SUBSTANCE EVALUATION REPORT

Public Name: **Beryllium**

EC Number(s): **231-150-7**

CAS Number(s): **7440-41-7**

Submitting Member State Competent Authority: Federal Institute for Occupational Safety and Health, Friedrich-Henkel-Weg 1-25, D-44149 Dortmund, Germany, Tel: 049-231-9071-0, Fax: 049-231-9071-2611, Email: chemG@baua.bund.de

Year of evaluation (as given in the CoRAP): 2013

VERSION NUMBER: 2.1 **DATE: September 2014**

Conclusions of the most recent evaluation step*	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	
Concern clarified; Need for risk management measures; RMO analysis to be performed	**X**
Other:	

**Include details in the executive summary.*

DISCLAIMER

The report has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the report. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the report are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Executive summary

Grounds for concern

Beryllium is classified as a Carcinogen. This is a cause to closer view whether or not this substance reveals a risk for humans. It was chosen for substance evaluation to clarify whether employees are exposed to the substance and as a result bear an unacceptable risk.

Procedure

First substance evaluation: 2013

Human Health

The evaluation of the toxicity of beryllium has been based on the registration dossiers as well as on reviews by a variety of international bodies/regulatory programs and original publications. Data available up to September 2013 for all endpoints have been assessed.

Risk Communication, Labelling

The labelling of beryllium as provided by the lead registrant was reviewed based on the Classification and Labelling as listed under Index number 004-001-00-7 in Annex VI, Part 3, Table 3.1 of Regulation (EC) No 1272/2008 (CLP).

Worker exposure

No Chemical Safety Report has been provided by the registrants since the marketed tonnage for each individual registrant is below the limit of 10 t/a. Therefore, the exposure assessment of the eMSCA is based on data taken from literature and monitoring data from available sources.

Consumer Exposure

The evaluation of consumer uses and consumer exposure resulting thereof has been based on the information given in the registration dossiers as well as information taken from publications available in open literature, data bases and European national product registers. Registration data by the registrants/suppliers available before November 2013 were assessed. They were checked and verified against the information taken from the other sources.

Conclusions

Human Health

Evaluation of the existing information on the toxicity of beryllium indicated that the legal classification for acute oral toxicity as “Acute Tox. 3*; H301: Toxic if swallowed”, for irritation as “Eye Irrit. 2; H319: Causes serious eye irritation” and “Skin Irrit. 2; H315: Causes skin irritation”, might have been based on a combined evaluation of beryllium and its compounds.

A GLP compliant study following OECD TG 423 included in the registration dossiers reveals that beryllium metal does not produce significant toxic effects in rats following single oral exposure up to the limit dose of 2000 mg/kg bw. Furthermore, irritation on skin or eyes was neither observed in humans nor could it be induced in test animals in GLP compliant studies carried out in accordance with EU Regulation (EC) No 440/2008 or current OECD guidelines for the testing of chemicals

with pure beryllium metal. Therefore beryllium metal does not appear to fulfil the criteria according to Annex I of Regulation (EC) No 1272/2008 (CLP) for classification as "Acute Tox. 3*; H301", "Eye Irrit. 2; H319" or "Skin Irrit. 2; H315".

The classification of beryllium as "Acute Tox. 2, H330: Fatal if inhaled" as a minimum classification following Annex VI 1.2.1 of Regulation (EC) No 1272/2008 (CLP) was confirmed. An acute toxicity estimate (ATE) of 170 mg/m³ was calculated, thus Category 2 classification is warranted according to CLP Annex I, Table 3.1.1 (50-500 mg/m³ range). The ATE is based on a single inhalation exposure study in which 27 % of the male rats died 12-15 days post exposure to 800 mg/m³ of beryllium dust for 50 min and exposure time extrapolation to the 4-hour reference period for direct comparison with the criteria by applying Haber's Law ($C^n \cdot t = k$ with $n = 1$).

Available human data demonstrated that inhalation exposure of beryllium can be attributed to the lung damage seen in occupationally exposed persons developing chronic beryllium disease (CBD). The current legal classification of beryllium for specific target organ toxicity repeated exposure has been translated from classification as "T; R48/23: Toxic: danger of serious damage to health by prolonged exposure through inhalation" under 67/548/EEC (DSD) with a general hazard statement not specifying the route of exposure. An explicit indication of inhalation as the route of exposure in the specific target organ toxicity repeated exposure hazard statement "STOT RE 1; H372: Causes damage to lungs through prolonged or repeated exposure by inhalation." is therefore justified.

CBD is characterized by initial beryllium sensitization (BeS) and the progressive development of granulomas and mononuclear cell infiltrates primarily in lung tissue. Past exposure to beryllium and evidence of beryllium sensitization are important parts of the clinical diagnosis of CBD. Beryllium sensitization is an early event associated with the development of CBD. Therefore beryllium appears to fulfill the criteria for classification as "Resp. Sens. 1, H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled." according to Regulation (EC) No. 1272/2008 (CLP). As such a classification would not change risk management measures for a substance already classified as Carc. 1B, the evaluating Member State Competent Authority (eMSCA) is currently not planning to harmonise classification and labelling for this endpoint.

Beryllium is classified as Carc. 1B, H350i:"May cause cancer by inhalation." according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 as a minimum classification and as Carc. Cat. 2, R49: "May cause cancer by inhalation." according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008. The eMSCA considers this classification as justified.

Consumer Exposure

No further data is needed. The assessed data do not indicate a concern based on consumer exposure to beryllium via consumer uses.

The assessed data indicate a negligible exposure of consumers to beryllium. In the registration dossier consumer uses of beryllium are advised against. The registration data covers consumer contacts with articles containing parts comprising beryllium. In accordance with the information derived from other sources incorporated alloys have low beryllium content (details in Confidential Annex).

Worker Exposure

Exposure to beryllium and its compounds is expected in the aerospace, automotive, energy, defence, medical devices, and electronics industries where it is used as beryllium alloy, beryllium

metal, and beryllia ceramics. Publicly available data indicates that exposure is not sufficiently controlled, with the highest exposures occurring in industry sectors such as manufacture of basic metals, thermal handling / machining of beryllium products, especially in glass production and melting, pouring, casting, and grinding of beryllium alloys, in foundries and in recycling of electronic scrap. About 65,000 workers are assumed to be exposed in Europe according to Cherrie, J. et al., 2011.

Further steps

During the substance evaluating process, a long-term systemic DNEL (inhalation) of 60 ng/m^3 has been derived based on chronic beryllium disease as a critical health effect in workers exposed to beryllium. Considering the available exposure data, this DNEL is significantly exceeded for almost all industrial uses where aerosol formation occurs. At critical uses the exposure exceeds the DNEL by up to two orders of magnitude. It should be noted, that the DNEL does not set a safe level for work with beryllium due to the fact that beryllium is carcinogenic and no exposure risk relation can currently be established. Even for exposure levels lower than the DNEL a remaining risk for the worker cannot be excluded.

Based on the arguments above, regulatory steps need to be taken.

