June 2023

The SCOEL recommendation document covers the following substances:

Substance name	EC number	CAS RN
Beryllium	231-150-7	7440-41-7
Beryllium acetylide	208-050-7	506-66-1
Beryllium, bis(carbonato(2-))dihydroxytri- (Beryllium carbonate)	-	66104-24-3
Beryllium carbonate	236-030-8	13106-47-3
Beryllium chloride	232-116-4	7787-47-5
Beryllium diammonium tetrafluoride	238-948-4	14874-86-3
Beryllium diboride	235-443-0	12228-40-9
Beryllium diboride	235-694-6	12536-51-5
Beryllium dibromide	232-115-9	7787-46-4
Beryllium diiodide	232-119-0	7787-53-3
Beryllium fluoride	232-118-5	7787-49-7
Beryllium hexaboride	235-657-4	12429-94-6
Beryllium hydroxide	236-368-6	13327-32-7
Beryllium nitrate (Beryllium nitrate (anhydrous))	237-062-5	13597-99-4
Nitric acid, beryllium salt, tetrahydrate (Beryllium dinitrate tetrahydrate)	690-699-4	13510-48-0
Beryllium orthosilicate	239-251-8	15191-85-2
Beryllium silicate (phenakite) *	-	13598-00-0
Beryllium oxide	215-133-1	1304-56-9
Phosphoric acid, beryllium salt (2:3) (Beryllium phosphate)	-	13598-26-0
Beryllium phosphide	261-137-1	58127-61-0
Beryllium selenide	235-450-9	12232-25-6
Beryllium sulphate (Beryllium sulphate (anhydrous))	236-842-2	13510-49-1
Beryllium sulphate (dihydrate) *	-	14215-00-0
Beryllium sulfate tetrahydrate	629-461-1	7787-56-6
Beryllium sulphide	237-064-6	13598-22-6
Beryllium telluride	235-451-4	12232-27-8
Beryllium zinc silicate	247-151-0	25638-88-4
Phosphoric acid, beryllium salt	252-356-3	35089-00-0
Silicic acid, beryllium salt	261-293-0	58500-38-2
Tetraberyllium boride	235-695-1	12536-52-6
Triberyllium nitride	215-132-6	1304-54-7

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Substance name	EC number	CAS RN
Bertrandite	235-299-9	12161-82-9
Beryl (Al2Be3(SiO3)6)	215-101-7	1302-52-9

*: not found in ECHA database – note: Beryllium silicate is found with other identifiers.

This text is not part of the official SCOEL Recommendation and is provided to give additional helpful information to the reader as regards chemicals addressed by the SCOEL Recommendation. The list is non-exhaustive and is presented for information purposes only.

SCOEL/REC/175 Beryllium and Inorganic Beryllium Compounds

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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Adopted 8th of February 2017

EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
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SCOEL/REC/175
Beryllium and Inorganic Beryllium Compounds

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR BERYLLIUM AND INORGANIC BERYLLIUM COMPOUNDS

8-hour TWA:	0.02 µg/m^3 beryllium (inhalable fraction)
STEL:	0.2 µg/m^3 beryllium (inhalable fraction)
BLV:	None recommended
BGV:	0.04 µg beryllium/l urine (sampling time not critical)
Additional categorisation:	Carcinogenicity group C (genotoxic carcinogen with a mode-of action based threshold)
Notations	Sensitisation (dermal and respiratory) No skin notation

The present Recommendation was adopted by SCOEL on 2017-02-08.

This evaluation is mainly based on ATSDR (2002), Greim (2005), JRC (2012), NTP (2005), US EPA (2008), WHO (2001, 2009), OSHA (2015), the references cited in these reviews and a literature update (time period 2002–2015).

RECOMMENDATION EXECUTIVE SUMMARY

This Recommendation comprises beryllium and its inorganic compounds. It is assumed that the toxicity of these substances is attributable to the beryllium ion, which makes them similar from a toxicity and hazard point of view.

Inhaled beryllium is deposited in the lung tissue, particularly in pulmonary lymph nodes. It is distributed from the lungs to the skeleton, after being very slowly absorbed into the blood. The skeleton is the ultimate site of beryllium storage. Trace amounts are distributed throughout the body. Less than 1 % of orally administered beryllium is absorbed via the gastrointestinal tract.

The lung is the main target organ at inhalation exposure to beryllium and beryllium compounds. At relevant exposure concentrations, critical health effects comprise carcinogenicity, beryllium sensitization (BeS) and chronic beryllium disease (CBD).

Carcinogenicity and genotoxicity

Beryllium and its inorganic compounds are carcinogenic in human and animals. Increased mortality from lung cancer has been shown in a number of studies in exposed workers, at concentrations of 10 µg/m^3 and higher. With respect to genotoxicity, soluble beryllium compounds showed inconsistent results regarding the induction of sister chromatid exchanges, chromosomal aberrations and gene mutations in mammalian cells *in vitro*. Two *in vivo* studies were negative: in workers exposed up to 20 µg/m³ for more than 4 hours per week, no sister chromatid exchange or micronuclei were induced, compared to persons exposed for 4 hours per week or less (no further data available). An oral mouse micronucleus test showed no genotoxic effects of beryllium sulphate; however, due to the limited absorption and thus low systemic availability of beryllium via the gastrointestinal tract, this exposure route is not very informative. Another oral *in vivo* study in mice gave positive results for chromosomal aberrations in somatic cells after oral treatment with beryllium chloride, albeit at very high concentratons.

The genotoxic effects *in vitro* may be the result of induction of DNA-protein complexes and interaction with DNA polymerases. Furthermore, the hypermethylation of promotor sequences has been discussed as an indirect mechanism linked to carcinogenicity. Also, beryllium sulphate and extracts of beryllium metal were shown to induce cell transformation, in BALB/c-3T3 cells and in embryonic Syrian Hamster cells.

In summary, even though the mechanism of action of the carcinogenicity of beryllium is not yet elucidated, it appears to involve indirect genotoxicity and cell transformation rather than direct genotoxicity.

Therefore, beryllium and its inorganic compounds must be considered as human carcinogens and are categorised in SCOEL *carcinogen group C (genotoxic carcinogen for which a practical threshold may exist)* (Bolt and Huici-Montagud 2008).

Local non-cancer effects

Single inhalation exposures to high beryllium concentrations (> 100 µg/m³) can cause acute beryllium disease (ABD) in humans. Signs and symptoms of ABD range from mild inflammation of the upper respiratory tract to tracheo-bronchitis and severe pneumonitis.

In humans, repeated exposure to low concentrations of beryllium and beryllium compounds can cause beryllium sensitisation (BeS) and chronic beryllium disease (CBD). Both endpoints correlate with dust exposure intensity to beryllium. Several cases of BeS have been observed at total dust levels around 0.1 µg/m^3. This is supported by a recent risk assessment published by the Occupational Safety and Health Administration (OSHA), Department of Labor, USA, estimating risks for BeS and CBD of 7 to 35 cases and 3 to 26 cases per 1000 workers, respectively, at 0.1 µg/m^3 (OSHA 2015). Some studies considered exposure to respirable beryllium; one single case of BeS was seen at a median lifetime-weighted respirable exposure of 0.035 µg/m³ and two cases of CBD at 0.024 µg/m^3 and 0.038 µg/m^3 (Kelleher *et al* 2001). No sensitisation was observed in

workers who had a median lifetime-weighted exposure to 0.02 µg beryllium/m³ (NOAEC) (Kelleher *et al* 2001, Rosenman *et al* 2005). In the study of Schuler *et al* (2012), the lowest level of respirable dust associated with BeS was 0.04 µg/m³ (average life-time exposure), 0.01 µg/m³-years (cumulative exposure), and 0.04 µg/m³ (highest exposed job).

Systemic effects

After repeated inhalation, cardiovascular, renal, hepatic and haematological effects, and weight loss were observed in humans, which may be a consequence of functional respiratory restrictions.

Reproductive toxicity

There were no data on reproductive toxicity in humans and no animal data after inhalation exposure. In rats and dogs, beryllium sulphate after oral administration did not exert any reproductive toxicity. However, due to the low systemic bioavailability of beryllium compounds including beryllium sulphate, this study is not informative for relevant worker exposure via inhalation.

Recommendation for an OEL

Recent studies have shown that individuals who are sensitised to beryllium (BeS) are considered to be at risk of developing subclinical and clinical CBD. An OEL should therefore protect from both these endpoints, as well as from carcinogenicity. Protection from BeS is also in agreement with OSHA, stating that "sensitization to beryllium is an essential step for worker development of CBD" (OSHA 2015). BeS and CBD have been correlated to respirable and total dust exposure. As evident from the studies listed in Tables 8a and 8b, several cases of BeS have been observed at mean total dust levels around 0.1 µg/m^3. Considering the severity of the effects, an OEL of 0.02 µg/m^3 for the inhalable dust fraction is recommended. This value also covers the NOAEC for BeS and CBD of 0.02 µg respirable beryllium/m³ derived out of a human lifetime-weighted median exposure (Kelleher *et al* 2001), which is also supported by Schuler *et al* (2012) who reported a LOAEC of 0.04 µg/m^3 at an average concentration for the respirable fraction. A NOAEL for the carcinogenic effects cannot be determined from the studies available. Since beryllium is not directly genotoxic and a synopsis of available data indicate that the described carcinogenic effects occurred at considerably higher concentrations, it can be assumed that this OEL will protect also from carcinogenic effects.

STEL

In addition to long-term exposure, high short-term exposure may correlate with the development of CBD. Based on the evaluation within the Madl study (Madl *et al* 2007), which revealed that beryllium-sensitised workers and those exerting CBD were exposed to concentrations higher than 0.2 µg/m^3 (95th percentile), a STEL of 0.2 µg/m^3 is proposed.

Sensitisation

Beryllium is a respiratory sensitiser. BeS is the immune response to beryllium and a predictor for CBD. Beryllium and beryllium compounds can cause allergic contact dermatitis or a granulomatous skin reaction in humans. Beryllium compounds have been shown to be skin sensitisers in animal experiments. A notation for sensitisation is therefore recommended, for both the skin and the respiratory tract.

Skin

The absorption of beryllium through intact skin is low, as beryllium is bound by epidermal constituents. However limited studies suggest that beryllium particles may be able to penetrate into human skin and induce BeS, which can progress to CBD. Although further research is needed, it is prudent to reduce both skin and inhalation exposures. Therefore skin contact has to be avoided, but a skin notation referring to skin absorption is not recommended.

Biological Guidance Value

Available data are not sufficient to allow a correlation to define a safe biological limit value (BLV). However, studies have shown that the analytical measurement of beryllium in urine can be used as an indicator of current exposure to beryllium. Beryllium can be detected in the urine of not occupationally exposed persons, the 95th percentile was determined as 0.02 or 0.042 µg/l urine in two studies (Heitland and Köster 2004, Goullé *et al* 2005). In a further study of non-occupationally exposed people the 95th percentile of urinary beryllium was 0.012 µg/l (Morton *et al* 2014). Based on the available data, SCOEL recommends a Biological Guidance Value (BGV) of 0.04 µg beryllium/l urine.

Sampling, measurement and analysis

Analytical measurement systems exist to determine the recommended levels with an appropriate level of precision and accuracy.

RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR BERYLLIUM AND INORGANIC BERYLLIUM COMPOUNDS

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

This Recommendation comprises beryllium and its inorganic compounds. As such it is not dealing with one monoconstituent substance but with a group of inorganic (no carbon-hydrogen bonds) monoconstituent substances with one communality, they contain beryllium. It is assumed that the toxicity of these substances is attributable to the beryllium ion, which makes them similar from a toxicity and hazard point of view.

Below, the 'chemical agent' that is the subject of the current recommendation is introduced. Subsequently, a tabled list is provided of inorganic beryllium compounds by name, including the usual molecular formula, the EC No., the CAS No., the molecular weight, solubility in water, melting and boiling point, vapour pressure and density. The structural formula is not indicated for each compound in order not to make the overview too complicated and as it is straightforward for most inorganic beryllium compounds. Furthermore, beryllium and inorganic compound are solid at relevant (room) temperature. Therefore, conversion factors are not applicable.

The list itself including CAS No., EC No. and molecular formula is based on the ECHA substance list (ECHA 2016a). For physical and chemical properties of beryllium and inorganic compounds several references were use (ATSDR 2002, WHO 2001, US EPA 1998, Greim 2005, Strupp 2011b, BeST 2011b).

Beryllium is the 4th element on the periodic table (atomic number of 4) with the symbol "Be". It is a steel-grey, shiny, hard and brittle metal with an atomic weight of 9.01 (Group IIA of the periodic table) (ATSDR 2002, Greim 2005). It has several exclusive physical and chemical properties, which differ considerably from those of the other alkaline earth metals. Beryllium is the lightest of all solid and chemically stable substances. It is lighter than aluminium (two-thirds the density of aluminium) and 40-50 % harder than steel (it has six times the specific stiffness of steel) (BeST 2011a, US EPA 2008). The melting point is unusually high (1 278 °C), the density low, accompanied by a very high specific heat, heat of fusion, sound conductance, and strength-to-weight ratio. Beryllium has two common oxidation states, Be(0) and Be(+2) and the chemical properties are similar to aluminium although aluminium has a different oxidation state [Al(+3)]. With fluoride or oxide, beryllium creates the most stable structures (US EPA 2008). In addition beryllium has a strong tendency for covalent bond formation (e.g. it can form organometallic compounds (ATSDR 2002, WHO 2001, US EPA 2008).

