (1989)

SCE: Sister chromatid exchange

Non-significant increases in the number of tumours were observed in rats and mice exposed to 1 mg Be/kg bw/day (as beryllium sulphate) in the drinking water for 2.3 and 2.5 years, respectively (Schroeder and Mitchener 1975a, 1975b – quoted from ATSDR 2002). Non-neoplastic effects are addressed in section 4.4.2.

Non-significant increases in the number of neoplasms were observed in dogs exposed to 1 or 12 mg Be/kg bw/day (as beryllium sulphate) in the diet for 172 or 33 weeks, respectively (Morgareidge et al. 1976 – quoted from ATSDR 2002). Non-neoplastic effects are addressed in section 4.4.2.

4.7.3 Dermal contact

No data have been located.

5 Regulations

5.1 Ambient air

Denmark (C-value):	Beryllium compounds as inorganic dust: 0.00001 mg Be/m^3 (MST 2002).
WHO:	-
US-EPA:	-

5.2 Drinking water

Denmark:	-
WHO:	Beryllium is included in the plan of work of the rolling revision of the WHO Guidelines for Drinking-water Quality.
US-EPA:	DWEL (Drinking water equivalent level): 70 µg/l MCL (Maximum Contaminant Level): 40 µg/l (US-EPA 2004).

5.3 Soil

Denmark:	-

5.4 Occupational Exposure Limits

Denmark:	Beryllium powder and beryllium compounds: 0.001 mg/m^3, Notation K (At 2007).
ACGIH:	Threshold limit values (TVLs): Time-weighted average (TWA) 0.002 mg Be/m^3, Short-term exposure 0.01 mg Be/m^3 (ACGIH 2001).
Germany:	Beryllium and beryllium compounds on list of allergens (MAK 2005).
UK:	Beryllium and beryllium compounds (as Be): Long term exposure limit (TWA) 0.002 mg/m^3 (HSE 2007).

5.5 Classification

Beryllium:
Carc2;R49 T;R25-48/23 Tx;R26 Xi;R36/37/38 R43 (MM 2005).

Beryllium compounds (except aluminium beryllium silicates):
Carc2;R49 T;R25-48/23 Tx;R26 Xi;R36/37/38 R43 N;R51/53 (MM 2005).

Beryllium oxide:
Carc2;R49 T;R25-48/23 Tx;R26 Xi;R36/37/38 R43 (MM 2005).

5.6 IARC

Beryllium and beryllium compounds are *carcinogenic to humans (Group 1)*, based on sufficient evidence in humans and experimental animal for the carcinogenicity of beryllium and beryllium compounds (IARC 1997).

5.7 US-EPA

Oral reference dose (RfD) of 0.002 mg/kg bw/day based on a BMD_{10} of 0.46 mg/kg bw/day (as $BeSO_4$) for small intestinal lesions observed in a 172 weeks oral study in dogs (Morgareidge et al. 1976) and an uncertainty factor of 300 consisting of 10 for extrapolation for interspecies differences, 10 for consideration of intraspecies variation, and 3 for database deficiencies (human toxicity data by the oral route are lacking, and reproductive/developmental and immunotoxicologic endpoints have not been adequately assessed in animals). Since the principal study is of chronic duration and a benchmark dose is used, there are no uncertainty factors for duration or NOAEL/LOAEL extrapolation. No modifying factor was proposed for this assessment. (IRIS 2008).

Evidence for human carcinogenicity: B1; probable human carcinogen. Based on the limited evidence of carcinogenicity in humans exposed to airborne beryllium (lung cancer) and sufficient evidence of carcinogenicity in animals (lung cancer in rats and monkeys inhaling beryllium, lung tumours in rats exposed to beryllium via intratracheal instillation, and osteosarcomas in rabbits and possibly mice receiving intravenous or intramedullary injection), beryllium is reclassified from a B2 (inadequate human data) to a B1 probable human carcinogen (limited human data) using criteria of the 1986 Guidelines for Carcinogen Risk Assessment. Using the 1996 proposed Guidelines for Carcinogen Risk Assessment, inhaled beryllium would be characterized as a "likely" carcinogen in humans, and the human carcinogenic potential of ingested beryllium cannot be determined. (IRIS 2008).