The eMSCA intends to identify the substance as SVHC following Article 57a (based on the harmonised classification as Carc. 1B as a non-threshold-carcinogen) and 57f (based on STOT RE 1) with the goal of adding this substance to Annex XIV of REACH. In this way it is expected to enhance the use of state-of-the-art techniques for exposure reduction and to get an evaluation whether or not the specific uses are socio-economically justified.

In parallel, the current initiative of SCOEL to derive a binding occupational exposure limit (BOEL) is appreciated.

CONTENTS

TABLES

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

Public Name:	Beryllium
EC number:	231-150-7
EC name:	Beryllium
CAS number (in the EC inventory):	7440-41-7
CAS number:	7440-41-7
CAS name:	Beryllium
IUPAC name:	Beryllium
Index number in Annex VI of the CLP Regulation	004-001-00-7
Molecular formula:	Be
Molecular weight range:	9.01218 g/mol
Synonyms:	Beryllium element, Glucinium

Structural formula: Be

1.2 Composition of the substance

Name: Beryllium

Description: mono-constituent substance, Beryllium metal in its elemental form

Degree of purity: ≥ 96.5 %

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
beryllium, EC number: 231-150-7	confidential	confidential	Further information in confidential annex

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
confidential	confidential	confidential	Further information in confidential annex

Table 4: Additives

Additives	Typical concentration	Concentration range	Remarks
confidential	confidential	confidential	Further information in confidential annex

1.3 Physico-chemical properties

Table 5: Overview of physicochemical properties1

<table>
<tr><th>Property</th><th>Value</th><th>Remarks</th></tr>
<tr><td>Physical state at 20°C and 101.3 kPa</td><td>solid (odourless solid, steel grey metal)</td><td>Handbook data</td></tr>
<tr><td>Melting/freezing point</td><td>1278°C</td><td>Experimental data</td></tr>
<tr><td>Boiling point</td><td>2471°C</td><td>Handbook data</td></tr>
<tr><td>Vapour pressure</td><td>–</td><td>In accordance with column 2 of REACH Annex VII section 7.5, a study does not need to be conducted if the melting point is above 300 °C.</td></tr>
<tr><td>Surface tension</td><td>–</td><td>In accordance with column 2 of REACH Annex VII section 7.6. a study does not need to be conducted if the water solubility is below 1 mg/L at 20 °C.</td></tr>
<tr><td>Water solubility</td><td>< 0.5 µg/L (20°C, pH 6.11)</td><td>The water solubility was determined according to OECD Guideline 105/ EU Method A.6 (column elution method).
Experimental data</td></tr>
<tr><td>Partition coefficient n-octanol/water (log value)</td><td>–</td><td>In accordance with column 2 of REACH Annex VII section 7.8. a study does not need to be conducted if the substance is inorganic.</td></tr>
<tr><td>Flash point</td><td>idem</td><td>idem</td></tr>
<tr><td>Flammability</td><td>idem</td><td>idem</td></tr>
<tr><td>Explosive properties</td><td>idem</td><td>idem</td></tr>
<tr><td>Self ignition temperature</td><td>idem</td><td>idem</td></tr>
<tr><td>Oxidising properties</td><td>idem</td><td>idem</td></tr>
<tr><td>Granulometry</td><td><table><tr><th>Micron Size</th><th>Cumulative Weight % less than</th></tr><tr><td><5</td><td>1.5</td></tr><tr><td><10</td><td>10</td></tr><tr><td><15</td><td>27</td></tr><tr><td><20</td><td>48.7</td></tr><tr><td><25</td><td>65.4</td></tr><tr><td><30</td><td>76</td></tr></table></td><td>The beryllium sample was analyzed using a Coulter Counter analysis method.</td></tr>
</table>

[1] *The references of the values reported in Table 5 will be available in the technical dossier. In case references need to be included an additional column could be added manually to Table 5.*

	<37 | 86 <44 | 93.8	
Stability in organic solvents and identity of relevant degradation products	–	*The substance is solid at environmentally relevant temperature and pressure, and hence no test is necessary.*
Dissociation constant	*idem*	*idem*
Viscosity	*idem*	*idem*
Auto flammability	*idem*	*idem*
Reactivity towards container material	*idem*	*idem*
Thermal stability	*solid (odourless solid, steel grey metal)*	*Handbook data*
[*enter other property, if relevant, or delete row*]	*1278°C*	*Experimental data*

2 MANUFACTURE AND USES

2.1 Quantities

There is no manufacturing of beryllium metal and no employees involved in the production of beryllium metal in the European Union (EU). Beryllium metal is imported into Europe for use in industrial, scientific, defence and medical applications that requires further processing and/or assembly.

Table 6: Aggregated tonnage (per year)

1 – 10 t	10 – 100 t	100 – 1000 t	1000- 10,000 t	10,000-50,000 t
-	x	-	-	-

2.1.1 Manufacturing processes

Not relevant since Beryllium is not manufactured in the EU but only imported from outside the EU.

2.2 Identified uses

Beryllium is an essential material in the manufacture of products for the aerospace, automotive, energy, defence, medical, and electronics industries for more than half a century (Kolanz, 2010). It is a unique material exhibiting physical and mechanical properties unmatched by any other metal. Beryllium is one-third lighter than aluminium, making it one of the lowest-density metals. It is also one of the most rigid with a specific stiffness six times greater than steel. It possesses high heat-absorbing capability and has dimensional stability over a wide range of temperatures.

Because of its unique combination of qualities, beryllium is a strategic and critical material for many industries. The beryllium industry produces three primary forms of beryllium: beryllium alloy (copper beryllium) is the largest, followed by beryllium metal, with beryllia ceramics (beryllium oxide) third. Beryllium alloys with metals such as copper, nickel, or aluminium have high strength and hardness. Depending on the desired strength and electrical conductivity, copper-beryllium wrought products typically contain 0.15 percent to 2.0 percent beryllium. Copper-beryllium alloys for engineered materials are common in the electronics, automotive, defence, and aerospace industries because of their unique properties of strength, electrical and thermal conductivity, magnetic transparency, and corrosion resistance.

In the following a tabular list of all identified uses is given (cf. Table 7). Chemical Safety Reports were not provided by any of the registrants because the marketed tonnage of beryllium did not exceed the 10 t/a limit. There are no occupational uses advised against.

Table 7: Uses and applications of beryllium (according to: Darby, A. and Fishwick, D., 2011)

Technology	**Application**
Aerospace	• Engines and rockets • Brakes and landing gear • Satellites and gyroscopes • Precision tools • Altimeters • Mirrors
Energy and Electrical	• Heat exchanger tubes • Microelectronics • Microwave devices • Nuclear reactor components • Oil field drilling devices • Relays and Switches
Telecommunications	• Undersea repeater housings • Mobile phones • Personal computers • Transistor mountings • Electrical connectors • Switches and springs • electromagnetic shielding
Biomedical	• X-ray tube windows • Scanning electron microscopes • Dental prostheses • Medical lasers
Defence	• Tank mirrors • Springs on submarine hatches • Mast mounted sights • Missile guidance • Nuclear triggers
Fire prevention	• Non-sparking tools • Sprinkler systems
Automotive	• Air-bag triggers • Anti-lock braking systems • Steering wheel connectors
Miscellaneous	• Plastic moulds • Bellows • Jewellery – aquamarine and emerald • Golf clubs • Bicycle frames • Camera shutters • Fishing rods • Pen clips • Scrap metal recovery and recycling • Ceramics

2.2.1 Uses by workers in industrial settings

Table 8 shows all given process categories (PROC) and sectors of end-use (SU) given by all registrants.