Beryllium oxidises easily in air and water (WHO 2001, Greim 2005). The metal is not soluble in water at neutral pH. However, at pH values between 5 and 8, beryllium metal will react to form insoluble hydroxides and hydrated complexes. Of the beryllium compounds, the carbonate, hydroxide, sulphate (anhydrous) and oxide, are sparingly water soluble, whereas the chloride, fluoride, nitrate, phosphate, and sulphate (tetrahydrate) salts are all soluble. Aqueous solutions of the soluble beryllium salts are

acidic which is a result of the formation of the tetrahydrate $Be(OH_2)_4^{2+}$ (US EPA 1998, WHO 2001).

With atmospheric cosmic-ray particles beryllium forms several radionuclides including beryllium-7 (Be-7) and beryllium-10 (Be-10). The radioactive half-lives of Be-7 and Be-10 are 53.29 and 1.51×10^6 years, respectively (ATSDR 2002).

Further physico-chemical data are provided as tabular overview below.

Substance	CAS No.	EC No.	Molecular Formula	MW (g/mol)	Solubility in water (mg/l)	Melting point (°C)	Boiling point (°C)	Vapour pressure	Density (g/cm^3)
Beryllium	7440-41-7	231-150-7	Be	9.01	< 0.00005 (20°C) (insoluble)	1 287–1 292	2 970 (at 5 mm Hg)	1 mm Hg (1 520 °C); 10 mm Hg (1 860 °C)	1.846 (20 °C)
Beryllium acetylide	506-66-1	208-050-7	CBe_2	30.03					
Beryllium carbonate [a c]	66104-24-3	--	$Be_2CO_3(OH)_2$	112.05	Insoluble in cold water; decomposes in hot water ?	-	-	-	-
Beryllium carbonate	13106-47-3	236-030-8	$BeCO_3$	69.02	Insoluble in cold water; decomposes in hot water ?				
Beryllium chloride	7787-47-5	232-116-4	$BeCl_2$	79.92	71.5; Very soluble, Readily soluble	399.2; 405; 415	482.3; 520	1.291 mm Hg	1.899 (25 °C)
Beryllium diammonium tetrafluoride	14874-86-3	238-948-4	$BeF_4N_2H_8$	121.08					
Beryllium diboride	12228-40-9	235-443-0	B_2Be	30.63					
Beryllium diboride [b]	12536-51-5	235-694-6	BBe_2	28.82					
Beryllium dibromide	7787-46-4	232-115-9	$BeBr_2$	168.82					
Beryllium diiodide	7787-53-3	232-119-0	BeI_2	262.82					
Beryllium fluoride	7787-49-7	232-118-5	BeF_2	47.01	Extremely soluble, readily soluble	555	1 175	-	1.986 (25 °C)
Beryllium hexaboride	12429-94-6	235-657-4	BeB_6	73.87					
Beryllium hydroxide	13327-32-7	236-368-6	$Be(OH)_2$	43.03	3.44 (insoluble to slightly soluble)	Decomposes when heated	-	-	1.92 (20 °C)
Beryllium nitrate (anhydrous)	13597-99-4	237-062-5	$Be(NO_3)_2$	133.02	Very soluble	60	142	-	1.557
Beryllium dinitrate tetrahydrate	13510-48-0	--	$Be(NO_3)_2 \times 4 H_2O$	205.08	1.66×10^6 (readily soluble at 20 °C); 0.2 (30 °C)	2 530 ± 30	3 900	-	3.01
Beryllium orthosilicate	15191-85-2	239-251-8	Be_2SiO_4	110.11					
Beryllium silicate (phenakite) [c]	13598-00-0	--	Be_2SiO_4	110.107					
Beryllium oxide	1304-56-9	215-133-1	BeO	25.01	0.2; 0.00005 (barely soluble [d]	2 508–2 547	3 787	-	3.016 (20 °C)
Beryllium phosphate [c]	13598-26-0	--	$Be_3(PO_4)_2$	216.98			-	-	-
Beryllium phosphide	58127-61-0	261-137-1	Be_3P_2	88.98					
Beryllium selenide	12232-25-6	235-450-9	BeSe	87.98					
Beryllium sulphate (anhydrous)	13510-49-1	236-842-2	$BeSO_4$	105.07	Insoluble in cold water; converted to tetrahydrate in hot water	550–600 (decomposes)	-	-	2.44; 2.443 (20 °C)

Substance	CAS No.	EC No.	Molecular Formula	MW (g/mol)	Solubility in water (mg/l)	Melting point (°C)	Boiling point (°C)	Vapour pressure	Density (g/cm^3)
Beryllium sulphate (dihydrate) [c]	14215-00-0	--	$BeSO_4 \times 2\ H_2O$	141.12					
Beryllium sulphate (tetrahydrate) [c]	7787-56-6	--	$BeSO_4 \times 4\ H_2O$	177.13	3.91×10^5 mg/l (readily soluble at 20°C)	100 (loses 2 H_2O)	400 (loses 4 H_2O)	-	1.713 (10.5 °C)
Beryllium sulphide	13598-22-6	237-064-6	BeS	41.08					
Beryllium telluride	12232-27-8	235-451-4	BeTe	136.61					
Beryllium zinc silicate	25638-88-4	247-151-0	$Be.xH_4O_4Si.xZn$						
Phosphoric acid, beryllium salt	35089-00-0	252-356-3	$Be.xH_3O_4P$						
Silicic acid, beryllium salt	58500-38-2	261-293-0							
Tetraberyllium boride	12536-52-6	235-695-1	BBe_4						
Triberyllium nitride	1304-54-7	215-132-6	Be_3N_2						
Bertrandite	12161-82-9	235-299-9	$4\ BeO \times 2\ SiO_2 \times H_2O$	238.24	-	-	-	-	-
Beryl	1302-52-9	215-101-7	$3\ BeO \times Al_2O_3 \times 6\ SiO_2$	537.5	-	-	-	-	-

[a] Basic beryllium carbonate (mixed salt).
[b] Name is not in line with molecular formula. Name should probably be "Diberyllium boride"
[c] Not in ECHA inventory (ECHA 2017)
[d] The solubility depends on the temperature: beryllium oxide heated to 500 °C is more soluble than if heated to 1 000 °C (no other details) (US EPA 1998).

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonized classification and labelling (CLH) for beryllium and beryllium compounds was taken from the ECHA website (ECHA 2016b). In the EU, CLH exists for two clear identities, i.e. beryllium and beryllium oxide. In addition, one group entry exists for many beryllium-containing compounds. The chemical identification that is used for this group (that contains obviously several not specified CAS No's and EC No's) is as follows: "beryllium compounds with the exception of aluminium beryllium silicates and with those specified elsewhere in Annex VI of CLP". With respect to physical hazards and human health hazards, the entries are identical and presented in Table 1.

Table 1. Classification of beryllium and inorganic beryllium compounds according to Regulation (EC) No 1272/2008, Annex VI, Table 3.1 "List of harmonised classification and labelling of hazardous substances" (ECHA 2016b).

Index no.	**CAS No.**	**EC No.**	**Internat. Chemical Identification**
004-001-00-7	7440-41-7	231-150-7	beryllium
004-003-00-8	1304-56-9	215-133-1	beryllium oxide
004-002-00-2	various	various	beryllium compounds with the exception of aluminium beryllium silicates, and with those specified elsewhere in Annex VI to CLP

Classification		**Labelling**	
Hazard Class & Category Code (s)	**Hazard statement code (s)***	**Hazard statement code (s)***	**Pictogram Signal Word Code (s)**
Acute Tox. 3	H301	H301	GHS06 GHS08 Dgr**
Skin Irrit. 2	H315	H315	
Skin Sens. 1	H317	H317	
Eye Irrit. 2	H319	H319	
Acute Tox. 2	H330	H330	
STOT SE 3	H335	H335	
Carc. 1B	H350i	H350i	
STOT RE 1	H372	H372***	

**Acute Tox. 3 H301 Toxic if swallowed*
Skin Irrit. 2 H315 Causes skin irritation
Skin Sens. 1 H317 May cause an allergic skin reaction
Eye Irrit. 2 H319 Causes serious eye irritation
Acute Tox. 2 H330 Fatal if inhaled
STOT SE 3 H335 May cause respiratory irritation
Carc. 1B H350i May cause cancer by inhalation
STOT RE 1 H372 Causes damage to organs through prolonged or repeated exposure

***Signal word code 'Dgr' for 'Danger*

****The classification under 67/548/EEC indicating the route of exposure has been translated into the corresponding class and category according to this regulation, but a general hazard statement not specifying the route of exposure as the necessary information is not available*

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Beryllium and beryllium compounds are hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and fall within the scope of this legislation.

Beryllium and beryllium compounds are also carcinogens or mutagens for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and fall within the scope of this legislation.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits for beryllium exist in a number of countries including various EU Member States as well as outside the EU. These OEL's are presented in Table 2 as examples and the list should not be considered as exhaustive listing of all limit values within the EU and other countries.

No *BLV* (Biological Limit Value) has been adopted yet for beryllium and beryllium compounds neither at EU level nor in any EU Member State. However, DFG did set a *BAR* (Biologischer Arbeitsstoff-Referenzwert) of *0.05 µg/l beryllium/L urine*, expressed as beryllium mass (based on ICP-MS analytics) (Drexler and Hartwig 2010). The BAR is defined as the background level of a substance in biological material in a reference population of persons of working age not occupationally exposed to this substance; BARs are based on the 95th percentile without regarding effects on health (Göen et al 2012).

Table 2. An overview of existing OELs for beryllium and beryllium compounds (expressed as Be).

EU	TWA (8 hrs)		STEL (15 min)		Remarks	References
	ppm	mg/m³	ppm	mg/m³		
Austria		0.002		0.008	TRK	AT GKV (2011)
Belgium		0.002		0.01	8 hrs TGG (TWA)	BE KB (2014)
Denmark		0.001				DK BEK (2011)
Germany (DFG)					*BGV (BAR): 0.05 µg/l beryllium/L urine*	Drexler and Hartwig (2012)
Finland		0.0001		0.0004	STEL = 15 min. average	FI MSAH (2012)
France (INRS)		0.002			VME = TWA 8 hrs	FR INRS (2012)
France (ANSES)		0.00001			Skin notation	FR ANSES (2010)
Ireland		0.0002				IE HSA (2011)
Sweden		0.002			Total dust	SE SWEA (2015)
UK		0.002			TWA	GB HSE (2011)
Non-EU						
Australia		0.002			TWAEV	AU SWA (2011)
CA (Ontario)		0.002		0.01	TWA	CA OML (2013)
CA (Québec)		0.002				Canada (2016)
Japan		0.002				JA JSOH (2015)
New Zealand		0.002				NZ HS (2013)
Norway		0.001				NO NLIA (2011)
Switzerland		0.002			inhalable aerosol	CH SUVA (2015)

USA (OSHA)		0.002		0.005	PEL	US OSHA (2006)
USA (NIOSH)		0.0005		0.0005	REL	US NIOSH (2016)
USA (ACGIH)		0.00005			TLV-TWA	US ACGIH (2012)

- BAR [Biologischer Arbeitsstoff Referenzwert] = biological reference value: background level of a substance in biological material in a reference population of persons of working age not occupationally exposed to this substance; BARs are based on the 95th percentile without regarding effects on health (Göen *et al* 2012)
- TWA = Time-Weighted Average (usually 8 hours average).
- STEL = Short Term Exposure Limit (usually 15 minutes average).
- TGG [TijdGewogen Gemiddelde] = TWA.
- TRK [Technische RichtKonzentration] = indicative concentration. Used when no 'safe' exposure level can be derived. Value based on technical feasibility.
- REL = Recommended Exposure Limit (NIOSH)
- TWAEV = Time-Weighted Average Exposure Value = TWA
- PEL = Permissible Exposure Level (OSHA)
- VME [Valeur Moyenne d'Exposition] = TWA.

5. Occurrence, Use and Occupational Exposure

5.1. Occurrence and use

Beryllium occurs naturally in the earth's crust and in the air, soil and water. In the earth's crust it is the 44th most abundant element (1–15 mg/kg) (ATSDR 2002, BeST 2011a). Due to its high reactivity it does not occur as free beryllium, but only in combination with other elements in minerals, especially silicates or aluminium silicates (aluminosilicates). Two of the most commercially used minerals are bertrandite ore and beryl, a by-product of small scale emerald gemstone mining operations. Approximately 45 mineralized forms of beryllium occur in nature (ATSDR 2002). These beryllium-containing minerals are processed to beryllium metal, beryllium alloys and beryllium oxide.

Beryllium is found in rocks, coal, soil, and volcanic dust and is released by windblown dust, volcanic particles, and the combustion of coal and fuel oil (ATSDR 2002). In rocks and minerals beryllium is found in concentrations ranging from 0.038 to 11.4 mg/kg. Beryl contains up to 4% beryllium. Total world reserves of beryllium recoverable by mining have been estimated at 200 000 tonnes (WHO 2001).

Beryllium is naturally occurring in ground water and surface water. Concentrations of beryllium in drinking water range from 0.010 to 1.22 µg/L with an average of 0.19 µg/L. An Australian survey found 0.08 µg/L beryllium in rainwater (BeST 2011c).

Atmospheric emissions of beryllium from production and processing are estimated to be 8.9 tonnes per year, which are only 4.4% of the total beryllium emissions to the air from all sources. The combustion of fossil fuels, especially coal is the primary source of beryllium in the atmosphere (187.1 tonnes per year and 93% of all atmospheric beryllium). The mean concentration in coal is 1.8–2.2 mg beryllium/kg dry weight with up to 15 mg beryllium/kg. Fuel oil contains up to 100 µg beryllium/litre (WHO 2001).