5.8 ATSDR

ATSDR derived a chronic-duration oral minimal risk level (MRL) of 0.002 mg Be/kg bw/day based on a BMD_{10} of 0.56 mg Be/kg bw/day for small intestinal lesions observed in dogs (Morgareidge et al. 1976) and an uncertainty factor of 100 (10 for interspecies and 10 for intraspecies variations) and a modifying factor of 3 (account for lack of studies to support the gastrointestinal effects found in the study by Morgareidge et al. 1976 and the uncertainty as to whether the BMD is the NOAEL) (ATSDR 2002).

6 Summary and evaluation

6.1 Description

Beryllium is a naturally occurring alkaline earth metal. It exists in the oxidation states 0 and +2 and belongs to group IIA of the periodic table together with magnesium and calcium. Chemically it is very similar to aluminium, which like beryllium has a high charge-to-radius ratio. Beryllium is highly reactive and exists only under normal environmental conditions associated with other elements. Two radionuclides, ^{7}Be and ^{10}Be, are formed in the atmosphere by the interaction of cosmic-ray particles. The radioactive half-life of ^{7}Be and ^{10}Be is 53.29 days and 1.51×10^{6} years, respectively.

6.2 Environment

Beryllium is the 44th most abundant element in the earth's crust, with an average content of about 2-5 mg/kg. The natural average contents of beryllium in fossil fuels are 1.8-2.2 mg/kg (dry weight) in coal and up to 100 µg/l in oil. Beryllium is an element and thus does not degrade in the environment.

Beryllium is naturally released to surface water and groundwater by the weathering of rocks and soils and from the deposition of windblown dusts and volcanic particles. Anthropogenic sources of beryllium released into water include wastewater effluents from the industry and from the deposition of atmospheric combustion particles. In Denmark, beryllium was found in 90 of 313 groundwater samples across the country. The concentrations range from 0.002 (detection limit) to 2.2 µg/l with an average concentration of 0.15 µg/l and a median of 0.02 µg/l. The concentrations of sixteen of these samples (located in the counties of Sønderjylland, Ribe or Ringkøbing) were above 0.2 µg/l.

Beryllium is naturally present in soil and atmospheric beryllium particles return to earth through wet and dry deposition. Disposal of coal fly ash and municipal solid waste incinerator ash in landfills, and land application of sewage sludge may increase the concentration of beryllium in soil. Beryllium concentrations in ammonia, nitrate, and phosphorus fertilizers used in agriculture have been reported to be in the ranged from <0.2 to 13.5 mg/kg. Within the environmental pH range of 4-8, beryllium is strongly adsorbed by sedimentary minerals and thus prevented from release to groundwater. In Florida and California the average concentration of beryllium in soil were 0.46 mg/kg and 1.14 mg/kg, respectively.

6.3 Human exposure

The general population is exposed to beryllium by inhalation of air and ingestion of drinking water and food. Individuals may be exposed to high levels of beryllium from implanted dental prostheses. A release up to 8 µg/day per dental crown was measured in an artificial oral environment.

Using the average and highest reported concentrations of beryllium in Danish ground water of 0.15 and 2.2 µg/l, respectively, and consumption rates of 0.03 and 0.08 l/kg bw/day, (median value and 95th percentile, respectively, for children

1-10 years old), the intake of beryllium from drinking water would be 0.005 and 0.18 µg/kg bw/day, respectively, (assuming no dilution of groundwater). For an adult, assuming an average consumption rate of 1.4 litre/day and a 90th percentile consumption rate of 2.3 litre/day, respectively, the daily exposure to beryllium from drinking water would be 0.2 and 5.1 µg/day (about 0.003 and 0.07 µg/kg bw/day, respectively, assuming an adult body weight of 70 kg).

Reliable data on the daily dietary intake of beryllium are lacking. In the US, the estimated daily intake of beryllium in food is 0.12 µg. In two studies from Japan, the average daily intake of beryllium was determined to be 5 and 84.4 µg/day, respectively. Other reported daily intakes of beryllium from food range from 5 to 100 µg/day.