Table 8: Summary of PROCs and SUs at industrial side and by professional workers (data taken from the registration dossiers)

	PROC resp. SU																		
	0	1	2	4	5	8	9	14	15	16	17	19	20	21	22	23	24	25	26
3.5.2 Formulation of alloys at industry side		x	x	x	x	b,a		x						x	x	x	x	x	x
3.5.3 Use of alloys at ind. side		x	x	x	x	b,a		x	x	x	x			x	x	x	x	x	x
Sector of end-use (SU)	x		b					x	x	x	x					x	x		
Use in ind. laboratories									x					x					
Sector of end-use (SU)	x						x	x	x	x	x	x				x	x		
3.5.4 Use by prof. workers									x										
Sector of end-use (SU)								x	x	x	x		x			x	x		
3.5.6 Article service life								x						x	x	x	x	x	

2.2.2 Uses by consumers

No consumer uses of beryllium have been identified. However, consumers use articles comprising parts containing beryllium. According to the registration data (ECHA 2013a) these articles belong to the article categories “AC 01: Other (non intended to be released): electronic articles” and “AC 1: Vehicles”. Their Environmental release category is classified as “ERC 11a: Wide dispersive indoor use of long-life articles and materials with low release”.

Further information on the uses by consumers is given in the confidential part of this report.

2.3 Uses advised against

2.3.1 Uses by workers in industrial settings advised against

There are no uses advised against.

2.3.2 Use by professional workers advised against

There are no uses advised against.

2.3.3 Uses by consumers advised against

Use of beryllium by consumers is a use advised against (ECHA 2013a).

Further information is given in the confidential part of this report.

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

Beryllium is listed by Index number 004-001-00-7 in Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 as follows:

Table 9: Classification and Labelling according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 (CLP)

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M - Factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. Hazard statement Code(s)		
004-001-00-7	beryllium	231-150-7	7440-41-7	Carc. 1B Acute Tox. 2 * Acute Tox. 3 * STOT RE 1 Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Skin Sens. 1	H350i H330 H301 H372 ** H319 H335 H315 H317	GHS06 GHS08 **Dgr**	H350i H330 H301 H372 ** H319 H335 H315 H317			

* For certain hazard classes, including acute toxicity and STOT repeated exposure, the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under this Regulation. In these cases the classification in this Annex shall be considered as a minimum classification.

** 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 with a general hazard statement not specifying the route of exposure as the necessary information is not available.

Pictograms:	GHS06:	Skull and crossbones
	GHS08:	Health hazard
Signal word:	Dgr:	Danger
Hazard statements:	H350i:	May cause cancer by inhalation.
	H330:	Fatal if inhaled.
	H301:	Toxic if swallowed.
	H372.	Causes damage to organs through prolonged or repeated exposure.
	H319:	Causes serious eye irritation.
	H335:	May cause respiratory irritation.
	H315:	Causes skin irritation.
	H317:	May cause an allergic skin reaction.

Beryllium is covered by Index number 004-001-00-7 in Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Directive 67/548/EEC) of Regulation (EC) No 1272/2008 as follows:

Table 10: Classification and Labelling according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Directive 67/548/EEC) of Regulation (EC) No 1272/2008 (CLP)

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
004-001-00-7	Beryllium	231-150-7	7440-41-7	Carc. Cat. 2; R49 T+; R26 T; R25-48/23 Xi; R36/37/38 R43	T+ R: 49-25-26-36/37/38-43-48/23 S: 53-45		E
Note E (Table 3.2): Substances with specific effects on human health (see Chapter 4 of Annex VI to Directive 67/548/EEC) that are classified as carcinogenic, mutagenic and/or toxic for reproduction in categories 1 or 2 are ascribed Note E if they are also classified as very toxic (T+), toxic (T) or harmful (Xn). For these substances, the risk phrases R20, R21, R22, R23, R24, R25, R26, R27, R28, R39, R68 (harmful), R48 and R65 and all combinations of these risk phrases shall be preceded by the word 'Also'.							

Indications of danger:	T+:	Very toxic
Risk phrases:	R49:	May cause cancer by inhalation.
	R25:	Also toxic if swallowed.
	R26:	Also very toxic by inhalation.
	R36/37/38:	Irritating to eyes, respiratory system and skin.
	R43:	May cause sensitization by skin contact.
	R48/23:	Also toxic: danger of serious damage to health by prolonged exposure through inhalation.
Safety phrases:	S53:	Avoid exposure - obtain special instructions before use.
	S45:	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

Note of the eMSCA:

No studies were located regarding effects in humans after **oral** exposure to beryllium or its compounds by ATSDR 2002. **Systemic effects** were observed in animals after oral exposure to **beryllium compounds**.

No data were located regarding the **dermal or ocular irritancy** of beryllium in laboratory animals by WHO 2001.

3.2 Self-classification

The following information including Precautionary statements is provided by the lead registrant:

Table 11: Classification and Labelling according to Regulation (EC) No 1272/2008 (CLP) as provided by the lead registrant

Name	Classification		Labelling		Precautionary statements
	Hazard Category	Hazard statement	Signal Word Hazard Pictogram Code	Hazard statements	
beryllium, pure substance	Acute Tox. 2 Carc. 2 STOT RE 1	H330 H351 H372	Danger GHS06: Skull and crossbones GHS08: health hazard	H330: Fatal if inhaled. H351: Suspected of causing cancer by inhalation. H372: Causes damage to lung through prolonged or repeated exposure by inhalation.	P201: Obtain special instructions before use. P260: Do not breathe dust.

Table 12: Classification and Labelling according to 67/548/EEC (DSD) as provided by the lead registrant

Name	Classification	Labelling		
		Indication of danger	Risk phrases	Safety phrases
beryllium, pure substance	T+; R26 Very toxic by inhalation. T; R48/23 Toxic: danger of serious damage to health by prolonged exposure through inhalation. Carc. Cat. 3; R40 Limited evidence of a carcinogenic effect.	T+ - very toxic	R26 - Very toxic by inhalation. R40 - Limited evidence of a carcinogenic effect. R48/23 - Harmful: danger of serious damage to health by prolonged exposure through inhalation.	S45 - in case of accident or if you feel unwell, seek medical advice immediately (show the label where possible) S53 - avoid exposure - obtain special instructions before use

Note of the eMSCA:

The proposed self-classification is NOT compliant with the harmonised classification.