Man-made sources of beryllium are landfill disposal of coal ash and municipal waste combustor ash, land burial of industrial wastes and land application of beryllium enriched sewage sludge (WHO 2001).

Because of the military relevance of beryllium, information on reserves and applications is limited (EC 2010). It is not significantly bioconcentrated by aquatic species, bottom feeding molluscs or plants (WHO 2001).

5.2. Production and use information

Production

Although beryllium was discovered in 1798, it did not become commercially important until the 1930s (NTP 2005).

The commercial production of beryllium starts with the mining of raw materials. Beryllium is usually obtained from two naturally occurring sources, bertrandite ore and beryl. Beryl contains 3-5% beryllium, but it is much harder than bertrandite (NTP 2005, BeST 2011a) which contains <1% beryllium (ATSDR 2002). An overview of the production processes is summarized below:

1. Before refining beryl it must be melted in industrial furnaces, solidified and crushed, then treated with sulphuric acid to produce a water-soluble sulphate, which can be chemically processed with the Bertrandite ores (BeST 2011a).
2. Bertrandite ore is crushed, made into slurry and treated with sulphuric acid to form a sulphate. A series of chemical extraction steps produce extremely pure beryllium, beryllium alloys, beryllia ceramics and pure beryllium metal manufacturing beryllium (ATSDR 2002, BeST 2011a).
3. Drying out beryllium hydroxide by heating to a high temperature, results in dehydration of beryllium hydroxide to pure beryllium oxide.
4. Beryllium fluoride is produced by dissolving beryllium hydroxide in an ammonium hydrogen fluoride solution to produce ammonium tetrafluoroberyllate, which is crystallized, separated and dissociates into ammonium fluoride and beryllium fluoride after heating it (IARC 1993). Beryllium metal is produced by first forming beryllium fluoride from the beryllium oxide. Beryllium fluoride is reduced by magnesium metal at 900–1300°C to yield beryllium metal (BeST 2011a).
5. Beryllium chloride is produced either directly from beryl by the chloride process or by chlorination of beryllium oxide under reducing conditions.
6. Beryllium sulphate is formed by the reaction of beryl ore or beryllium oxide with sulphuric acid or by heating beryllium sulphate dihydrate in air to 400°C.
7. The beryllium tetrahydrate is produced by fractional crystallization from a beryllium sulphate solution.
8. Beryllium carbonate is prepared in the reaction of beryllium salt solutions with alkali metal or ammonium carbonate solutions. Mild calcining leaves beryllium basic carbonate, with further heating beryllium hydroxide is formed.
9. Beryllium nitrate (hydrated) is obtained by crystallizing beryllium hydroxide or carbonate solution after treating with concentrated nitric acid. Treating an ethyl acetate solution of beryllium chloride with dinitrogen tetroxide produces anhydrous beryllium nitrate.
10. Beryllium phosphate is formed by the reaction of disodium hydrophosphate with a beryllium salt solution or by reaction of beryllium hydroxide solution with phosphoric acid. There is no information on the production of beryllium silicates (IARC 1993).

Another form of beryllium production is recycling (ATSDR 2002, BeST 2011a).

Currently, only the US, China and Kazakhstan process commercially viable quantities of beryllium from ores into beryllium metal or other beryllium-containing materials; other countries producing beryllium are Brazil and several nations in Africa, such as Nigeria, Madagascar and Mozambique.

It should be noted that the overall market volume of beryllium is relatively small. Total world production of beryllium in 2008 was about 200 tonnes (IOM 2011).

In 2010, the annual worldwide production/consumption of beryllium was estimated at 280 metric tonnes but is estimated to grow to 350 metric tonnes by 2020 and 425 metric tonnes by 2030, due to the application for fusion reactor power generator construction (JRC 2012). In 2010, beryllium was designated as a critical material, as the risks for supply shortage and their impacts on the economy are higher compared to other raw materials according to the European Commission (EC 2010).

Use

Beryllium. Due to its unique combination of physico-chemical properties (beryllium is one of the lightest metals and very rigid with a very high melting point), it has many uses in industry for very specific applications, such as medical diagnostics, nuclear/fusion reactors, and aerospace applications where lightweight structures are required which are resistant to deformation under high stresses or high temperatures.

Only a few products contain pure beryllium metal or high beryllium containing composite parts, while in most cases beryllium is used in copper alloys (IOM 2011, WHO 2001).

In alloys, beryllium increases thermal and electrical conductivity and strength (ATSDR 2002, BeST 2011 b, NTP 2005, Strupp 2011a). In the US in 1998, approximately 80% of the total consumption of beryllium as metal, alloy, or oxide is its use in electrical components and aerospace and defence applications (ATSDR 2002, NTP 2005). Pure beryllium is used in aircraft disc brakes, in the manufacture of x-ray windows, space vehicles optics and instruments, aircraft and satellite structures, missile parts, nuclear reactor neutron reflectors, nuclear weapons, fuel containers, precision instruments, rocket propellants, navigational systems, heat shields, mirrors, high speed computer, and audio components, as well as other uses (ATSDR 2002, BeST 2011c, Greim 2005, NTP 2005).

As a component in an alloy with copper, aluminium, or other metals, beryllium increases their rigidity, resistance to corrosion and a high modulus of elasticity combined with a low density. Beryllium alloys are therefore suitable as lightweight materials that must withstand high acceleration or centrifugal forces. They are used for the manufacture of watch coils, surgical and precision instruments, valve springs, aircraft brakes and high-temperature materials as well as for special applications in the electronics (connectors and relays, automotive, defence, and aerospace industries, in automobile racing as parts of motor, gear and brake systems, in special sports equipment, telecommunications devices, computers, dental alloys and many other applications (BeST 2011 b, Greim 2005, NTP 2005, US EPA 1998).

Beryllium oxide is the most important commercial beryllium compound produced (NTP 2005). Beryllium oxide is used in high-temperature equipment, in high technology ceramics, as an insulating material, electronic heat sinks, electrical insulators, microwave oven components, gyroscopes, military vehicle armour, special crucibles, nuclear reactor fuels, thermocouple tubing, laser structural components, substrates for high-density electrical circuits, automotive ignition systems, aircraft ignition plugs, as additive to glass, ceramics, and plastics, and as radar electronic countermeasure systems (ATSDR 2002, Greim 2005, NTP 2005). It is also is used in the production of other beryllium compounds and as a catalyst for organic reactions. In the past beryllium oxide was used in the manufacture of phosphors for fluorescent lamps (NTP 2005). Beryllium chloride is used as acid catalyst in organic reactions, but primarily to manufacture beryllium metal by electrolysis in the laboratory.

Beryllium nitrate is used as a chemical reagent to harden incandescent mantles in gas and acetylene lamps (Greim 2005, NTP 2005). Until the late 1960s, beryllium nitrate was used for stiffening incandescent gas mantles.

Beryllium fluoride is used in the manufacture of glass and nuclear reactors. Beryllium fluoride and beryllium hydroxide are used in the production of beryllium metal and beryllium alloys. Beryllium hydroxide is used as an intermediate in the manufacture of beryllium and beryllium oxide (IARC 1993).

The primary use of beryllium sulphate is the production of beryllium oxide powder for ceramics, whereas beryllium sulphate tetrahydrate is used as a chemical intermediate in

the processing of beryl and bertrandite ores (NTP 2005). Beryllium sulphate tetrahydrate is used as an intermediate in the production of beryllium oxide powder for ceramics (IARC 1993).

Until about 1950 beryllium silicate was used as a fluorescent lamp phosphor. Beryllium phosphate and beryllium silicate are not known to be produced commercially (IARC 1993). It is no longer used in fluorescent lamps (EC 2009).

5.3. Occupational exposure

The average concentration of beryllium in outdoor air is < 0.03–0.07 ng/m³, with higher concentration in cities up to 6.7 ng/m³, and up to 100 ng/m³ near beryllium processing plants (ATSDR 2002, WHO 2001). Humans who are living near sources of beryllium emissions are likely to be exposed to higher levels than the general population.

Today, in the EU, Japan and the US, there are effective environmental control measures to minimize the exposure of the general public (Strupp 2011b).

Exposure to beryllium and its compounds occurs in the workplace (NTP 2005), where inhalation and dermal contact are most important (Strupp 2011b). Several reviews are available (ATSDR 2002, IOM 2011, NTP 2005, Strupp 2011b, WHO 2001), of which one (IOM 2011) reflects in detail the current situation in Europe.

Occupational exposure to beryllium occurs in various industries, the majority during production of beryllium metal and beryllium containing alloys (Strupp 2011b). Processes most likely to generate airborne beryllium are related to melting, casting, hot working, or abrasion of beryllium containing alloys (IOM 2011), accordingly the workers with the highest exposure potential are employed in processes of mining, production of beryllium alloys, phosphorus manufactures, ceramic production, nuclear reactors, production of electric and electronic equipment, missile technicians and jewelers (NTP 2005).

In the European Union (EU), approximately 65000 workers are estimated to be potentially exposed to beryllium; about 1250 of them are employed in foundry or similar processes, most of them in Italy, France, Germany, the United Kingdom, Switzerland and Hungary. These workplaces are of particular concern as the highest exposure levels exceed 2 µg/m^3. Because of the trend to move foundry work to China, the number of workers in this sector in the EU may decrease in the future (IOM 2011).

In France, a large assessment of beryllium occupational exposure was conducted from the end of 2004 through the end of 2006. About 15 % of the exposure measurements exceeded the French occupational exposure limit (OEL) which at that time was 2 µg/m^3. Relatively high exposure levels were noted in foundries and in electrometallurgy (aluminium production), activities requiring the use of hot-process alloys. Lower exposure levels were observed in metalworking, in which a larger number of potentially exposed personnel are employed; however, about 30 % of the exposure measurements in this sector still exceeded the TWA of 0.05 µg/m^3 recommended by the ACGIH. Surface contamination levels were also high, and showed a strong correlation with beryllium air concentrations (Vincent *et al* 2009).

For the industrial sectors "Research and Development" and "Public Administration and Defence" (NACE codes 73 and 75), no European exposure data were available. However, these groups include the lowest number of exposed workers and the beryllium exposure is probably low. Thus, they are unlikely to contribute significantly to total exposure in the EU (IOM 2011). In the study by Vincent *et al* (2009), high exposure values were shown in the industrial sectors "Manufacture of other non-metallic mineral products" (geometric mean (GM) 0.707 µg/m^3, n=4 measurements) and "Manufacture of basic metals" (GM 0.494 µg/m^3, n=159). Foundry workers had the highest exposures of all occupational

groups (0.882 µg/m^3, n=58) (Vincent *et al* 2009). Exposure data from other European countries are limited. The results are geometric means ranging from 0.03 µg/m^3 in Finland to 0.17 µg/m^3 in Germany. The estimated 90th percentile did not exceed 2 µg/m^3 in any country (IOM 2011). IOM (2011) assumed that the French exposure data reported by Vincent *et al* (2009) are typical for exposures in EU countries. Recent studies on production and recycling operations show airborne concentrations below 0.2 µg/m³ at these workplaces (Strupp 2011b, no further data available).

IOM (2011) stated that exposure levels are likely to have remained relatively unchanged at many facilities in the 10 to 20 years preceding their report, although they acknowledged that at some facilities reductions of exposure of about 3-4% per year have been observed due to upgrading of equipment and exposure controls.

5.4. Routes of exposure and uptake

The general population is continuously exposed to trace amounts of naturally occurring beryllium (for example in coal, wood, foodstuffs, gemstones) through inhalation of air, consumption of food and water, and skin contact with air, water or soil that contains beryllium (ATSDR 2002).

The largest contributions are from food and drinking water with smaller contributions from air and dust (WHO 2001).

In 1987, the US EPA estimated a total daily beryllium intake of 423 ng for the general population. Smokers may also be exposed to higher levels of beryllium than non-smokers because cigarette smoke contains beryllium (ATSDR 2002, WHO 2001).

6. MONITORING EXPOSURE

6.1. Monitoring airborne beryllium in the workplace

Beryllium and its compounds can be monitored in the air of the workplace by applying the following fully or partially evaluated methods:

- OSHA 1991. Method ID-125G
- NIOSH 1994. Method 7102
- OSHA 2002. Method ID-206
- NIOSH 2003a. Method 7300
- NIOSH 2003b. Method 7301
- NIOSH 2003c. Method 7303
- NIOSH 2007. Method 7704
- DFG 2012. Method BGI 505-13-02 (Parlar *et al* 2012)
- NIOSH 2014a. Method 7302
- NIOSH 2014b. Method 7304
- NIOSH 2015a. Method 7306

These methods and their key performance characteristics are explained with details in Table 3. Sampling of air (including airborne particles and gasses) in order to monitor airborne beryllium is usually carried out by air collection on filters, which are digested. The analytical methods used are Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES), Inductively Coupled Argon Plasma-Atomic Emission Spectroscopy (ICAP-AES,) Graphite Furnace Atomic Absorption Spectroscopy (GF-AAS) and field-portable UV/Vis fluorimetry.