Using the highest average atmospheric concentrations measured in urban air in the US of 6.7 ng Be/m^3 and assuming the inhalation rate as 0.5 m^3/kg bw/day (for children 1-5 years old), the inhalation exposure of beryllium will be 0.003 µg/kg bw/day. For an adult, assuming an average inhalation rate as 13 m^3/day or a high inhalation rate as 20 m^3/day, the daily inhalation exposure to beryllium from ambient air would be about 0.09 µg/day (average, about 0.001 µg/kg bw/day assuming an adult body weight of 70 kg) or about 0.13 µg/day (high, about 0.002 µg/kg bw/day).

6.4 Toxicokinetics

No data regarding absorption, distribution or excretion in humans after oral exposure to beryllium were located.

Animal data indicate that beryllium and its compounds are poorly absorbed through the gastrointestinal tract. Studies in pigs, rats, mice, monkeys, dogs and cows showed that <1% of the oral administered doses of radioactive beryllium chloride were absorbed.

Absorbed beryllium is distributed throughout the body. The greatest amount of beryllium has been measured in liver and skeleton in mice and rats, respectively. In rats, dietary exposed to beryllium sulphate for 2 years, the beryllium accumulation in the bones was proportional to the administered dose.

Beryllium and its compounds are not biotransformed. In mice, dogs and monkeys, exposed to radioactive beryllium chloride by gavage, most of the radiolabel was excreted in the faeces. The primary routes of elimination of absorbed beryllium are through the urine. In rats, exposed to beryllium sulphate in drinking water, the urinary excretion was 0.5% of the total dose.

A study on human colostrum, maternal and umbilical cord sera, indicates that beryllium is transferred across the placenta and excreted via breast milk. The levels of beryllium in umbelical cord serum and in colostrum were higher than in maternal serum. In cows, less than 0.002% of ingested doses of radioactive beryllium chloride were secreted in the milk.

6.5 Human toxicity

6.5.1 Single dose toxicity

No relevant data have been located.

6.5.2 Irritation and sensitisation

Irritation and beryllium sensitisation have been reported in workers following occupational contact with beryllium.

6.5.3 Repeated dose toxicity

No human data regarding repeated dose toxicity following oral exposure to beryllium compounds have been found.

6.5.4 Toxicity to reproduction

No human data regarding toxicity to reproduction following exposure to beryllium compounds have been found.

6.5.5 Mutagenic and genotoxic effects

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

6.5.6 Carcinogenic effects

No human data regarding carcinogenicity following oral exposure to beryllium compounds have been found.

6.6 Animal toxicity

6.6.1 Single dose toxicity

In mice, reported oral LD_{50}-values were 6.95 and 140 mg Be/kg bw for beryllium sulphate and 19.1 mg Be/kg bw for beryllium fluoride. In rats, reported oral LD_{50}-values were 7.02 and 120 mg Be/kg bw for beryllium sulphate, 9.8 and 200 mg Be/kg bw for beryllium chloride and 6.5 mg Be/kg bw for beryllium phosphate.

6.6.2 Irritation and sensitisation

Beryllium sensitisation has been observed in C3H mice following application of beryllium sulphate to the dorsal side of the ear for 3 consecutive days per week for 2 weeks.

6.6.3 Repeated dose toxicity

The toxicity of beryllium compounds following repeated exposure was studied in rats, mice and dogs using the oral route, in studies with durations ranging from 13 days to 172 weeks.

Gastrointestinal effects were observed in dogs at dose levels from 1.1 mg Be/kg bw/day (ulcerative and inflammatory lesions - beryllium sulphate tetrahydrate in the diet for 172 weeks).

Skeletal effects were observed in rats at dose levels from 70 mg Be/kg bw/day (rickets – beryllium carbonate in the diet for 21 days).

A number of other effects in dogs, rats and mice were reported following chronic oral exposure to beryllium compounds. Effects on the body weight were observed in mice, dogs and rats from 1, 12.2 and 480 mg Be/kg bw/day, respectively. Increased mortality was observed in dogs at 12 mg Be/kg bw/day. Metabolic effects were observed in rats (transient glucosuria and increases in serum cholesterol) from 0.7 mg Be/kg bw/day. Haematological effects were observed in dogs (erythroid hypoplasia of the bone marrow and slight decrease in erythrocyte, haemoglobin and haematocrit levels) at 12.2 mg Be/kg bw/day. In a two-year study in rats a slight increase in the kidney weight was observed at 31 mg Be/kg bw/day.