4 ENVIRONMENTAL FATE PROPERTIES

not assessed

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

5.1.1 Non-human information

Table 13: Basic toxicokinetics **according to registration dossier**

Method/ Guideline	**Route Dose levels, Duration of exposure**	**Species, Sex, No/group**	**Results (excretion via respiration, urine, faeces, bile, half-life time plasma, residues in tissue)**	**Remarks**	**Reference**
Acute Toxicity of Inhaled Beryllium Metal, Excretion, no guideline followed, non-GLP	nose-only aerosol inhalation, single (50 min) 800 mg/m³ (625 µg Be metal/rat), sacrifices after 3, 7, 10, 14, 31, 59, 115, 171 d	Rat 74 M divided into groups of 6 per sacrifice time point	Be-clearance: half-life ~240 d	Key study Particle size distribution: 50 % effective cut off diameter = 1.7 µm MMAD/GSD: 1.4 +/– 0.1 µm/ 1.9 +/– 0.1 µm	P.J. Haley, G.L. Finch, M.D. Hoover, R.G. Cuddihy; Fundamental and applied Toxicology 15, 767-778, (1990)
Effects of Inhaled Beryllium on Lung Clearance, no guideline followed, non-GLP	inhalation, single, ^{85}Sr-FAP followed by metallic Be at Be-burdens of 0, 1.7, 2,6, 12, 34 µg/mouse, followed up for 350 d	**Mouse** no data on sex or number	clear retardation of lung clearance of the ^{85}Sr-FAP (fused aluminosilicate particles) marker and of Be from Be-burdens of 12 µg/mouse	supporting study **Abstract only of early results of study published in 1998**	G.L. **Finch**, L.J. Reddick, M.D. Hoover, K.J. Nikula; Toxicologist, Vol 13, No 1, March **1993**
Low Lung Burdens of Beryllium Metal, no guideline followed, non-GLP	Be-burdens from 1.5 to 50 µg co-exposure to ^{85}Sr-FAP observation period (for Be-clearance) 90 d, interim sacrifices at 8, 16, 40 d Clearance of ^{85}Sr-FAP 60 d	Rat no data on sex or number	Clearance half life times: ^{85}Sr-FAP 38, 64, 112, 135, 232 d for burdens of 0, 1.5, 2, 10 and 50 µg, respectively	supporting study **Abstract only**	G.L. **Finch**, P.J. Haley, M.D. Hoover, A.F. Eidson and R.G. Cuddhy; Toxicologist Vol 11, No 1, February 1991
Ion Formation test in Artificial Biological Fluids GLP, no guideline available	100 mg/l into **Gamble's solution (pH 7.1)** or **Artificial lung fluid (pH 4.5)**, incubated at 37 °C in the dark under non-abrasive shaking for 1, 7, 14, 28 d.	cell-free	solubility at acidic pH (4.5) was higher than at neutral pH (7.1): 1.01, 10.5, 18.9, 33.9 mg/l vs. 0.166, 0.311, 0.325, 0.581 mg/l of **Be metal** for 1, 7, 14, and 28 d, respectively. Solubility was beryllium chloride >> copper-beryllium alloy > beryllium metal >> beryllium oxide ceramic	supporting study Beryllium Metal Powder (99.4 %) chemo-biokinetics general studies acidic pH (simulating a lysosomal environment)	TL1, unpublished record 2009a

5.1.2 Human information

This information is not available from the registration dossiers.

5.1.3 Summary and discussion on toxicokinetics

The data for toxicokinetics of beryllium were obtained from two rat studies and a mouse study. Inhaled beryllium particles in the 0.5–5.0 µm diameter range are deposited in the lower respiratory tract ($t_{½}$ ~ 240 d), whereas larger particles are filtered out by the upper airways (Haley et al., 1990; Welch 2012). Insoluble particles deposited in the upper respiratory tract and tracheobronchial tree are cleared by mucociliary transport, and those deposited in the lower regions are cleared primarily by alveolar macrophages. The clearance of insoluble compounds from the lungs has been generally shown to be biphasic, with clearance times of days (by mucociliary transport and alveolar macrophages) to years (by dissolution and other translocation mechanisms) (Welch 2012). Clearance of beryllium from the lungs of rats exposed to beryllium metal by inhalation was best described by a single-component negative exponential function from days 3 to 171 post exposure (Haley et al., 1990). Single, acute inhalation exposure to beryllium metal can chronically retard the general particle clearance rate by damaging alveolar macrophages (WHO 2001, ATSDR 2002) and can induce lung damage in rats (Haley et al., 1990) and mice (Finch et al., 1993).

Although inhalation is the primary route of uptake of occupationally exposed persons, no human data are available on the fraction of deposited or absorbed/translocated beryllium. The deposition and clearance of beryllium, like those of other inhaled particles, are governed by important factors such as dose, size, and solubility (WHO 2001, ATSDR 2002, MAK 2003). Absorption of inhaled beryllium occurs following its mobilization by clearance mechanisms. Animal studies have shown that clearance of sparingly soluble beryllium compounds is biphasic, with an initial rapid phase attributed to mucociliary transport of particles from the tracheobronchial tree to the gastrointestinal tract, followed by a prolonged slow phase of clearance via translocation to tracheobronchial lymph nodes, uptake by alveolar macrophages, and solubilisation of beryllium. Absorbed beryllium is eliminated primarily through urine, whereas excretion of unabsorbed beryllium is primarily via the faecal route shortly after exposure by inhalation, through mucociliary clearance from the respiratory tract and ingestion of swallowed beryllium (WHO 2001).

The slow clearance from the lungs means that beryllium may remain in the human lungs for many years after exposure. The amount of beryllium remaining in the lungs at any time after exposure is a function of the amount deposited and the rate of clearance, which depend in turn on the dose, size, and solubility of the specific beryllium particles inhaled. Such data are available for soluble beryllium salts, but they do not appear to be available for the sparingly soluble inorganic beryllium compounds and the metal (WHO 2001). After deposition of insoluble particles in the lungs, most beryllium is stored (MAK 2003) as beryllium is cleared incompletely from the lungs. Beryllium has been found in the lungs of beryllium disease patients long after cessation of occupational exposure. Beryllium cleared from the lungs and not excreted is translocated to the tracheobronchial lymph nodes, skeleton, liver, kidney, and blood (Welch 2012). The biological half-time of beryllium in human serum was calculated to be 2–8 weeks (ATSDR 2002). A half-life of 64 weeks has been estimated for beryllium in the human skeleton, the ultimate site of beryllium storage (WHO 2001).

A substantial portion of the inhaled material is transported to the gastrointestinal tract by the mucociliary escalator and by the swallowing of the insoluble material deposited in the upper respiratory tract. Oral administration results in <1% absorption and storage (WHO 2001). Small quantities of beryllium metal dusts that are dissolved by gastric juices result in trace amounts of beryllium chloride that might be absorbed from the stomach. The proportion of beryllium absorbed

by the gastrointestinal tract was estimated with 0.006 % (Welch 2012). Most of the beryllium taken up by the oral route passes through the gastrointestinal tract unabsorbed and is eliminated in the faeces (EPA 1998).

Beryllium is poorly absorbed through the intact skin (WHO 2001, ATSDR 2002). Skin contact may play an important role in sensitization to beryllium even if beryllium is not absorbed through the skin, however. Direct traumatic penetration of the skin can lead to dermal granulomas (Welch 2012).

Beryllium is not biotransformed (EPA 1998, WHO 2001).