Detection limits in air are in the range of ng/m^3 to µg/m^3 (ATSDR 2002, IRSST 2008). For water soluble forms of beryllium, a relatively mild digestion technique can be applied, and detection limits are low with ICP-AES and GF-AAS. For beryllium oxide, a more robust digestion is required, which results in a higher detection limit, and ICP-MS should instead be used, which typically has lower detection limits, is relatively expensive (Brisson and Ashley 2005), but is much more versatile and a common equipment in many laboratories. Recently, the IRSST (2008) published an ICP-MS method for beryllium metal and its compounds present in airborne particles. Another analytical technique based on fluorescence has been developed by Minogue *et al* (2005) and shows detection limits in the ng/m^3 range. This technique is field portable and also less expensive than ICP-MS. However it is not suitable to process large numbers of samples quickly (Brisson and Ashley 2005). A fluorescence technique is also published as NIOSH method 7704 (for air) and 9110 (for wipes) and recommended for occupational exposure monitoring by NIOSH (2011), as the estimated uncertainty for the ICP-MS method is significantly larger than for the molecular fluorescence method.

In the past, collection on filters was based on the use of "total dust" sampling equipment, with a 37-mm closed face filter cassette in the US. At present, health based dust sampling fractions are used and "inhalable dust" or "respirable dust" have been measured in different studies. "Inhalable dust" is the fraction which can penetrate the respiratory organ and also covers larger particles than the respirable fraction. To assess a potential conversion factor between both metrics, a study with 39 parallel samples was performed, collecting "total dust" and "inhalable dust" in parallel, the latter determined by the "Gesamtstaubprobenahmesystem". Exposures were at copper-beryllium (CuBe) alloy processing (drilling, milling, stamping, turning, saving, welding and annealing), which comprise by far the majority of the beryllium processing processes in Europe. Taking the mean of all measurements, the conversion factor was proposed to be to 2.88,

i.e. the total dust concentration should be multiplied by 2.88 for conversion to the inhalable dust concentration (Kock *et al* 2015). Nevertheless, SCOEL noted that the difference between total and inhalable dust strongly depends on the particle size distribution in a given situation, i.e. the smaller the particles, the less difference between total dust and inhalable dust. Relevant differences were only observed if the vast majority of the particles belonged to the extra-thoracic fraction, while in case of small particles a difference is neither expected nor has it been observed.

Table 3. Overview of sampling and analytical methods for monitoring total airborne beryllium in the workplace.

Method	Sorbent	Analysis	Recovery/ Extraction efficiency (%)	LOQ/LOD	Flow rate/ Sample volume/ time	Concentration range	Ref's
Method BGI 505-13-02	FILTER (cellulose nitrate membrane filter)	GF-AAS (after acid digestion)	100	Absolute: 0.62 pg of beryllium (LOQ) Relative: 0.0019 µg/m^3 *	10 L/min for 2 hours	0.002-0.013 µg/m^3 based on an air sample volume of 1.2 m^3	Parlar *et al* 2012
NIOSH 7102	FILTER (cellulose ester membrane)	GF-AAS	98.2	0.005 µg per sample (LOD)	1 to 4 L/min; 25-1000L	0.5-10 µg/m^3 for a 90L air sample	NIOSH 1994
NIOSH 7300	FILTER (cellulose ester membrane or polyvinyl chloride membrane)	ICAP-AES	98.4-106.8 (depending on the membrane and LOD used)	0.2 ng/ml (LOD)	1 to 4 L/min; 1250-2000L	0.005-2.0 mg/m^3 in a 500 L air sample	NIOSH 2003a
NIOSH 7302	FILTER (mixed cellulose ester membrane)	ICAP-AES	95.8-103	0.009 µg/sample (LOD)	1 to 4 L/min; 1250 - 2000L	Lower Level: 0.025 µg/sample Higher Level: 7.60 µg/sample	NIOSH 2014
NIOSH 7301	FILTER (cellulose ester membrane or polyvinyl chloride membrane)	ICAP-AES	81.1-100.6 (depending on the membrane and LOD used)	LOD: 0.2 ng/ml	1 to 4 L/min; 1250-2000L	0.005-2.0 mg/m^3 for each element in a 500-L air sample	NIOSH 2003b
NIOSH 7303	FILTER (cellulose ester membrane	ICAP-AES	90-110	0.0025 µg /ml (LOQ) 0.00075 µg /ml (LOD)	1 to 4 L/min; 35-25,000,00	up to 100 mg/m^3 for each element in a 500-L sample. Minimum depends on LOD	NIOSH 2003c
NIOSH 7304	FILTER, (polyvinyl chloride	ICAP-AES	102.38 - 107.71 (depending on the LOQ)	0.008µg/ Sample (LOD)	1 to 4 L/min; 1250-2000L	Lower Level: 0.0509µg/sample Higher Level: 15.2 µg/sample	NIOSH 2014
NIOSH 7306	Internal capsule cellulose acetate dome with inlet opening attached to mixed cellulose ester (MCE) membrane filter	ICP-AES	100-101	0.0064 µg/sample (LOD)	1 to 4 L/min; 10->2000 L	4 x 10^{-5} mg/m^3 to 10 mg/m^3 for each element in a 500-L air sample	NIOSH 2015a

NIOSH 7704	Filter (mixed cellulose ester or nylon membrane)	Field-portable uv/vis fluorometry	n.a	0.00075 µg per filter (LOD)	(1 to 4) L/min; 240-2,000L	0.005 µg/m^3 to 6 µg/m^3 for an air sample of 1000 L	NIOSH 2007
OSHA ID-206	Filter (mixed cellulose ester membrane filter)	ICP-AES	n.a.	0.00029 µg/mL (LOD, Qualitative)	2 L/min; 480 L	0.00086- 10 µg/mL	OSHA 1991
OSHA ID-125G	Filter (mixed-cellulose ester membrane filter)	ICAP-AES	n.a	0.013 µg (LOD, Qualitative) 0.043 µg (LOD, Quantitative)	2 L/min; 480 L	Upper Detection Limit: 5 µg/mL	OSHA 2002

** for an air sample of 1.2 m^3, a sample solution of 20 mL (dilution factor 4) and an injection volume of 20 µL*
n.a. not available

A new release of the NIOSH method 7704 was published in December 2015 for which the limit of detection (LOD) is now 0.1 ng (NIOSH 2015c).

The 7302, 7304, 7306 NIOSH methods are fully evaluated methods. OSHA method ID-206 and ID-125G are completely validated. The NIOSH methods 7300, 7301, 7302, 7303, 7304, 7306 are simultaneous elemental analysis and are therefore not considered compound (Be) specific.

It should however be noticed that the OSHA and NIOSH methods are not validated according to the European reference standards (EN 13890 and 482).

In addition, there are three relevant ISO methods:

- ISO 10882-1:2011 for the sampling of airborne particles and gases in the operator's breathing zone.
- ISO 15202-3:2004 (Workplace air) for the determination of metals and metalloids in airborne particulate matter by inductively coupled plasma atomic emission spectrometry.
- and ISO 30011:2010 (Workplace air) for the determination of metals and metalloids in airborne particulate matter by inductively coupled plasma mass spectrometry.

In a plant where beryllium oxide, metallic beryllium and beryllium alloys were produced from beryllium hydroxide, the particle size distribution was obtained from 198 personal impactor samples. The mass median aerodynamic diameters (MMADs) ranged from 2 to 38 µm with median MMADs from 5 to 14 µm for the different process areas. A large mass fraction (~60-70%) of the aerosol was in the non-respirable size fraction (Virji *et al* 2011).

6.2. Measurements of surface-deposited beryllium in the workplace

Beryllium and its compounds can be monitored on contaminated workplace surfaces by applying the fully or partially evaluated method as mentioned in Table 4.

Sampling of contaminated surfaces in order to monitor beryllium has been carried out by swiping. Analytical determination is performed using field-portable UV/VIS fluorimetry.

Table 4. Overview of sampling and analytical methods for monitoring beryllium contamination on workplace surfaces.

Method	Sample collection	Analysis	Recovery / Extraction efficiency (%)	LOQ/LOD	Surface area	Amount sampled	References
NIOSH 9110	WIPE (cellulosic)	Field-portable UV/VIS fluorimetry	n.a.	0.0001 µg/wipe	100 cm^2 minimum (wipe area)	0.005-6 µg/wipe	NIOSH 2015b
NIOSH 9102	WIPE sampling	ICP analysis	75-115	0.01 µg/wipe	n.a.	n.a.	NIOSH 2003d

NIOSH method 9102 is a simultaneous elemental analysis, not compound specific.

According to the Chronic Beryllium Disease Prevention Program of the US Department of Energy, removable contamination on equipment surfaces must not exceed 0.2 µg/100 cm^2 when released to the public or for non-beryllium use (US Department of Energy 1999).

6.3. Biomonitoring of beryllium in the workplace

Measurement techniques have been developed for the determination of beryllium in biological samples, including human tissue (liver, liver, lung, spleen, and kidney), blood, urine, faeces, hair and fingernails (ATSDR 2002, Paquette *et al* 2010).

Suitable methods are described for human (occupational) exposure monitoring of beryllium levels in blood, serum or plasma. ICP-AES (inductively coupled plasma-atomic emission spectroscopy) and GFAAS (graphite furnace atomic absorption spectrometry) or ET-AAS = electrothermal atomic absorption spectrometry with background correction (deuterium or Zeeman effect) are common analytical methods for beryllium with higher sensitivity than gas chromatographic or laser ion mass analysis. Stainless steel needles should not be used for sample collection to avoid sample contamination (ATSDR 2002).

ICP-MS was used by Krachler *et al* (1999a) for measuring beryllium in umbilical cord serum, colostrum and maternal serum at concentrations < 1 µg/l.

In urine, beryllium can be determined by GF-AAS, ICP-AES and ICP-MS.

The modern analytical techniques, in particular with the use of ICP-MS allow quantification of beryllium at levels as low as 0.01 µg/l (Drexler and Greim 2005, Drexler and Hartwig, 2010, Horng *et al* 2002). Morton *et al* (2011) reported a LQ of 0.006 µg beryllium/l urine with an ICP-MS method.

In the study of Hoet *et al* (2013) the limit of detection (LoD) for beryllium in urine measured with ICP-MS was 0.007 µg/L. In a recent study comparing analysis of beryllium in urine with atomic absorption spectrometry and inductively coupled plasma mass spectrometry the quantification limit was 0.002 µg/L (Devoy *et al* 2013). Furthermore Hulo *et al* (2016) determined beryllium in urine with Variant 820ICP-MS equipped with a collision-reaction interface; here, the limit of quantitation (LOQ) was 0.0064 µg/L.

In accordance with today standards, ICP-MS or optimised GF-AAS methods should be used and the urine samples should be collected in plastic vessels. The risk of contamination is low. The ICP-MS method is sensitive enough (0.01 µg/l urine) to measure background levels in the population; thus ICP-MS or optimised GF-AAS may be useful methods for occupational exposure monitoring (Drexler und Hartwig 2010).

7. HEALTH EFFECTS

7.1. Toxicokinetics (absorption, distribution, metabolism, excretion)

7.1.1. Human data

Inhaled beryllium is deposited in lung tissue, particularly in pulmonary lymph nodes. The absorbed fraction of beryllium, which is dependent on the particle size and the solubility of the respective compounds, is distributed from the lungs to the skeleton, which is the ultimate site of beryllium storage. Trace amounts are distributed through the body. Like inhaled beryllium, also orally or parenterally administered beryllium salts accumulate mainly in the skeletal system, but beryllium was found also in the stomach, intestines, liver, kidney, spleen, mesenteric lymph nodes and other soft tissues (WHO 2001). There is evidence that beryllium is transferred across the placenta and excreted via breast milk in humans (Krachler *et al* 1999a,b). Transport of beryllium across the placenta has been shown also in rats and mice treated with intravenous injection (WHO 2001).

Less than 1 % of orally administered beryllium is absorbed via the gastrointestinal tract, probably due to the precipitation as insoluble phosphate in the small intestine, making it no longer available for absorption. The absorption of beryllium through intact skin is negligible, as beryllium is bound by epidermal constituents such as alkaline phosphatase and nucleic acids (WHO 2001). Limited studies suggest that beryllium particles may be able to penetrate into human skin (Section 7.3.1).

Absorbed beryllium is excreted primarily in the urine, whereas elimination of unabsorbed beryllium is primarily via the faecal route. Beryllium and its compounds are not metabolised (WHO 2001).

In workers employed in two electric steel plants and two copper alloy foundries, beryllium urinary levels were elevated as compared to controls (Section 7.1.4).

7.1.2. Animal data

Animal studies show that the transfer of beryllium from the lungs into the blood takes place in two phases. The rapid elimination of beryllium via mucociliary clearance during the first one to two weeks is followed by a slower phase in which the beryllium is taken up by alveolar macrophages and transported to the tracheobronchiolar lymph nodes. The biphasic elimination of beryllium from the bronchi in rats yielded a half-life (time) of one to 60 days (rapid phase) and of 0.6 to 2.3 years (slow phase) (US EPA 1998 in Greim 2005).

In different animal studies, after inhalation of beryllium sulfate, fluoride or chloride the greatest amounts of beryllium were deposited in the lungs and the hilar lymph nodes, followed by the bones, liver and kidneys, with a particularly long retention time in the bones (Zorn and Fischer 1998 in Greim 2005).

After intravenous administration of radioactive beryllium to rabbits, 28.8 % of the initial amount was excreted with urine within the first 24 hours. After this first rapid elimination phase, the amount excreted daily with the urine in the second phase was between 0.5 % and 1.85 % and that with the faeces 0.2 % to 0.5 % (ATSDR 2002 in Greim 2005).

Rats excreted orally administered, radioactively labelled beryllium chloride with the urine (0.11 %) and with faeces (104.7 %). Similar values were found for mice, dogs and monkeys (ATSDR 2002 in Greim 2005).