6.6.4 Toxicity to reproduction

In a chronic duration study with dogs exposed to 1 mg Be/kg/day (as beryllium sulphate in the diet) no alterations in fertility and no developmental effects in the offspring were observed.

In rats, exposed for beryllium sulphate in the diet for 2 years, a significant decrease in the average absolute testes weight was observed at concentrations of 0.3 and 2.8 mg Be/kg/day, but not at 31 mg Be/kg/day. No histological alterations were observed in the reproductive tissues.

Effects on the behaviour were observed in the offspring of mice, which had received 11 intraperitoneal injections of 140 ng Be/day (as $BeSO_4$) during pregnancy.

6.6.5 Mutagenic and genotoxic effects

Beryllium sulphate was mutagenic in *in vitro* test with *B. subtilis* and Chinese hamster K1-BH4 ovary cells, but not with *S. typhimurium* or *S. cerevisiae.*

Beryllium chloride was mutagenic in *in vitro* test with *P. fischeri* and Chinese hamster V79 cells but not with *E. coli.*

Beryllium nitrate was not mutagenic in *in vitro* test with *S. typhimurium*

Beryllium sulphate caused a dose-related increase in sister chromatid exchanges in Syrian hamster cells and human lymphocytes *in vitro,* but no chromosomal aberrations were observed in Chinese hamster ovary cells or in Chinese hamster lung cells.

Beryllium sulphate showed a negative response in an *in vitro* DNA-repair test with rat hepatocytes and in an *in vivo* mammalian micronucleus test with CBA mice.

6.6.6 Carcinogenic effects

Three oral carcinogenicity studies with beryllium sulphate in animals have been located.

No difference in the number of lung reticulum cell carcinoma bearing rats and a non-significant increase in the number of lung reticulum cell carcinomas were

observed in rats exposed up to 31 mg Be/kg bw/day in the diet for 2 years compared to controls.

Non-significant increases in the number of tumours were observed in rats and mice exposed chronically to 1 mg Be/kg bw/day in the drinking water.

Non-significant increases in the number of neoplasms were observed in dogs exposed up to 12 mg Be/kg bw/day in the diet for 172 weeks.

6.7 Evaluation

The general population is primarily exposed to beryllium from food and drinking water.

Animal data indicate that less than 1% of ingested beryllium is absorbed through the gastrointestinal tract. Absorbed beryllium is excreted via the urine. Some studies indicate that transfer of beryllium through the placenta and breast milk of exposed mothers can take place.

The acute toxicity of beryllium compounds in experimental animals is high with reported LD_{50}-values ranging from 6.5 to 200 mg Be/kg bw in rats and from 6.95 to 140 mg Be/kg bw in mice. Signs of acute beryllium toxicity were respiratory disorders, spasms, hypoglycaemic shock (attributed to liver necrosis), and respiratory paralysis.

Signs of irritation and beryllium sensitisation in humans have only been reported after inhalation or dermal exposure to beryllium. In mice, beryllium sensitisation was reported after dermal application of beryllium sulphate.

Repeated dose toxicity of beryllium compounds has been extensively studied in a number of animal species using inhalation (rat, mouse, rabbit, guinea pig, hamster, dog, cat, monkey), oral (rat, mouse, dog) and dermal (guinea pig) exposure routes. The critical effects observed after oral exposure are extensive ulcerative and inflammatory gastrointestinal lesions in dogs exposed to beryllium sulphate tetrahydrate at a dietary dose of 12 mg Be/kg bw/day with less severe lesions in the small intestine, stomach, and large intestine observed in 1 of 10 dogs at 1.1 mg Be/kg bw/day, and beryllium rickets in rats exposed to beryllium carbonate from 70 mg Be/kg bw/day. Beryllium in the gut binds to soluble phosphorus compounds to form insoluble beryllium phosphate and beryllium rickets may be due to a phosphorus deficiency rather than to a direct effect of beryllium on the bone tissue.
A NOAEL of 0.12 mg Be/kg bw/day is considered for gastrointestinal effects in dogs based on the study by Morgareidge et al. (1976).
No human oral repeated-dose exposure data were located.