5.2 Acute toxicity

5.2.1 Non-human information

5.2.1.1 Acute toxicity: oral

Table 14: Overview of experimental studies on acute toxicity after oral administration according to registration dossier

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels	Value LD_{50}/LC_{50}	Remarks	Reference
Acute toxic class method, OECD Guideline 423 (Acute Oral Toxicity - Acute Toxic Class Method), GLP	Oral (gavage) Dosing volume 10 ml/kg bw	Rat (10 w old), Wistar (SPF), 6 F after fasting for 17-19 h	single dose, Beryllium Metal Powder 99.4 % (vehicle: PEG-300)	> 2000 mg/kg bw not classified	Key study No mortality or clinical signs. No macroscopic findings at necropsy.	TL1, unpublished record 2009b

5.2.1.2 Acute toxicity: inhalation

Table 15: Overview of experimental studies on acute toxicity after inhalation exposure according to registration dossier

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels	Value LC_{50}	Remarks	Reference
Acute Toxicity of Inhaled Beryllium Metal, no guideline followed, non-GLP	nose-only aerosol inhalation, sacrifices after 3, 7, 10, 14, 31, 59, 115, 171 d	Rat 11-13 w old 74 M, groups of 6 per sacrifice time point	single (50 min), Beryllium Metal dust MMAD 1.4 µm (no vehicle), **800 mg/m³** (625 µg Be metal/rat)	not suitable for setting an LC_{50}	Key study 20 animals died spontaneously between days 12 and 15 post exposure. ↑ lung weight, pneumonitis	P.J. Haley, G.L. Finch, M.D. Hoover, R.G. Cuddihy; Fundamental and applied Toxicology 15, 767-778, (1990)
Responses Induced by Inhaled Beryllium Metal, no guideline	nose-only aerosol inhalation sacrificed after 7 d (initial Be-	Mouse 6-8 w old A/j and C3H/HeJ 36 F of each strain	single (90 min), Beryllium Metal dust MMAD 1.4 µm, GSD 1.9 µm, (no vehicle),	not suitable for setting an LC_{50}	Supporting study No mortalities or clinical signs. Granulomatous pneumonia,	K.J. Nikula, D.S. Swafford, M.D. Hoover, M.D. Tohulka, G.L. Finch, Toxicologic

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels	Value LC_{50}	Remarks	Reference
followed, non-GLP	burden) or after 6 months		**1030 mg/m³** (60 µg Be/mouse)		minimal to mild interstitial fibrosis	Pathology 25, (1), 2 - 12, 1997
Effects of Inhaled Beryllium on Lung Clearance, no guideline followed, non-GLP	Inhalation: lung clearance marker (^{85}Sr-FAP), metallic beryllium	**Mouse** no data on sex/strain or number	Single, metallic beryllium, Be-burdens of 0, 1.7, 2,6, 12 and 34 µg/mouse, followed up for 350 d	not suitable for setting an LC_{50}	Supporting study **Abstract only** Pneumonic symptoms, increased lung weights from 12 µg burden.	G.L. **Finch**, L.J. Reddick, M.D. Hoover,, K.J. Nikula, Toxicologist, Vol 13, No 1, March **1993**
Low Lung Burdens of Beryllium Metal, no guideline followed, non-GLP	Inhalation, observation period (Be-clearance 90 d, ^{85}Sr-FAP 60 d), sacrifices at 8, 16, 40 d	**Rat** no data on sex/strain or number	Be-burdens 0, 1.5, 2, 10, 50 µg co-exposure to ^{85}Sr-FAP	not suitable for setting an LC_{50}	Supporting study **Abstract only** Lung clearance reductions	G.L. **Finch**, P.J. Haley, M.D. Hoover, A.F. Eidson and R.G. Cuddihy; Toxicologist Vol 11, No 1, February **1991**
Lung Carcino-genicity from Inhaled Beryllium (Be) Metal, no guideline followed, non-GLP	nose-only aerosol inhalation, observation period at least 365 d	Rat Fischer 344/N total no. 936 no data on sex	Single, metallic beryllium, MMAD 1.4 µm, GSD 1.9 µm, **Be lung burdens: 0, 33, 84, 420 µg/rat**	not suitable for setting an LC_{50}	Supporting study **Abstract only** Within the first 3 weeks 33 % males and 64 % females of the high dose died of acute pneumonitis.	G.L. **Finch**, F.F. Hahn, W.C. Griffith, M.D. Hoover, W.W. Carlton, A.H. Rebar, J.A. Mewhinney, R.G. Cuddihy; Toxicologist, Vol. 14, No 1, p 264, March **1994**
Acute inhalation exposure, no guideline followed, non-GLP	nose-only aerosol inhalation, follow up 350 d	**Mouse** 11 w old C3H F	single (10.5-90 min), Be metal (no vehicle), MMAD 1.4 µm, GSD 1.8 µm, burden 0, 1.7, 2.6, 12, 34 µg/mouse	not suitable for setting an LC_{50}	Supporting study No mortalities or clinical signs.	G.L. **Finch**, K.J. Nikula, M.D. Hoover; Toxicological Sciences 42, 36-48 (**1998**)

5.2.1.3 Acute toxicity: dermal

This information is not available from the registration dossiers.

5.2.1.4 Acute toxicity: other routes

Table 16: Overview of experimental studies on acute toxicity after intratracheal exposure **according to registration dossier**

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels	Value LD_{50}/ LC_{50}	Remarks	Reference
Pulmonary Toxicity of	intratracheal instillation 1 ml	Monkey Cynomologus	1, 50, 150 µg Be metal:		Supporting study	P.J. Haley, K.F. Pavia, D.S.

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels	Value LD_{50}/ LC_{50}	Remarks	Reference
Beryllium Metal and Beryllium Oxyde, no guideline followed, non-GLP	in anaesthetized monkey via lung catheter in deep part of specified lobe	(Macaca fascicularis) no data on sex or number	MMAD 1.4 µm, GSD 1.4 µm, suspended and diluted in 1 ml of saline (vehicle: water)		focal intense, interstitial fibrosis, discrete immune granulomas	Swafford, D.R. DAvila, M.D. Hoover, G.L. Finch; Immunopharmaco-logy and Immuno-tocicology, 16(4), 627-644 (1994)
Beryllium Administered by Intratracheal Instillation, no guideline followed, non-GLP	intratracheal infusion; 0.1 ml, under anaesthesia via a transoral intratracheal catheter	Mouse 7w old C3H/HeJ 40 F 24 F (control)	2, 8 µg Be/mouse, Ground metallic beryllium in physiological saline (vehicle: water)		Supporting study no deaths Sacrifice 1 h, 1, 7, 14, 28 d	J.M. Benson, A.M. Holmes, E.B. Barr, K.J. Nikula, T.H. March; Inhalation Toxiclogy, 12:733-749, 2000

5.2.2 Human information

This information is not available from the registration dossiers.

5.2.3 Summary and discussion of acute toxicity

The data for acute toxicity of beryllium were obtained from animal testing. Only the test on Acute Oral Toxicity was carried out in accordance with EU Regulation (EC) No 440/2008 or current OECD guidelines for the testing of chemicals. No signs of toxicity were seen in the GLP compliant study following OECD TG 423 at the highest possible dose of 2000 mg/kg bw. No lethality is observed for administration of beryllium metal via the oral route. No studies on dermal toxicity are available. However, given the absence of an indication on oral toxicity (TL1, unpublished record 2009a) and the poor absorption by the intact skin (WHO 2001, ATSDR 2002) acute dermal toxicity is unlikely.