7.1.3. In vitro data

Since the toxicity of particulate Beryllium and its inorganic compounds depend on the intracellular release of beryllium ions in macrophages after phagocytosis, the dissolution in lysosomes at a pH of about 4.5 is of particular importance. In this context, dissolution rates of production processing relevant compounds were investigated in an artificial phagolysosomal fluid. The long-term (dominating) dissolution half-time for powder of beryllium metal, finished product of beryllium oxide, beryl ore ball mill crushed product, beryllium hydroxide drumming product, and CuBe (0.36-1.82) alloy chips or blocks was 33, 172, ~4000, 900 and > 1600 days, respectively. Thus, the dissolution rate of beryllium metal was fast and the dissolution of crushed beryllium ore was slow. The long half-time of dissolution of CuBe alloys is due to the large particle size tested and thus, due to their low surface area. The other compounds have a particle size in the µm range and thus, the solubility of the particles is mainly reflected in the half-times (Stefaniak *et al* 2011).

7.1.4. Biological monitoring

Beryllium levels in blood, serum or plasma and urine are accurate biomarkers of exposure to certain forms of beryllium (ATSDR 2002). In a study of 65 workers employed in two electric steel plants and two copper alloy foundries, air exposure to beryllium and the concentration of beryllium in the urine after exposure were determined in order to analyse the relationship between external and internal beryllium exposure. The control group consisted of 30 workers employed in mechanical activities known not to be exposed to metals. The concentrations of beryllium in the air of the exposed group were as follows: Stationary measurements with a flow rate of 10–15 l/min and monitored for periods of 5-6 h yielded median values in the range of 0.04–0.9 µg/m³ in the copper alloy foundries and of 0.02–0.18 µg/m³ in the electric steel plants. The median values for beryllium in the urine of the workers in the electric steel plant were 0.06–0.09 µg/l and for those in the copper alloy foundries 0.125–0.25 µg/l. The value for the controls was < 0.03 µg/l. The regression analysis performed on the median values showed a significant correlation between external and internal exposure. No personal air samples have been collected in this study (Apostoli and Schaller 2001).

In a study of 57 gemstone cutters working in 12 factories in Germany, urinary concentrations of beryllium with a detection limit of 0.06 µg/l were measured. Mean beryllium levels of 0.13 µg/l urine before the shift and 0.08 µg/l urine after the shift were found in 27 subjects exposed for > 4 h/week (Wegner *et al* 2000).

A higher mean beryllium level of 1.1 µg/l urine before the shift and 1.8 µg/l urine at the end of the shift was measured for workers who cleaned oil-fired boilers (Cammarano *et al* 1985, cited in Drexler and Greim 2005). However, the results of earlier publications must be evaluated critically; both the sensitivity and the specificity of the methods used earlier were inadequate for reliably determining low beryllium concentrations in urine (Drexler and Greim 2005).

In a recent study using a Thermo ICP-MS series 1 the beryllium concentration was determined in the urine from 62 people with no known occupational exposure to beryllium and 167 workers with exposure to beryllium at an aluminium smelter. The analytical method has a detection limit for beryllium in urine of 6 ng/l. The mean and 90th percentiles of urinary beryllium for workers were 19.5 and 42.0 ng/l and for people not occupationally exposed to beryllium 11.6 and 20.0 ng/l (Morton *et al* 2011).

In another study at 9 different plants where different operations with exposure to beryllium were performed, the 90th percentiles of the beryllium concentration in urine was 29.7 ng/l which is below the BGV of 40 ng/l (Paul and Wenzlaff 2013). This value is

in agreement with the value of 90th percentiles of urinary beryllium for workers of 42 ng/l in the study of Morton *et al* (2011). People not occupationally exposed to beryllium showed values of median 5 ng/l and 95th percentile of 11.6 ng/l (Morton *et al* 2014).

Available data are not sufficient to allow a correlation to define a safe biological limit value (BLV). However, studies have shown that the analytical measurement of beryllium in urine can be used as an indicator of recent exposure to beryllium. Beryllium can be detected in the urine of not occupationally exposed persons, the 95th percentile was determined as 0.02 or 0.042 µg/l urine in two studies (63 persons; Heitland and Köster (2004) or 100 persons; Goullé *et al* (2005), summarized in Drexler and Hartwig 2010). In a further study of non-occupationally exposed people the 95th percentile of urinary beryllium was 0.012 µg/l (Morton et al 2014). Based on the available data, SCOEL recommends a Biological Guidance Value (BGV) of 0.04 µg beryllium/l urine.

7.2. Acute toxicity

7.2.1. Human data

Single inhalation exposure to high beryllium concentrations (> 100 µg/m³) can cause acute beryllium disease (ABD) in humans. Signs and symptoms of ABD range from mild inflammation of the upper respiratory tract to tracheo-bronchitis and severe pneumonitis. ABD is likely to be due to direct toxicity, unlike the immune mechanism of chronic beryllium disease (CBD) (Section 3.5.1) (ATSDR 2002, Greim 2005, US EPA 2008).

7.2.2. Animal data

In animals, inhaled beryllium compounds are highly toxic. In rats, the LC50 for 4 hours was 0.15 mg/m³ (WHO 2001). In a recent study, all animals survived, without any signs of adverse effects, an oral dose of 2 000 mg beryllium metal/kg bw given by gavage (Strupp 2011a).

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

Repeated inhalation exposure to low concentrations of beryllium or beryllium compounds can cause chronic beryllium disease (CBD) in humans. CBD is a cell-mediated immunological reaction of delayed type and is generally observed after a long latent period. CBD is a granulomatous lung disorder currently diagnosed by the parallel occurrence of non-caseating granulomas and a positive beryllium lymphocyte proliferation test (BeLPT) expand. Recent studies have shown that individuals with evidence of immunological sensitisation to beryllium (BeS) are considered to be at risk of developing subclinical and clinical CBD. Susceptibility to BeS and CBD is not evenly distributed in the population as polymorphisms in the human lymphocyte antigen (HLA) may contribute to the risk (Balmes *et al* 2014). For example, susceptibility to BeS was associated with the human lymphocyte antigen (HLA) Class II HLA-DRB1-E^{69} allele and independently, progression to CBD was associated with the HLA-DQB1-G^{86} and HLA-DRB1-S^{11} alleles (Rossman *et al* 2002). This is supported from a recent case-control study with beryllium-exposed nuclear weapon production workers who showed that a glutamic acid at position 69 of the HLA-DPB1 gene (HLA-DRB1-E^{69}) increased the risk of BeS and CBD (Van Dyke *et al* 2011).

BeS precedes chronic beryllium disease (CBD), but the progression from sensitisation to disease is not fully understood. Beryllium sensitisation could be considered a biomarker

of CBD. The prevailing view is that most individuals must first be sensitised before beryllium in the lungs can cause the lung damage of CBD, based on studies showing that almost all individuals with CBD with positive BeLPT are also sensitised. Whether CBD is related only to direct pulmonary exposures to beryllium, or whether sensitisation or disease outcome or both are also related to dermal exposure or to systemic burdens of beryllium is not clear (McCleskey *et al* 2009).

By applying the analytic Markov model, Harber *et al* (2009) studied the progression of CBD in the three stages: from beryllium exposure to beryllium sensitisation and then to CBD. They showed that the risk of progression is initially high and then declines over time and probably there are at least two populations which differ significantly in risk. No reference to the beryllium concentration in the air was given in this study.

Time-till progression from BeS to CBD seems to vary greatly among different studies (Seidler *et al* 2012, Balmes *et al* 2014). This is to some extent related to the design of the studies and the varying likelihood to pick up certain patient groups. The relationship was studied in a longitudinally clinical study in 55 BeS workers without CBD, where BeS workers were diagnosed through workplace medical surveillance with evaluations at 2-year intervals. CBD developed in 31% within 3.8 years (Range: 1-9.5 years). The remaining 69% were without CBD after an average follow-up time of 4.8 years (range: 1.7-11.6 years). Time from first exposure to development of CBD ranged from 3.5 to 44.5 years (Newman *et al* 2005). The similar type of follow-up was performed in 229 BeS workers, who were found positive on medical surveillance. Of those with BeS, 22 (~10%) developed CBD during the 30 year follow-up (Mroz *et al* 2009). However, a study with an average follow-up of 7.4±3.1 years in workers, being BeLPT positive at workplace screening, showed that only 2% (1 case) progressed to CBD (Duggal *et al* 2010). Even no progression from BeS to CBD was observed in 30 BeS workers followed-up for 7 years (Rossman *et al* 2002). Potentially, the progression rate may depend on the exposure level of beryllium (Newman *et al* 2005); however, no exposure concentrations are provided in the above mentioned studies. Furthermore, the method of CBD diagnosis also is supposed to play a role (Seidler *et al* 2012). Cross-sectional studies in U.S. beryllium industries found that the prevalence of CBD was in the range from 0 to 7.8% (Balmes *et al* 2014).

For risk assessment, SCOEL collected studies with appropriate exposure-response information, excluding studies where BeS and CBD were reported and exposure-response relationships were inadequate. Furthermore, SCOEL excluded studies with adequate exposure assessment, but where respirators were commonly used and therefore, the airborne concentrations do not simply represent inhaled concentrations. An overview of the retrieved studies is in Table 5.

Table 5. Overview of OEL risk-assessment relevant studies with airborne concentration-response relationships in the low-dose range.

Facility in the U.S.A [a)]	Processes with	Study	Number of exposed/number of participants	Range of exposure duration (year)	Concentration range [b)] ($\mu g/m^3$)Mean (M)[c)] Peak (P)	BeS alone (BeS) CBD
Cullman	Be metal, oxide and alloys	Kelleher *et al* 2001 Madl *et al* 2007 OSHA 2015	235/226 Year 1994-2005: 350/ ? ?/319	0.08–29 Not available Not available	<0.02–0.60 [d)] M : 0.02–8.48 M : 0.0–2.15	BeS: 7 CBD: 13 BeS: 9 CBD: 18 BeS: 7 CBD: 19
Tucson	Be ceramics	Henneberger *et al* 2001	167/151	0.25–40.1	M: 0.05–4.4 P: 0.05–307	BeS: 7 CBD: 8
Reading	CuBe alloys	Schuler *et al* 2005	185/153	<1– ≥45	M: <0.01–7.8	BeS: 4

						CBD: 6
Elmore	Be metal, CuBe alloys, and oxide	Schuler *et al* 2012	291/264	0.02–6	M: <0.09–16.26	BeS:20 CBD: 6
Closed facility in Pennsylvania[e)]	Beryl ore, Be metal, fluoride, hydroxide, and oxide	Rosenman *et al* 2005	715[f)]/457	Not available	M: 0.5–84	BeS: 40 CBD: 44

[a)] OSHA (2015)

[b)] Total mass beryllium concentration

[c)] Mean lifetime weighted average

[d)] Median lifetime weighted concentration

[e)] Rosenman *et al* (2005)

[f)] Potential participants

Kelleher *et al* (2001) conducted a nested case-control study in a plant using beryllium metal, oxide and alloys, which were processed by mechanical machining, polishing and acid etching. The plant had employed up to 300 workers at one time and at the time of the study employed 180 workers. 235 workers participated in the medical surveillance. A total of one hundred personal samples were obtained in the period 1996-1999, which together with 649 historical total exposure samples and 140 ambient samples (all in all 889 "total" dust samples) comprised the exposure assessment. Also the particle size distribution has been investigated in this plant, comprising personal sampling of total beryllium dust and personal impactor sampling (Martyny *et al* 2000). The total beryllium dust mean, median, minimum and maximum concentrations were 1.48, 0.29, 0.03 and 41.48 µg/m^3, respectively, in the machining area (64 samples). In the administrative area, the median concentration was 0.02 µg/m^3. The median total dust concentration by deburring, grinding, lapping, lathe operation and milling were 0.57, 0.26, 0.10, 0.40 and 0.20 µg/m^3, respectively. The impactor sampling showed a bimodal particle mass fraction with about 30% with a diameter above 10 µm, 70% with a diameter less than 10 µm and 35% with a diameter less than 0.6 µm. The median total respiratory tract deposition was estimated to about 50% and the alveolar deposition to about 7%. Working hours were from 40 to 55 hours per week. A screening for BeS was initially conducted in 1995 and repeated on a biennial basis. From the 1995-1997 surveillance, 7 BeS cases and 13 CBD cases were identified; duration of exposure for CBD cases was from 0.2 to 25 years. The authors created individual lifetime-weighted (LTW) beryllium exposure estimates for each subject, i.e.[median estimate of job title exposure x year in the job title]/[total years of employment], abbreviated LTW(median) (Table 6). The duration of exposure for BeS alone cases was from 0.21 to 21 years. No sensitisation was observed in workers who had a median lifetime-weighted (LTW(median)) exposure of 0.02 µg beryllium/m³ (NOAEC). One single case of BeS was seen at a lifetime weighted exposure of 0.035 µg/m³ and the 6/7 cases had an exposure from 0.25 µg/m^3 and higher levels.

Table 6. Comparison of lifetime-weighted median (LTW (median)) total dust exposure and prevalence (%) of BeS without CBD and CBD; modified from Kelleher *et al* (2001, table 7).