Animal data on reproductive and developmental toxicity of beryllium compounds are limited and no human data were located. No histological alterations were observed in reproductive tissues of rats orally exposed to beryllium sulphate and no developmental effects were observed in the offspring of dogs orally exposed to beryllium sulphate. However, due to limitations in the studies, the available data are not considered adequate in order to evaluate the reproductive and developmental potential of stable beryllium compounds.

The genotoxicity of beryllium compounds has been investigated in multiple *in vitro* tests but the results are inconsistent. The inconsistencies may have been due to differences in assay conditions and the physico/chemical properties of beryllium (e.g. binding of beryllium to phosphate, hydroxide, or proteins in the

culture media). One *in vivo* mammalian erythrocyte micronucleus test with negative result was located. No studies were located regarding genotoxicity in humans after exposure to beryllium compounds. Because the available data on genotoxicity are inconsistent, no firm conclusion can be drawn for beryllium compounds in this regard.

Beryllium is carcinogenic to humans following inhalation. Increased incidences of lung cancer deaths following inhalation exposure were reported in retrospective cohort mortality studies of workers at beryllium extraction, processing, and fabrication facilities. A positive association between length of latency and lung cancer deaths was found, with the highest cancer risks among workers with a latency of at least 25 years.

Beryllium was not carcinogenic in animals following oral exposure. However, no human data were located and the animal data are very limited. Thus, no firm conclusion can be drawn for the human carcinogenic potential of ingested beryllium compounds.

6.7.1 Critical effect and NOAEL

Animal data indicate that gastrointestinal effects are the critical effects following oral repeated exposure to soluble beryllium compounds. Ulcerative gastrointestinal lesions were observed in dogs following exposure to beryllium sulphate tetrahydrate in the diet.

A NOAEL for gastrointestinal effects of 0.12 mg Be/kg bw/day is considered for dogs based on the 143-172 days oral study with beryllium sulphate tetrahydrate (Morgareidge et al. 1976). This NOAEL could form the basis for the purpose of estimating a quality criterion in drinking water
Alternatively, a benchmark dose approach could be considered as has been done by the US-EPA (US-EPA 1998, IRIS 2008). Dose-response modelling of the data for small intestinal lesions in male and female dogs (0/10, 0/10, 0/10, 1/10 and 9/10) was conducted to derive a benchmark dose for beryllium. A BMD_{10} (the lower 95% confidence limit on the dose from the maximum likelihood estimate (MLE) of a 10% relative change, MLE = 1.4 mg/kg bw/day) of 0.46 mg/kg bw/day was derived for this lesion.

By using the newest version of the US-EPA BMD software, the calculated acceptable BMD_{10} values ranged from 0.773-1.37 mg Be/kg bw/day and the $BMDL_{10}$ values ranged from 0.328 to 0.434 mg Be/kg bw/day. The log-probit model gave the best fit with a $BMDL_{10}$ of 0.40 mg/kg bw/day, i.e., a little bit lower than the $BMDL_{10}$ of 0.46 mg/kg bw/day as derived by the US-EPA (US-EPA 1998, IRIS 2008). It should be noted that the newest version of the US-EPA BMD software include eight different models with three in the earlier version used by US-EPA (1998); only one (Weibull) of the three models in the earlier version is included in the newest version of the US-EPA BMD software.

A health based quality criterion in drinking water for repeated exposure to soluble inorganic beryllium salts will be estimated based on the $BMDL_{10}$ of 0.40 mg Be/kg bw/day derived from the Morgareidge et al. (1976) study.

7 TDI and quality criteria

7.1 TDI

The TDI is calculated based on the $BMDL_{10}$ of 0.40 mg Be/kg bw/day for small intestinal lesions from the dog study with beryllium sulphate tetrahydrate (Morgareidge et al. 1976).

$$TDI = \frac{BMDL_{10}}{UF_I * UF_{II} * UF_{III}} = \frac{0.40 \text{ mg Be/kg bw/day}}{10 * 10 * 5} = 0.80 \text{ µg Be/ kg bw/day}$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than the dog. 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 5 as the $BMDL_{10}$ is an effect level (1/10 animals affected at the $BMDL_{10}$) and taking into account that data on oral repeated toxicity, carcinogenicity and reproductive and developmental toxicity in general are very old and inadequate. In addition the data on genotoxicity was inconclusive.