A series of non-standard toxicity studies is available for acute inhalation toxicity. By means of a weight of evidence approach the information provided in the registration dossiers is sufficient to conclude that beryllium is fatal if inhaled. In rats fatalities of 33 % of the males and 64 % of the females within 3 weeks at 420 µg beryllium lung burden have been reported (Finch 1994). In the key study 27 % of the male rats died 12-15 days post exposure from a lung burden of 625 µg resulting from 50 min exposure at 800 mg/m³ of beryllium dust (Haley 1990). By extrapolation to a 4-hour period applying Haber's Law an **acute toxicity estimate of 170 mg/m³** within the Category 2 range of 50-500 mg/m³ for dusts according to the classification criteria can be calculated.

Beryllium is classified as Acute Tox. 2*, H330: "Fatal if inhaled." according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 as a minimum classification and as T+, R26: "Very toxic by inhalation." according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008. The acute toxicity estimate of 170 mg/m³ supports this classification according to CLP Annex I, Table 3.1.1. Classification for acute toxicity by the oral or dermal route is not warranted under Regulation (EC) 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP) or under Directive 67/548/EEC for dangerous substances.

5.3 Irritation

5.3.1 Skin

Table 17: Overview of experimental studies on skin irritation according to registration dossier

Method/ Guideline	Species, Strain, Sex, No/group	Average score 24, 48, 72 h		Reversibility yes/no	Results	Remarks	Reference
		Erythema	Oedema				
Primary Skin Irritation according to OECD 404 (Acute Dermal Irritation / Corrosion), GLP	Rabbit, New Zealand White, 1 M, 2 F	0 No erythema or oedema at any of the observation time points.			not irritating slight grey staining of the treated skin in all animals 1 h after test item exposure	Key study Beryllium Metal Powder 99.4 %, 0.5 g, unchanged (no vehicle) shaved, 4 h, semi-occlusive	TL1, unpublished record 2009c

5.3.2 Eye

Table 18: Overview of experimental studies on eye irritation according to registration dossier

Method/ Guideline	Species, Strain, Sex, No/group	Average Score 24, 48, 72h		Reversibility	Results	Remarks	Reference
		Cornea, Iris, Chemosis	Redness Conjunctiva				
Primary Eye Irritation according to OECD 405 (Acute Eye Irritation / Corrosion), GLP	Rabbit, New Zealand White, 1 M, 2 F	Chemosis: 1 h: 1/1/1 mean 0 of max. score 4	1h: 2/1/1 mean 1 of max. score 3	completely reversible 7 d after treatment Slight initial swelling after 1 h, but resolved by 24 h.	not irritating	Key study Beryllium Metal Powder 99.4 %, 0.1 g, unchanged (no vehicle), no washing	TL1, unpublished record 2009d

5.3.3 Respiratory tract

No specific studies are available from the registration dossiers.

5.3.4 Summary and discussion of irritation

The evidence for skin and eye irritation of beryllium was obtained from animal testing. Two GLP compliant studies following OECD TG 404 and 405, respectively, were submitted for beryllium. No signs of irritation were noted in the skin irritation study with beryllium metal powder (TL1, unpublished record, 2009b). Slight irritation of rabbit eyes, which was completely resolved after 7 days, was reported in the eye irritation study with beryllium metal powder (TL1, unpublished record, 2009d).

Single inhalation human exposure to levels above 100 µg Be/m³ can cause acute chemical pneumonitis with symptoms such as cough, pulmonary oedema, shortness of breath (dyspnea), and inflammation. This acute toxicity was most commonly reported after inhalation of soluble beryllium

salts but beryllium metal has been associated with acute beryllium disease as well. Most of the persons affected recovered within a few weeks (MAK 2003, Welch 2012).

Beryllium is classified as STOT SE 3, H335: "May cause respiratory irritation." according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 and as Xi, R37: "Irritating respiratory system." according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008. The available data indicate that this classification is justified. Classification as skin or eye irritant is not warranted under Regulation (EC) 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP) or under Directive 67/548/EEC for dangerous substances.

5.4 Corrosivity

No signs of corrosion were seen in the skin/eye irritation tests.

5.5 Sensitisation

5.5.1 Skin

Table 19: Overview of experimental studies on skin sensitisation according to registration dossier

Method/ Guideline	Species, Strain, Sex, No/group	No sensitised/ total no of animals	Results	Remarks	Reference
Contact Hypersensitivity Maximization-Test according to OECD Guideline 406 (Skin Sensitisation), GLP	Guinea Pig, Albino Dunkin-Hartley, 10 M	0/10	Not sensitising dermal induction: very slight skin reactions	Key study Beryllium Metal Powder, 99.4 %, c = 50 %, vehicle: PEG 300, shaved, induction: 1 intradermal, c = 50 %, 1 epidermal, c = 50 %, challenge: epicutaneous, occlusive	TL1, unpublished record 2009e
Patch Testing with Beryllium Alloy Samples according to OECD Guideline 406 (Skin Sensitisation), non-GLP	Guinea Pig, Dunkin-Hartley, 20 F	$BeSO_4$: 10-11/20, alloys: 6-12/20, Be metal: 12/20	Sensitisation with $BeSO_4$ test evaluates sensitising properties of $BeSO_4$, not beryllium metal or its alloys.	Supporting study no positive control intradermal and epicutaneous induction with $BeSO_4$ challenge: epicutaneous, occlusive 3% Beryllium Metal Powder vehicle: saline; water	Zissu D, Binet S, Cavelier C, Contact Dermatitis 34:196-200 (1996)
Patch Test: Cutaneous Hypersensitivity A Study of Thirteen Cases no guideline available; non-GLP	Human M/F pre-sensitized workers from Be industry control persons never exposed to Be	3/11 in test group slightly positive reactions controls: no reactions to powdered Be metal	no conclusion can be drawn due to the presence of BeF_2 in the test item	Supporting study powdered metallic Be / Be metal discs, BeF_2 (0.025-0.2%), no vehicle induction: epicutaneous challenge: epicutaneous, degree of closure not stated moistened unchanged substance	Curtis GH, A.M.A. Archives of Dermatology and Syphilology 64:470-482 (1951)

5.5.2 Respiratory system

Table 20: Calculated epidemiological data on beryllium sensitization (BeS) according to original publications (not in registration dossiers)