LTW (median) µg/m^3	Controls (n)	BeS alone n (%)	CBD n (%)	BeS alone+CBD n (%)
< 0.02	22	0 (0)	0 (0)	0 (0)

0.02-0.1	46	1 (2) [a)]	3 (6) [a)]	4 (8) [a)]
>0.1-1	138	6 (4) [a)]	10 (6.5) [a)]	16 (11) [a)]

[a)] Percentage of persons exposed in the respective concentration range

In the LTW (median) exposure range from 0.02-0.10 µg/m^3, three cases with CBD were observed, which had a LTW(median) exposure of 0.024, 0.038 and 0.08 µg/m^3, respectively. As there was one case with BeS alone in the interval with a LTW (median) of 0.035 µg/m^3, there were four cases with BeS alone plus CBD in the concentration interval from 0.024 to 0.1 µg/m^3. As there are more CBD cases than BeS cases, this might indicate that most BeS sensitized individuals have proceeded to CBD and BeS is a prerequisite for CBD. However, within this study, past exposure may have been underestimated.

Schuler *et al* (2012) conducted a cross-sectional study in a facility, which produced beryllium metal in powder (sheet, and solid forms, beryllium oxide powder) and copper-beryllium alloys in strip (sheet) and bulk (rod, bar and tube) forms. The participants were hired after 1 January 1993 and until the study in February-November 1999. Thus, the maximum period of exposure was six years and the median work tenure was 21 month (range: 0.2–72.7 months). A comprehensive personal exposure assessment was conducted in 1999 that comprised 4022 total mass samples and 198 size-separated impactor samples. Area samples (N=76,349) collected from 1994-1999 were used to create annual temporal adjustment factors for personal exposure. These factors were used in estimating personal exposures from the 1999 data and thus correcting for workplace changes over the study period. Tests for BeS were conducted with selected groups during the follow-up period and among all workers in 1999. Workers with one or more abnormal beryllium lymphocyte proliferation tests and indications suggestive of CBD were referred for voluntary clinical evaluation, including bronchoscopy with bronchoalveolar lavage and trancheobronchial biopsies. Six cases (2.3%) with CBD were identified among 264 participants. Both total and respirable beryllium mass cumulative concentrations were positively associated with CBD. The lowest average beryllium estimates at which CBD was observed was 0.20 µg/m³ for total mass concentrations and 0.17 µg/m³ for respirable concentrations. The lowest estimate of cumulative beryllium exposure at which CBD was observed was 0.38 µg/m³-years for total mass concentrations and 0.33 µg/m³-years for respirable concentrations. Among the highest mean exposures estimated for each person, the lowest exposures at which CBD was observed was 0.22 µg/m³ for total mass concentration and 0.19 µg/m³ for the respirable fraction. The shortest time till diagnosis of CBD was 1.9 years. The exposure-response relationships are summarized in Table 7a. In this study BeS was also investigated. 26 (9.8 %) workers were BeS cases, exposure-response relationships are listed in Table 7b. The lowest exposure quartile had the lowest prevalence of BeS. BeS increased significantly with increasing average and highest job total mass exposure concentration. For total mass concentration exposures the lowest average level at which BeS was observed was 0.09 µg/m³, the lowest cumulative exposure at which BeS was observed was 0.08 µg/m³-years and the lowest exposure at the highest job worked at which BeS was observed was 0.12 µg/m³. For the respirable fraction, the lowest average concentration at which BeS was observed was 0.04 µg/m^3, the lowest cumulative exposure at which BeS was observed was 0.01 µg/m³-years and the lowest exposure at the highest job worked at which BeS was observed was 0.04 µg/m^3. No BeS was observed when respirable concentration exposures as average and at the highest job worked were each below 0.04 µg/m³. No trend by years worked was observed for BeS. The authors defined average exposure as time-weighted average annual exposure of all jobs in the employee's work history and cumulative exposure as exposure levels for each job worked, multiplied by number of years at that job, summed over all jobs in the work history. The highest job exposure was taken as the exposure level for each participant's single job with the highest mean exposure. A limitation of the study is the short exposure period, mean 21 months. An estimate of the lost fraction of BeS cases if the study had been conducted as a long-term study may be suggested from the sensitisation of cases in

the Madl *et al* (2007) study (Table 8a), where 1/3 of the BeS were sensitized within the first year of exposure and another third within the exposure from ≥1-5 years.

Table 7a. Exposure-response relationship for chronic beryllium disease (CBD) based on total mass and respirable particle mass are condensed from data in Schuler *et al* (2012). Exposures are evaluated as average intensity, cumulative exposure and highest job exposure. There were 6 CBD cases and 238 non-BeS cases and thus 244 workers who were compared. Workers were employed in the period 1993-1999. Where upper quartiles have the same or nearly the same prevalence of CBD as in the second quartile, the two upper quartiles have been combined.

Total mass		Respirable particle mass	
Exposure	Fraction and (%) CBD	Exposure	Fraction and (%) CBD
Average (µg/m^3)		Average (µg/m^3)	
<0.09	0/61 (0)	<0.05	0/61 (0)
0.09-0.55	2/61 (3.3)	0.05-0.39	2/61 (3.3)
>0.55-16.26	4/122 (3.3)	>0.39-3.56	4/122 (3.3)
0.20	Lowest concentration with CBD	0.17	Lowest concentration with CBD
Cumulative (µg/m^3 x year)[a)]		Cumulative (µg/m^3 x year)[a)]	
<0.12	0/61 ((0)	<0.09	0/61 (0)
0.12-0.63	1/61 (1.6)	0.09-0.50	2/61 ((3.3)
>0.63-2.20	2/61 (3.3)	>0.50-1.83	1/61 (1.6)
>2.20-34.44	3/61 (4.9)	>1.83-15.54	3/61 (4.9)
0.38	Lowest concentration with CBD	0.33	Lowest concentration with CBD
Highest job (µg/m^3)		Highest job (µg/m^3)	
<0.1	0/60 ((0)	<0.07	0/61 (0)
0.1-0.92	2/75 (2.7)	0.07-0.86	2/61 (3.3)
>0.92-17.54	4/109 (3.7)	>0.86-5.54	4/122 (3.7)
0.22	Lowest concentration with CBD	0.19	Lowest concentration with CBD

[a)] The cumulative groups were the only metrics, where CBD was statistically significantly increased.

The authors observed a high correlation (r: 0.82-0.93) between total mass and respirable particle mass estimates.

It is noted that the number of CBD cases is only six, also mentioned as a limitation by the authors. The shortest tenure to CBD diagnosis was 1.9 years and the median tenure 21 month, which limits the possibility to generalize the results as mentioned by the authors. As the number of size-separated samples (198) is much lower than the number of total dust samples (4022), the precission of the total dust metrics can be expected to be much better than that of the respirable metrics estimates, which is in agreement with the authors information that the fewer size-separated samples necessitating a broader grouping of jobs in completing job-exposure matrix.

Table 7b. Exposure-response relationship for beryllium sensitization (BeS) based on total mass and respirable particle mass from Schuler *et al* (2012). Exposures are evaluated as average intensity, cumulative exposure and highest job exposure. Exposures were devided intoquartiles. There were 26 BeS cases (BeS alone plus CBD) among 264 investigated workers employed in the period 1993-1999.

Total mass		Respirable particle mass	
Exposure	Fraction and (%) BeS	Exposure	Fraction and (%) BeS
Average (µg/m^3)		Average (µg/m^3)	
<0.10	2/66 (3)[a)]	<0.06	4/66 (6.1)
0.10-0.60	7/66 (10.6)	0.06-0.42	5/66 (7.6)
>0.60-1.09	8/66 (12.1)	>0.42-1.02	9/66 (13.6)
>1.09-16.26	9/66 (13.6)	>1.02-3.56	8/66 (12.1)
0.09	Lowest concentration with BeS	0.04	Lowest concentration with BeS
Cumulative (µg/m^3 x year)		Cumulative (µg/m^3 x year)	
<0.13	4/66 (6.1)	<0.09	4/66 (6.1)
0.13-0.63	7/66 (10.6)	0.09-0.51	7/66 (10.6)
>0.63-2.21	6/66 (9.1)	>0.51-1.85	6/66 (9.1)
>2.22-34.44	9/66 (13.6)	>1.85-15.54	9/66 (13.6)
0.08	Lowest concentration with BeS	0.01	Lowest concentration with BeS
Highest job (µg/m^3)		Highest job (µg/m^3)	
<0.11	0/66 (0)[a)]	<0.08	3/64 (4.7)
0.11-0.93	12/79 (15.2)	0.08-0.86	9/68 (13.2)

>0.93-1.57	5/54 (9.3)	>0.86-1.30	7/67 (10.5)
>1.57-17.54	9/65 (13.9)	>1.30-5.54	7/65 (10.8)
0.12	Lowest concentration with BeS	0.04	Lowest concentration with BeS

[a)] Significant trend among the four exposure quartiles

Madl *et al* (2007) conducted a new investigation in the same plant as studied by Kelleher *et al* (2001). The study collected all BeS and CBD cases. The reported detailed exposure assessment allows an evaluation of the exposure of each case. At the time of the study, the plant had 208 employees. New and comprehensive exposure assessments were established, comprising current and historical data from the period from 1980 to 2005 with 3831 personal samples and 616 area samples of "total" beryllium dust. The mean, median and 95th percentile for beryllium time-weighted average (TWA) concentrations were calculated. Exposure assessment comprised LTW(mean) values based on TWA exposures for all years worked at each job title and weighted according to work history prior to BeS ascertainment or CBD diagnosis; workers were tested every second year for being BeS and if positive evaluated for CBD. CBD was divided into subclinical CBS (sCBD), where CBD was established, but where a person had no physical symptoms, and clinical CBD, where X-ray or pulmonary function changes were present. There were 9 BeS alone cases, 16 sCBD and 2 CBD cases. The authors indicated that most CBD cases were mild. However, as both sCBD and CBD are adverse reactions they are combined in one CBD group with 18 cases and analysed for time to BeS alone or CBD and for LTW exposures in the different time groups (Table 8a).

Table 8a. Clinical evaluation of beryllium sensitized cases without chronic beryllium disease (BeS) and chronic beryllium disease (CBD) cases. Exposure concentrations are lifetime weighted (LTW) mean concentrations (total dust). Data are calculated from Madl *et al* (2007, table 3).

Exposure time before BeS or CBD (year)	Beryllium sensitized cases without chronic beryllium disease		Chronic beryllium disease	
	N (%)	Mean (range) ($\mu g/m^3$)	N (%)	Mean (range) ($\mu g/m^3$)
0-1	3 (33)	0.76 (0.12-1.48)	2 (11)	0.095 (0.09-0.1)
>1-5	3 (33)	2.81 (0.15-7.89)	–	–
>5-15	0	–	3 (17)	0.23 (0.10-0.40)
>15	3 (33)	1.47 (0.12-4.15)	13 (72)	0.93 (0.14-3.52)

Table 8a shows there were more CBD cases than BeS alone cases as was observed in the Kelleher *et al* (2001) study. BeS alone appeared faster, 2/3 within the first 5 years of exposure, whereas CBD appeared among 11% of the cases in this period and 89% after 5 years of exposure. Thus, the occurrence of BeS alone and CBD was clearly time dependent, showing pronounced increases pf CBD after 15 years of exposure The lower concentrations that had caused BeS and CBD were around 0.1 $\mu g/m^3$ (highlighted in the table by italics) that is little influenced by the length of the exposure period, although a longer exposure period before BeS or CBD was associated with a higher mean exposure

and higher upper range concentration. For risk assessment it is noted that cases occurred at concentrations around 0.1 µg/m^3, irrespective of the length of the exposure period.

As the employees in Madl *et al* (2007) were examined for BeS every second year, this allowed an estimation of the exposures in the two year period preceding the sensitization and thus the concentration that may have caused BeS alone, if BeS is caused by recent exposures. This evaluation is shown in Table 8b, where the year of BeS diagnosis (column 2) and exposure estimates (columns 3 and 4) are shown. It can be seen from this summary table that 5 BeS cases had been exposed to an immediately preceding concentration of about 0.1 µg/m^3. Similar concentrations are derived from LTW (mean) concentrations (column 4). Thus, both approaches suggest a LOAEC of about 0.1 µg/m^3. For comparison, LTW (median) values from Kelleher *et al* (2001) are also inserted in the table (column 5).

Table 8b. Summary of relationships between beryllium (Be) exposures and sensitisation (BeS) in cases without chronic beryllium disease (CBD). Data from Madl *et al* 2007 and comparison with Kelleher *et al* 2001.

Date of BeS diagnosis	Exposure period for determination of exposure concentration	Exposure concentration, as total dust (µg/m^3)		
		Mean	Lifetime weighted average [a]	Lifetime weighted median [b]
	Madl *et al* 2007 [c]			Kelleher *et al* 2001
1997	1995–2003	0.64	4.15	0.35
1996	1986–1990, 1996–2000	1.94 0.08	7.89	0.35
1996	1995–1997	0.34	0.38	0.60
1995	1978–1996	0.12	0.14	0.035
1996	1996	0.92	0.67	0.25
1997	1996–1997	1.48	1.48	0.25
1997	1997–1998	0.12	0.12	0.25
2004	2002–2005	0.12	0.15	–
1999	1972–1994, 1999–2005	0.12 0.06	0.12	–

[a] Calculated by multiplying the airborne Be concentration by the years in each job title divided by the total years of employment prior to diagnosis.
[b] Calculated individually as Σ[(median estimate of job title exposure) x (year in job title)/(total years employed)], Kelleher *et al* (2001).
[c] The Madl *et al* study was conducted in the same plant as the Kelleher *et al* study from where the lifetime weighted median values were taken. In the Madl *et al* study, workers were tested by the blood beryllium lymphocyte proliferation test each 2nd year and thus, assessment of exposures preceding each date of diagnosis was attempted, referred to in the "mean" column.

The authors also concluded that maintaining beryllium concentrations below 0.2 µg/m^3 95 percent of the time may prevent BeS and CBD (Madl *et al* 2007). This observation was considered by SCOEL to provide a basis for setting a STEL value.