7.2 Allocation

The general population is exposed to beryllium by inhalation of air and ingestion of drinking water and food.

Using the average and highest reported concentrations of beryllium in Danish ground water of 0.15 and 2.2 µg/l, respectively, and consumption rates of 0.03 and 0.08 l/kg bw/day, (median value and 95th percentile, respectively, for children 1-10 years old), the intake of beryllium from drinking water would be 0.005 and 0.18 µg/kg bw/day, respectively, (assuming no dilution of groundwater). For an adult, assuming an average consumption rate of 1.4 litre/day and a 90th percentile consumption rate of 2.3 litre/day, respectively, the daily exposure to beryllium from drinking water would be 0.2 and 5.1 µg/day (about 0.003 and 0.07 µg/kg bw/day, respectively, assuming an adult body weight of 70 kg).

Reliable data on the daily dietary intake of beryllium are lacking. In the US (1987), the estimated daily intake of beryllium in food was 0.12 µg (0.002 µg Be/kg bw/day assuming an adult body weight of 70 kg). In two studies from Japan, the average daily intake of beryllium was determined to be 5 (1996) and 84.4 µg/day (1994) (0.07 and 1.2 µg Be/kg bw/day, respectively). . Other reported daily intakes of beryllium from food range from 5 to 100 µg/day (0.07-1.4 µg Be/kg bw/day, respectively).

Using the highest average atmospheric concentrations measured in urban air in the US of 6.7 ng Be/m^3 and assuming the inhalation rate as 0.5 m^3/kg bw/day (for children 1-5 years old), the inhalation exposure of beryllium will be 0.003 µg/kg bw/day. For an adult, assuming an average inhalation rate as 13 m^3/day or

a high inhalation rate as 20 m^3/day, the daily inhalation exposure to beryllium from ambient air would be about 0.09 µg/day (average, about 0.001 µg/kg bw/day assuming an adult body weight of 70 kg) or about 0.13 µg/day (high, about 0.002 µg/kg bw/day).

Table. Estimated exposures from various media

Medium	Adults (body weight 70 kg)		Children (1-2/3 years)	
	Average	High exposure	Average	High exposure
Ambient air [a]	0.001 µg Be/ kg bw/day	0.002 µg Be/ kg bw/day	0.003 µg Be/ kg bw/day	-
Drinking water	0.003 µg Be/ kg bw/day [b]	0.07 µg Be/ kg bw/day [c]	0.005 µg Be/ kg bw/day [b]	0.18 µg Be/ kg bw/day [c]
Soil	-	-	-	-
Diet	0.002-1.4 µg Be/ kg bw/day [d]	-	-	-

a) Based on the highest average atmospheric concentration in US urban air of 0.0067 µg Be/m^3.
b) Based on the average value for the concentration of beryllium in Danish groundwater of 0.15 µg Be/l.
c) Based on the highest reported concentration of beryllium in Danish groundwater of 2.2 µg Be/l.
d) Range of reported values.

Based on these data, the contribution of beryllium from food and air is considered as being at the same order of magnitude as the contribution of beryllium from the drinking water. Therefore, only 50% of the TDI is allocated to ingestion of drinking water.

7.3 Quality criterion in drinking water

The quality criterion in drinking water QC_{dw} is calculated based on the TDI of 0.80 µg Be/kg bw/day derived by using the benchmark dose approach and assuming a daily ingestion of 0.03 l/kg bw of drinking water for children 1-10 years old:

$$QC_{dw} = \frac{TDI * Y}{ingestion_{dw}} = \frac{0.80\ \mu g\ Be/kg\ bw/day * 0.5}{0.03\ l/kg\ bw/day}$$

$$= 13.4\ \mu g\ Be/l$$

7.3.1 Quality criterion in drinking water

15 µg Be/l

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Beryllium, inorganic and soluble salts

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to the inorganic and soluble salts of beryllium. This resulted in 2009 in the present report which includes estimation of a quality criterion in drinking water for the mentioned substances.

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