Method/ Guideline	Route of exposure Duration	Species, Sex, No	Dose levels µg/m³	Results Main effects/ Target organs	Remarks	Reference
Population-based **Cross-sectional** health survey	**occupational exposure** at a copper–beryllium alloy strip and wire finishing facility	Human, 153 workers	median concentration 0.03 97 % < 0.2 no sample > 2	Prevalence: **BeS** 7% (10/153), CBD 4% (6/153) in area > 0.2 µg/m³ Be	Key study small number of employees limited statistical power	C. R. Schuler, M. S. Kent, D. C. Deubner, M. T. Berakis, M., McCawley, P.K. Henneberger, M. D. Rossman, K. Kreiss, Am. J. Ind. Med. 47, 195–205 (2005)
Exposure response analysis for beryllium sensitization and CBD	**occupational exposure** in a beryllium metal-machining plant	Human, 27 workers with BeS or sub-clinical CBD	100 analytical results: 50 samples < 0.2, median concentration 0.13 LTWA > 0.05	**BeS**: 9 workers CBD: 18 workers since 1995 LTWA < 0.2, but > 0.05 µg/m³	Key study comparison population not included	A. K. Madl, K. Unice, J. L. Brown, M. E. Kolanz, and M. S., Kent, J. Occup. Environ. Hyg. 4, 448–466 (2007)
Exposure response relations for beryllium sensitization (BeS) and CBD	**occupational exposure** among short-term workers (≤ 6 years tenure in 1999)	Human, 264 workers: 26/264 cases of BeS 6/26 cases of CBD	Lowest EC (average exp.) BeS: 0.09 (total) 0.04 (respirable) CBD: 0.20 (total) 0.17 (respir.)	**BeS** was associated with average and highest job exposures, CBD with cumulative exposure	Key study limited power to detect an effect for CBD, due to truncated period of exposure	Schuler, C.R.; Virji, M.A.; Deubner, D.C.; Stanton, M.L.; Stefaniak, A.B.; Day, G.A.; Park, J.Y.; Kent, M.S.; Sparks, R.; Kreiss, K. (2012) Scandinavian Journal of Work, Environment and Health, 38, 270-281
Case control study	**occupational exposure** in the nuclear weapons industry	Human, 181 workers: 35 cases of **BeS** 19 cases of CBD 127 controls	LTWA mean (median) concentration BeS: 0.12 (0.02) CBD: 0.32 (0.11) control: 0.13 (0.03)	susceptibility affected by genetic host factor, a glutamic acid residue at position 69 of the HLA-DPβ chain	Supporting study confounder - healthy worker effect - exposure misclassification	van Dyke, M.V.; Martyny, J.W.; Mroz, M.M.; Silveira, L.J.; Strand, M.; Cragle, D.L.; Tankersley, W.G.; Wells, S.M.; Newman, L.S.; Maier, L.A. (2011a) Occupational and Environmental Medicine, 68, 842-848
Case control study	**occupational exposure** in nuclear workers	Human, 386 workers: 70 BeS, 61 CBD, and 255 control subjects	LTWA mean (median) concentration **BeS**: 0.25 (0.01) CBD: 0.64 (0.07) control: 0.15 (0.03)	glutamic acid at position 69 (E69) and beryllium exposure both contribute to the odds of CBD	Supporting study - unconstrained regression model - misclassification	van Dyke, M.V.; Martyny, J.W.; Mroz, M.M.; Silveira, L.J.; Strand, M.; Fingerlin, T.E.; Sato, H.; Newman, L.S.; Maier, L.A. (2011b) American Journal of Respiratory and Critical Care Medicine, 183, 1680-1688

5.5.3 Summary and discussion on sensitisation

The data for sensitisation of beryllium were obtained from animal testing and human data. One GLP compliant study following OECD TG 406 was submitted for beryllium. No signs of skin sensitisation were observed in the guinea pig maximisation test with beryllium metal powder (TL1,

unpublished record 2009e), but it is generally thought that beryllium as a free metal does not significantly penetrate the intact skin (Welch 2012 and chapter 5.1.3). Delayed hypersensitivity reactions developed in a guinea pig maximisation test according to OECD TG 406 with metallic beryllium after intradermal sensitisation with beryllium sulphate (Zissu 1996).

The reactions of occupationally pre-sensitized workers to powdered beryllium metal cannot reliably be attributed to the beryllium metal due to impurities of beryllium fluoride in the test item (Curtis 1951). Granulomatous lesions of the skin may occur at the site of subcutaneous implantation of beryllium, which occurs when beryllium contaminates a wound or a beryllium splinter penetrates the skin. Healing rarely occurs until the contaminated skin lesions are excised (Welch 2012). Biopsied skin granulomas from beryllium workers had the same mononuclear infiltrates as detected in the lungs (ATSDR 2002).

The granulomas formed as a result of an immune reaction to beryllium particles in the lung following the inhalation of beryllium by humans, are distinct from other allergic reactions of the respiratory system (EPA 1998, WHO 2001, MAK 2002). The initial response is of an inflammatory nature caused by beryllium-induced phagocytosis and the subsequent release of lysosomal enzymes. The release of such enzymes is thought to be responsible for the damaging effects observed with respect to lung architecture. Unlike other particles (e.g., alpha quartz), beryllium is unusual in that it does not cause an antibody reaction (type I hypersensitivity), but rather a cell-mediated (type IV hypersensitivity), antigen-driven immune response (WHO 2001, Welch 2012). Because the beryllium ion is too small to be antigenic per se, it may function as a hapten, binding with a large carrier molecule (e.g., protein) to form an antigen. Once the antigen is created by the macrophage, it is presented to helper T-cells, which form sensitized T-cells. Once a population of sensitized T-cells is created, these cells transform and actively secrete lymphokines (WHO 2001).

Specific respiratory hypersensitivity of type I, normally seen as asthma, rhinitis/conjunctivitis and alveolitis, is not expected in case of the delayed type IV hypersensitivity. Chronic beryllium disease (CBD) begins as a sensitizing cell-mediated response to beryllium antigen and progresses to granulomatous lung disease (ATSDR 2002). For chronic beryllium disease it is not unusual to begin slowly after a practically (clinically) symptom-free latency period which can last up to 20 years. The course of the disease (at the tissue level) is often progressive, even after cessation of beryllium exposure (MAK 2003). Progression of the chronic disease is often slow (Welch 2012).

A key aspect of the identification of CBD is the demonstration of beryllium sensitization in a beryllium lymphocyte proliferation test (BeLPT). The basis of the test is that beryllium-reactive lymphocytes proliferate when presented with the beryllium antigen (presumably Be binding with a large carrier molecule (haptene)). The test involves an *in vitro* challenge of lymphocytes either from bronchoalveolar lavage fluid or from peripheral blood of exposed people with beryllium salts. The observation of beryllium-specific T lymphocyte proliferation indicates beryllium sensitization (WHO 2001, Welch 2012).

Beryllium is already classified as Skin Sens. 1, H317: “May cause an allergic skin reaction.” according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 and as Xi, R43: “May cause sensitization by skin contact.” according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008.

Based on the available human data, beryllium appears to fulfil the criteria for classification for respiratory sensitisation category 1 as Resp. Sens. 1, H334: “May cause allergy or asthma

symptoms or breathing difficulties if inhaled." according to Regulation (EC) No. 1272/2008 and Xn, R42: "May cause sensitisation by inhalation." according to Directive 67/548/EEC.

5.6 Repeated dose toxicity

5.6.1 Non-human information

5.6.1.1 Repeated dose toxicity: oral

This information is not available from the registration dossiers.