OSHA (2015) published an update of the surveillance program results in the Cullman facility. This facility opened in 1969 and control of beryllium exposure was realised by engineering and administrative measures rather than by personal protective equipment. Previous investigations in the facility were conducted by Kelleher *et al* (2001) and Madl *et al* (2007). The new data were provided by the National Jewish Research Centre and involved an elaborate exposure-response analysis. The dataset includes exposure samples collected between 1980 and 2005, and provides updated work history and

screening information for several hundred workers through 2003. The air measurements include 4370 breathing zone (personal lapel) and 712 area samples. The exposure-response relationships for long-term average, cumulative and highest exposed job are shown in Table 9a below:

Table 9a. Prevalence of sensitization and chronic beryllium disease (CBD) among 319 beryllium exposed workers in the OSHA (2015) update for long-term average (Average), cumulative exposure (Cumulative) and highest exposed job (HEJ).

Exposure	Group size	Sensitized only; N (%)	CBD; N (%)	Total sensitized; N (%)
Average (µg/m^3)				
0.0-0.080	91	1 (1.1)	1 (1.1)	2 (2.2)
0.081-0.18	73	2 (2.7)	4 (5.5)	6 (8.2)
0.19-0.51	77	0 (0)	6(7.8)	6 (7.8)
0.51-2.15	78	4 (5.1)	8 (10.3)	12 (15.4)
Cumulative (µg/m^3 x year)	81	2 (2.5)	2 (2.5)	4 (4.9)
0.0-0.147	79	0 (0)	2 (2.5)	2 (2.5)
0.148-1.467	79	3 (3.8)	8 (8.0)	11 (13.9)
1.468-7.008	80	2(2.5)	7 (8.8)	9 (11.3)
7.009-61.86				
HEJ (µg/m^3)				
0.0-0.086	86	1 (1.2)	0 (0)	1 (1.2)
0.091-0.214	81	1 (1.2)	6 (7.4)	7 (8.6)
0.387-0.691	76	2 (2.6)	9 (11.8)	11 (14.5)
0.954-2.213	76	3 (3.9)	4 (5.3)	7 (9.2)

In the long-term average exposure group, there were two sensitized workers in the lowest quartile and among whom, one had CBD. The sensitized worker without CBD had worked in the facility as an inspector since 1972, one of the lowest-exposed jobs in the plant. Due to the low exposure, exposure measurements were not available before 1998 and the exposure was based on measurements in the period of 1998-2003; therefore it is possible that earlier exposures may have been higher and underestimated. The worker diagnosed with CBD was hired in 1996 in production control and had an estimated average exposure of 0.08 µg/m^3. He was diagnosed with CBD in 1997.

OSHA (2015) evaluated exposure-response relationships by the log-log proportional hazard model, a generalization of logistic regression that allows for time-dependent exposures and different time at risk; cases were included up the diagnosis of sensitization or CBD. Exposure dependent effects were observed for sensitization and cumulative exposure (p=0.05), but not as clear for average exposure (p=0.09), while associations were absent for HEJ (p=0.30) and duration of exposure (p=0.31). No statistically significant relationship was observed for CBD and cumulative exposure (p=0.09), although there was a clear trend. The associations for average exposure and HEJ were clearly flat and statistically not significant (p=0.58, p=0.93, respectively), For duration of exposure a positive but statistically non-significant trend was observed (p=0.10) The association was strongest for cumulative exposure. OSHA therefore selected to use cumulative exposure for risk estimation for exposure levels at 0.1, 0.2, 0.5, 1.0 and 2.0 µg/m^3. They predicted cases of sensitization and chronic beryllium disease (CBD) per 1000 workers evaluated from the cumulative exposure metric. Risk estimates derived for exposure at the lowest concentration, 0.1 µg/m^3, and exposure duration at 5 and 45 years, respectively, are summarized in Table 9b; 95% confidence intervals are stated in parentheses. The estimates are given separately for 1995 and 1999, the years with the highest and lowest baseline rates, respectively.

Table 9b . Predicted number of cases with sensitization and chronic beryllium diseases (CBD) per 1000 workers evaluated from the cumulative exposure metric by different combinations of exposure level and duration.

		Estimated number of cases/1000 individuals at the given exposure level and exposure duration			
Exposure Level ($\mu g/m^3$)	Baseline year	Exposure duration for sensitization		Exposure duration for CBD	
		5 years	45 years	5 years	45 years
0.1	1995	30.8 (30.3-31.3)	34.8 (30.3-40.1)	23.1 (22.8-23.6)	26.2 (22.8-30.7)
0.1	1999	6.3 (6.2-6.4)	7.1 (6.2-8.2)	2.8 (2.7-2.8)	3.1 (2.7-3.7)

OSHA recommends the model-based risk estimates being interpreted with caution, in particular because very similar case numbers were obtained after 5 and 45 years of exposure. One significant source of uncertainty may be the comparatively short follow-up time, and models might underestimate the number of cases at longer exposure durations considerably. On the other hand, sensitivity analyses with different models did not yield substantially different results. The OSHA study was not able to address uncertainty due to exposure misclassification error (information bias) and the influence of varying particle sizes and particle solubility.

In 1998, a cross-sectional study was conducted in the US Tucson beryllium ceramic plant founded in 1981. Of 167 eligible workers not previously diagnosed with beryllium disease, 151 (90%) participated in the study. Of these, 77 were long-term workers (hired before 1992) and 74 were short-term workers (hired since 1992). The median year since first exposure was 14.1 (range: 8.0-40.1) for long-term workers and 1.0 (range: 0.25-12.75) for short-term workers. Engineering control was improved in the period of 1993-1996. In the period of 1981-1998, 18,903 beryllium air-level measurements were taken with a limit of detection of 0.1 $\mu g/m^3$. BeS was assessed as a positive BeLPT, which is positive at BeS alone as well as in case of CBD. CBD was evaluated in employees with a positive BeLPT. Among long-term and short-term workers, 8/77 (10.4%) and 7/74 (9.5%), respectively, had a positive BeLPT and 7/77 (9.1%) and 1/74 (1.4%), respectively, had CBD. For long-term workers, there was no clear exposure dependent relationship with time of exposure, and mean (range: 0.1-2.16 $\mu g/m^3$) and cumulative exposure (range: 0.9-41 $\mu g/m^3$ x year). Long-term workers not sensitized (0/19) had a positive peak exposure at ≤ 5.5 $\mu g/m^3$. However, it was mentioned that a healthy worker effect may have influenced the results. Among the short-term workers all 7 BeLPT positive workers had been exposed for less than two years. This suggests that sensitization may be a fast process. Two of the 7 BeLPT positive (2/19; 11%) positive workers had mean exposures below 0.1 $\mu g/m^3$ and peak exposures below 0.4 $\mu g/m^3$. There was no systematic use of respirators in the plant (Henneberger *et al* 2001). This observation may be important for setting a STEL.

In 2000, a cross-sectional study was conducted in the US Reading plant that converted semi-finished copper-beryllium alloy strip and wire into finished strip, wire and rod. Current employees were 185 and 153 (83%) participated in the study. Median time since hire was 16 years (range: <1-45) for participants. However, 11 participants had beryllium exposure prior to hire with an additional time from 1-16 years of exposure. From 1969 to 2000, 650 personal, 4524 general area and 815 short-term high-volume breathing zone task samples were collected. The median total mass personal beryllium exposure was 0.06 (range: <0.01-7.8) $\mu g/m^3$ in the rod and wire production, 0.02 (range: < 0.01-0.072) $\mu g/m^3$ in the strip metal production, and 0.01 (range: <0.01-0.06) $\mu g/m^3$ in office administration employees. The overall prevalence of consistent BeLPT positive workers was 7% (10/153), and 4% (6/153) had CBD. Thirteen percent (2/15) of workers with one year or less since first exposure were sensitized, but none of them had CBD. Employees with BeS or CBD reported levels of respiratory symptoms similar to non-sensitized workers. None (0/26) of the office administration employees had CBD or were BeS. The median personal sample concentration at rod and wire production was 0.06 $\mu g/m^3$ (210 samples) and the general area samples had an

arithmetic mean concentration of 1.75 µg/m^3. The median of personal sample exposure was 0.02 µg/m^3 for strip metal production (320 samples) and the general area sample arithmetic mean was about 0.09-0.14 µg/m^3. None of the individual processes or jobs where fewer than 5% of samples may have exceeded 0.2 µg/m^3 had a statistically significant risk of either BeS or CBD. Use of respirators was limited and use was on an intermittent basis for special tasks (Schuler *et al* 2005). Again, this may have implications for setting an STEL.

Rosenman *et al* (2005) established a retrospective cohort in a beryllium producing plant in Pennsylvania that operated from 1957 to 1978. In the period from 1957-1962, representative exposures for tasks ranged from 0.9–84 µg/m³. However, most time-weighted averages were below 2 µg/m^3 and in the range from 1 to 2.5 µg/m^3. In the period from 1971-1976, the representative task exposures were from 0.5-16.7 µg/m^3 and the time weighted average exposure concentrations from 0.7–3.5 µg/m³. In total, 1,351 had worked at the plant. At the end of 1988, a study was initiated with 715 eligible participants; 427 (63.9%) participated both in the screening for BeS and evaluation for CBD. Among the screened workers, 44 individuals (7.6 %) had a definite or probable CBD, 12 more participants possible CBD. No difference in mean duration of exposure for individuals with CBD (9.4 years) versus those who had no evidence of CBD (8.7 years) was observed. Neither was there a difference between the two groups in mean cumulative exposure (181 versus 209 µg/m^3), mean average exposure (8.7 versus 8.3 µg/m^3), and mean peak exposure (81 versus 87 µg/m^3). Another 40 individuals (7.0 %) were sensitized and 23 individuals possibly sensitized The authors mention the uncertainty in the exposure estimated as the exposure metrics were based on sparse data. SCOEL realizes the limitations in the epidemiological design, the data analysis and the lack of exposure-response relations, which excludes the study being used for risk assessment.

Johnson *et al* (2001) reported results from the UK Cardiff Atomic Weapons Establishment in the UK that operated from 1961 to 1997. Beryllium processing included melting and casting, powder production, impact milling, ball milling, pressing, machining, and heat and surface treatment. The annual mean area concentrations were from 0.02 to 0.32 µg/m^3 and annual personal mean concentrations from 0.11 to 0.72 µg/m^3 in the period from 1981-1997. The airborne beryllium concentrations were in the majority of measurements below 2.0 µg/m³. In the period from 1981 to 1997, 194 full-time workers were employed at the plant. Based exclusively on medical surveillance, only one case of CBD was observed during the operation of the plant. This case had a minor cut to a finger on a beryllium oxide-contaminated grinding wheel, causing ulceration, which progressed and necessitated amputation of the finger. Nevertheless, it progressed into the forearm and possibly the lungs. As workers routinely wore half-masks or full-face respirators, the dose is unknown but expected to correlate with external exposure.

In 1969, a beryllium ore processing plant was established in Utah in the US, where beryllium hydroxide was produced from beryl (beryllium aluminium silicate) and brandite (hydrated beryllium silicate). The exposures were to the raw materials, beryllium salts and beryllium hydroxide. The annual area arithmetic mean concentration decreased from about 2 µg/m^3 in the early phase of production to 0.3 µg/m^3 in 1999. The daily-weighted average concentration ranged from 0.1 to 0.4 µg/m^3. Of the current workers (N=87), 75 participated in a cross-sectional survey, which revealed 3/75 (4%) with BeS and one with CBD. The worker with CBD had previously worked 10 years in another plant using beryllium before attending the Utah plant. The mean tenure of workers with BeS was 21.3 years compared with 14.9 years in non-sensitized workers. The authors concluded that observation of exposure-response relationships are hampered by the low number of cases (Deubner *et al* 2001). However, the study seems to suggest that BeS may increase at longer tenure and that beryllium ore dust might be less powerful to induce CBD.

In another study, a beryllium-sensitised individual had an average lifetime weighted exposure below 0.2 µg/m³ (97 % of all measurements were below 0.2 µg/m³) (Stanton *et al* 2006).

The prevalence of BeS and CBD were evaluated in the period 1999–2005 in 1875 current and former employees of the Lawrence Livermore National Laboratory in the US. Mean latency (from first exposure) to time of evaluation was 32 years (range: 12-48 years) The annual average exposure was maximum in 1964 (0.0365 µg/m^3) and decreased to a recent level of about 0.001 µg/m^3. There was no correlation between area and personal air concentrations. Mean duration of employment was 18 years (range: 0.5-41 years). Of 59 BeS positive employees (3.1%), 49 BeS cases were further evaluated by high-resolution computer tomography (HRCT) and 40 by bronchoalveolar lavage and transbronchial biopsy, which showed that 5 had CBD, indicating a transition rate from exclusively being BeS positive to CBD of 10.2%. Additionally, 3 had possibly CBD based on HRCT scan and/or bronchoalveolar lavage abnormalities, but not meeting the criteria for the CBD diagnosis. This corresponds to a disease rate of about 0.3% (5/1875) or 0.4 % (8/1875) of the population. As stated by the authors, the area sampling showed low exposure levels, but personal air sample concentrations were not available from the relevant exposure period (Arjomandi *et al* 2010).

In a recent review, a special role of skin exposure in the development of CBD has been proposed, as cases of CBD have occurred despite large reductions in respiratory exposures below regulatory standards (Redlich and Herrick 2008). Limited studies suggest that beryllium particles may be able to penetrate into human skin. Altogether, available data support the hypothesis that in addition to respiratory exposure, skin exposure to beryllium particles may induce sensitisation, which can progress to CBD following inhalation exposure (Redlich and Herrick 2008).

The study of Deubner *et al* (2007) contains no information which can be used to derive exposure-response relationships. It is mentioned that beryllium (Be) salts and possibly BeO and metal particles might also cause sensitisation. In the period 2000–2003, the 1-year incidence was 4.1 % for BeS, whereas in the period 2004–2005, it was 1.1 %, indicating that improvement of working conditions decreased sensitisation.

In a study at a beryllium oxide ceramics manufacturing facility, the sensitisation prevalence for the workers at the production employed in the period 2000–2004 was 1 % and that for the workers employed in the period of 1993–1998 was 8.7 %. Airborne beryllium levels for the workers were similar for the two time periods but the preventive measures for the period of 2000–2004 were more comprehensive. The beryllium concentration in the air was 0.21–0.18 µg/m³ (geometric mean) measured as "total mass" (Cummings *et al* 2007).

It was shown that a programme of extensive enhanced preventive measures had an impact on reducing sensitisation in beryllium-exposed workers, although sensitisation had not been entirely eliminated. Sensitisation prevalence was 8.9 % for the Pre-Program Group and 2.1 % for the Program Group (Bailey *et al* 2010). In this study, no data on the air concentration of beryllium at the workplace was given.

As a consequence of functional respiratory restrictions, repeated inhalation exposure to beryllium may also lead to secondary systemic effects. Cardiovascular, renal, hepatic and haematological effects, and weight loss were observed (Greim 2005). Two cases of granulomatous myocarditis were identified at the Department of Forensic Medicine in Stockholm. The first case was a 30-year old man exposed to beryllium for about 10 years and the second case was a 40-year old man exposed to beryllium for more than 10 years (WHO 1990).

7.3.2. Animal data

7.3.2.1. Inhalation

The lung is the main target organ in animals (rats, mice, hamsters, guinea pigs, rabbits, cats, dogs, pigs and monkeys) after repeated inhalation exposure to beryllium and its compounds (beryllium oxide, sulphate, fluoride or hydrogen phosphate). In rats, the lowest concentration tested of 0.006 mg/m³ (6 hours/day, 5 days/week for life) caused lung inflammation and fibrotic changes (Vorwald and Reeves 1959).

7.3.2.2. Oral exposure

Due to the low absorption from the gastrointestinal tract, SCOEL does not consider oral exposure as informative for risk assessment of occupational exposure.

7.4. Irritancy and corrosivity

Contact with soluble beryllium compounds causes conjunctivitis in humans (Van Ordstrand *et al* 1945). No data were available regarding dermal or eye irritation by beryllium compounds in laboratory animals. Beryllium metal was shown not to be irritant to skin or eye in animals (Strupp 2011a).

7.5. Sensitisation

7.5.1. Human data

Beryllium and beryllium compounds can cause allergic contact dermatitis or a granulomatous skin reaction in humans. In addition, beryllium induces respiratory sensitisation. Individuals who are sensitised to beryllium (BeS) can be identified by the beryllium lymphocyte proliferation test (BeLPT). In the BeLPT, blood or bronchoalveolar lavage fluid lymphocytes are cultivated and stimulated by a beryllium sulfate and the stimulation index is evaluated for exceeding the normal range. As the test has a considerable inherent and interlaboratory variability, a test is usually repeated to confirm an initial result (Balmes *et al* 2014). Cross-sectional studies in the U.S. beryllium industries found the prevalence of BeS were from 0.9 to 14.6%, associated with both total and respirable beryllium (Balmes *et al* 2014).

For further information, especially with respect to quantitative risk assessment concerning BeS see section 7.3.1.

7.5.2. Animal data

Respiratory sensitisation to beryllium has been demonstrated in the different animal models of guinea pigs, mice, dogs and monkeys. However, the histopathological findings do not closely correlate with the respective pathological conditions in human (Greim 2005).

Beryllium compounds have further been shown to be skin sensitisers in animal experiments. However some of these experiments were not carried out in accordance with standardised procedures. In a recent study, beryllium metal powder did not cause skin sensitisation in guinea pigs (Strupp 2011b).

7.6. Genotoxicity

7.6.1. Human data

In vivo

Humans which were exposed up to 20 µg beryllium/m³ for more than 4 hours per week (no more details on the duration of exposure are given) did not show induction of sister

chromatid exchange or micronuclei in lymphocytes compared to persons exposed for 4 hours or less per week (Wegner *et al* 2000).

7.6.2. Animal data

In vivo

A micronucleus test in the bone marrow in mice orally dosed with up to 117 mg beryllium (as sulphate)/kg bw was negative (Ashby *et al* 1990). However, absorption after oral administration is low, which limits the systemic bioavailability of beryllium and therefore the significance of the study.

Beryllium chloride induced a statistically significant increase in the percentage of chromosomal aberrations in both somatic and germ cells in mice after single and repeated (up to 3 weeks) oral administration. Doses of 93.75, 187.50, 375, and 750 mg $BeCl_2$/kg bw were applied for single and 93.75, 187.50 and 375 mg $BeCl_2$/kg bw for repeated treatment. In the same study beryllium chloride induced a significant increase in the percentage of abnormal sperm in the treated mice (Fahmy *et al* 2008). However SCOEL noted that concentrations were extremely high. The evaluation of chromosomal aberrations in spermatocytes was not convincing, since the positive effect was mainly ascribed to the occurrence of autosomal and gonosomal univalents, for which the significance as chromosome aberrations is unclear (Adler 1993). Changes in sperm morphology are no reliable indicators for mutations. The relevance of these effects for germ cell mutagenicity is questionable (ICPEMC 1983, Salamone 1988, Wild 1984). The results should be interpreted as cytotoxicity.

7.6.3. In vitro

Soluble beryllium compounds such as beryllium nitrate, sulphate and chloride can induce sister chromatid exchanges, chromosomal aberrations and gene mutations in mammalian cells. However the results of genotoxicity assays in vitro for soluble beryllium compounds are inconsistent, since both positive and negative results were obtained (ATSDR 2002, Greim 2005, WHO 2001). Beryllium metal was not found to be mutagenic or clastogenic in vitro in a recent study (Strupp 2011a). Nevertheless, this study is not particularly meaningful since the authors tested only beryllium metal extracts with negligible solubility of the particles, reaching only concentrations in the low nanomolar range. No particles small enough to be phagocytosed or endocytosed have been tested, which may get solubilised inside the cell within the lysosomes in a far more acidic environment, giving rise to elevated levels of beryllium ions inside the cell as demonstrated for other particulate metal compounds (Costa *et al* 1981, Schwerdtle and Hartwig 2006). However, interestingly, even these low concentrations of solubilised beryllium provoked dose-dependent increase in cell transformation, suggesting that this may be one relevant mechanism in beryllium-induced carcinogenicity.

7.7. Carcinogenicity

7.7.1. Human data

Increased mortality from lung cancer, associated with beryllium exposure, was shown in a number of studies. These studies are considered to provide evidence of the carcinogenicity of beryllium in humans. Death from lung cancer correlated with increasing time since the beginning of employment and previous beryllium disease, but not with duration of employment. It was shown that exposure to high beryllium concentrations (> 1 000 µg/m³), which is regarded as a trigger for ABD, is associated with significantly increased risk for lung cancer (ATSDR 2002, Greim 2005, JRC 2012, NTP 2005, US EPA 2008, WHO 2001).

The conducted regression analyses of cancer risk and exposure to beryllium showed the increase in lung cancer risk (SMR 1.17; 95 % CI 1.08–1.28) at exposure concentrations higher than 10 µg/m³, for both mean and maximum time-weighted average exposure (Schubauer-Berigan *et al* 2011). It is not stated whether inhalable or respirable dust was measured.

However, recently there has been some controversy about the interpretation of the epidemiological evaluations of the carcinogenicity of beryllium (Hollins *et al* 2009, Levy *et al* 2002, 2007 and 2009, MacMahon 1994, Boffetta *et al* 2012). Some of the critical comments on the epidemiological studies concern the inadequate consideration of confounding factors like smoking, age matching of controls and exposed, and exposure to other occupational agents. Furthermore, according to some authors, the lack of relationship with duration of employment or cumulative exposure, whereas average and maximum exposure were associated with lung cancer, indicates that there is no clear casual association between occupational exposure to beryllium and the risk of cancer. For example, in a reanalysis of the NIOSH cohort mortality study, the SMRs for lung cancer were calculated using an alternative approach for the statistical analysis. City mortality rates rather than county or US rates were used as well as a different indirect method for adjusting for smoking. Furthermore, cases were pooled among plants to calculate an overall SMR. No statistically significant increases in the incidence of lung cancer among beryllium workers were found (Levy *et al* 2002). However, since the recommended OEL is not based on carcinogenicity and is considerably lower as compared to exposure estimates leading to lung cancer in humans, this controversy does not need to be resolved within this evaluation.

7.7.2. Animal data

Beryllium sulphate has been shown to cause morphological transformations in Syrian hamster embryo (SHE) cells and in BALB/c-3T3 cells (DiPaolo and Casto 1979, Kesheva *et al* 2001). Beryllium metal extract induced increased transformation rates of SHE cells (Strupp 2011a).

In animal inhalation studies, it was shown that beryllium metal, sulphate, chloride, fluoride or oxide cause malignant lung tumours in rats and monkeys (for summary, see Table 6 in Greim, 2005).

After intratracheal and intraperitoneal administration of beryllium compounds, lung tumours were found in rodents. The intravenous and intramedullary administration of beryllium carbonate, oxide and phosphate caused osteosarcomas in rabbits (Table 7 in Greim 2005, Hollins *et al* 2009, US EPA 2008, WHO 2001). No tumours were observed after life-time oral administration of beryllium sulphate (0.025–0.75 mg Be/kg bw and day, given with the diet or drinking water) in rats and mice or after 172 weeks of oral administration (1 mg Be/kg bw and day with the diet) in dogs, probably as a result of low gastrointestinal absorption (Greim 2005).

The mechanism of action of the carcinogenicity of beryllium is not yet elucidated, but appears to involve indirect genotoxicity and cell transformation rather than direct genotoxicity.

7.8. Reproductive toxicity

7.8.1. Human data

There were no data on reproductive toxicity in humans (ATSDR 2002, WHO 2001).

7.8.2. Animal data

No animal data on the reproductive toxicity of inhaled beryllium or its compounds were available. Beryllium sulphate did not exert any reproductive toxicity in rats and dogs after oral administration (ATSDR 2002, WHO 2001).

A study conducted by Selivanova and Savinova (1986) examined the developmental toxicity of 50 mg beryllium/kg as beryllium chloride and beryllium oxide administered via intratracheal injection on gestational days 3, 5, 8, or 20. An increase in fetal mortality was observed in rats dosed on gestational day 3 with beryllium oxide and in rats dosed on gestational day 5 with either beryllium compound. Exposure to beryllium oxide or beryllium chloride on gestational day 3 resulted in decreased fetal body weights and an increased percentage of pups with internal abnormalities. The latter effect was also observed in the pups of rats exposed to beryllium chloride or beryllium oxide on gestational day 5 and beryllium oxide on gestational day 8. There were no differences in the number of live births per dam or in fetal length (Selivanova and Savinova 1986 in ATSDR 2002).

7.9. Mode of action and adverse outcome pathway considerations

In humans, the primary target of beryllium toxicity following inhalation exposure is the respiratory tract, leading to BeS, acute and chronic beryllium disease and lung cancer as the principal effects. Regarding acute beryllium disease, high levels of exposure can result in inflammation of the upper and lower respiratory tract and airways, bronchiolitis, pulmonary edema, and chemical pneumonitis. Repeated inhalation exposure to low concentrations of beryllium or beryllium compounds can cause chronic beryllium disease (CBD) in humans. CBD is a cell-mediated immunological reaction of delayed type and is generally observed after a long latent period. BeS precedes chronic beryllium disease (CBD), but the progression from sensitisation to disease is not fully understood. The prevailing view is that most individuals must first be sensitised before beryllium in the lungs can cause the lung damage of CBD, based on studies showing that almost all individuals with CBD with positive BeLPT are also sensitised. (ATSDR 2002, Greim 2005, OSHA 2015).

The underlying mechanisms for the carcinogenicity of beryllium and its compounds are not well understood. Soluble beryllium compounds revealed inconsistent results with respect to sister chromatid exchanges, chromosomal aberrations and gene mutations in mammalian cells. A few interactions on the molecular level have been identified, such as the displacement of magnesium ions in DNA polymerases, leading to an increased error frequency during DNA replication and thus DNA base substitutions. Another indirect mechanism consists in the hypermethylation of promotor sequences, which leads to the inactivation of the corresponding genes. Beryllium may also influence cell cycle progression, and there are indications for cell transforming activities. Altogether, the mode of action appears to be indirect and restricted to comparatively high concentrations. Therefore, beryllium can be considered as a Category C carcinogen, *i.e.* a genotoxic carcinogen for which a practical threshold can be identified (Bolt and Huici-Montagud, 2008). In consequence, the OEL and STEL that prevents BeS and CBD should be protective also with regard to carcinogenicity.

7.10. Lack of specific scientific information

SCOEL considers the available data basis sufficient for the recommendation of an OEL.

8. GROUPS AT EXTRA RISK

Susceptibility to BeS has been associated with the human lymphocyte antigen (HLA) Class II HLA-DRB1-E69 allele whereas progression to CBD was associated with HLA-DQB1-G86 and HLA-DRB1-S11 (Rossman *et al* 2002).

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