5.6.1.2 Repeated dose toxicity: inhalation

Table 21: Overview of experimental studies on repeated dose toxicity after **inhalation exposure** according to registration dossier

Method/ Guideline	**Route of exposure Duration**	**Species, Strain, Sex, No /group**	**Dose levels mg/m³**	**NO(A)EC mg/m³**	**LO(A)EC mg/m³**	**Results Main effects/ Target organs**	**Remarks**	**Reference**
Lympho-cytic Responses Induced by Inhaled Beryllium Metal, no guideline followed, non-GLP	nose-only aerosol **inhala-tion one single** (90 min), **sacrificed after 6 months**	Mouse 6-8 w old A/J, C3H/He J 36 F of each strain	**1030** 60 µg Be/ mouse initial Be-burden after 7 d	no	1030	interstitial compact aggregates of lymphocytes in lung, chronic granulo-matous pneumonia, minimal to mild interstitial fibrosis	Supportin g study **Refe-renced here due to long ob-servation period.**	K.J. Nikula, D.S. Swafford, M.D. Hoover, M.D. Tohulka, G.L. Finch, Toxicologic Pathology 25, (1), 2 – 12, 1997
Dose-Response Relation-ships between Inhaled Be Metal and Lung Toxicity, no guideline followed, non-GLP	nose-only aerosol **inhala-tion one single** (10.5-90 min), **follow up 350 d**	**Mouse** 11 w old C3H F	0, 1.7, 2.6, 12, 34 µg/ mouse	no	no	> 12 µg: ↑ lung weight, granulo-matous pneumonia, lymphocytic interstitial aggregates, mononuclear infiltrates	Supportin g study **Refe-renced here due to long ob-servation period.**	G.L. **Finch**, K.J. Nikula, M.D. Hoover; Toxicologic al Sciences 42, 36-48 (**1998**)
Toxicity of Inhaled Beryllium Metal, no guideline followed, non-GLP	nose-only aerosol **inhala-tion one single** (50 min), **sacrifices after** 3, 7, 10, 14, 31, 59, 115,	Rat 11-13 w old 74 M divided into groups of 6 per sacrifice time	**800** 625 µg Be metal/ rat	no	800	↑ lung weight, pneumonitis fibrosis, inflammation alveolar macrophage and epithelial hyperplasia,	Supportin g study **Refe-renced here due to long ob-servation period.**	P.J. Haley, G.L. Finch, M.D. Hoover, R.G. Cuddihy; Funda-mental and applied Toxicology

Method/ Guideline	Route of exposure Duration	Species, Strain, Sex, No /group	Dose levels mg/m³	NO(A)EC mg/m³	LO(A)EC mg/m³	Results Main effects/ Target organs	Remarks	Reference
	171 d	point				mortality		15, 767-778, (1990)
Reduced Lung Clearance induced by Low Lung Burdens of Beryllium Metal, no guideline followed, non-GLP	**Inhala-tion obser-vation period** (for Be-clearance) **90 d**, interim sacrifices at 8, 16, 40 d	**Rat**	0, 1.5, 2, 10, 50 µg/ rat	no	no	Lung clearance reductions	Supportin g study **Abstract only**	G.L. **Finch**, P.J. Haley, M.D. Hoover, A.F. Eidson and R.G. Cuddihy; Toxicolo-gist Vol 11, No 1, February **1991**

5.6.1.3 Repeated dose toxicity: dermal

This information is not available from the registration dossiers.

5.6.1.4 Repeated dose toxicity: other routes

This information is not available from the registration dossiers.

5.6.2 Human information

Table 22: Calculated supporting epidemiological data according to the registration dossier

Method/ Guideline	Route of exposure Duration	Species, Sex, No	Dose levels DWA µg/m³	Results Main effects/ Target organs	Remarks	Reference
Estimating Historical Exposures of Workers in a Beryllium Manu-facturing Plant	occupational exposure in Be facility at Reading (PA), USA (extrapolated 1935), 1947 – 1992 estimated by calculation	Human, 7347 analytical results 325 different jobs in 23 departments	Beryllium (ore, BeOH, BeF, BeO, BeCu) (fume or aerosol-dust) Be dust: 0.03 – 5.0	Exposures were variable from job to job, but regularly declining by period of observation (1953-1960, 1961-1970, 1971-1980, 1981-1992) at statistically signific. levels. The cumulative exposure correlates with tenure (r = 0.84), and average and max. exposure correlate (r = 0.90).	Supporting study estimates for early period 1935-1970 based on low number of samples	Sanderson T.W., Peterson M.R. and Ward E.M., Am. J. Ind. Med. 39:145-157, 2001

Table 23: Calculated epidemiological data on chronic beryllium disease according to original publications (not in the registration dossier)

Method/ Guideline	Route of exposure Duration	Species, Sex, No	Dose levels µg/m³	Results Main effects/ Target organs	Remarks	Reference
Popula-tion-based	**occupational exposure** at a	Human, 153	median concentration	Prevalence: BeS 7%	Key study small	C. R. Schuler, M. S. Kent, D. C. Deubner, M. T.

Method/ Guideline	Route of exposure Duration	Species, Sex, No	Dose levels µg/m³	Results Main effects/ Target organs	Remarks	Reference
Cross-sectional health survey	copper–beryllium alloy strip and wire finishing facility	workers	0.03 97 % < 0.2 no sample > 2	(10/153), CBD 4% (6/153) in area > 0.2 µg/m³ Be	number of employees limited statistical power	Berakis, M., McCawley, P.K. Henneberger, M. D. Rossman, K. Kreiss, Am. J. Ind. Med. 47, 195–205 (2005)
Exposure response analysis for beryllium sensitiza-tion and CBD	**occupational exposure** in a beryllium metal-machining plant	Human, 27 workers with BeS or sub-clinical CBD	100 analytical results: 50 samples < 0.2, median concentration 0.13 LTWA > 0.05	BeS: 9 workers CBD: 18 workers since 1995 LTWA < 0.2, but > 0.05 µg/m³	Key study comparison population not included	A. K. Madl, K. Unice, J. L. Brown, M. E. Kolanz, and M. S., Kent, J. Occup. Environ. Hyg. 4, 448–466 (2007)
Exposure response relations for beryllium sensitiza-tion (BeS) and CBD	**occupational exposure** among short-term workers (≤ 6 years tenure in 1999)	Human, 264 workers: 26/264 cases of BeS 6/26 cases of CBD	Lowest EC (average exp.) BeS: 0.09 (total) 0.04 (respirable) CBD: 0.20 (total) 0.17 (respir.)	BeS was associated with average and highest job exposures, CBD with cumulative exposure	Key study limited power to detect an effect for CBD, due to truncated period of exposure	Schuler, C.R.; Virji, M.A.; Deubner, D.C.; Stanton, M.L.; Stefaniak, A.B.; Day, G.A.; Park, J.Y.; Kent, M.S.; Sparks, R.; Kreiss, K. (2012) Scandinavian Journal of Work, Environment and Health, 38, 270-281
Case control study	**occupational exposure** in the nuclear weapons industry	Human, 181 workers: 35 cases of BeS 19 cases of CBD 127 controls	LTWA mean (median) concentration BeS: 0.12 (0.02) CBD: 0.32 (0.11) control: 0.13 (0.03)	susceptibility affected by genetic host factor, a glutamic acid residue at position 69 of the HLA-DPβ chain	Supporting study - confounder - healthy worker effect - exposure misclassi-fication	van Dyke, M.V.; Martyny, J.W.; Mroz, M.M.; Silveira, L.J.; Strand, M.; Cragle, D.L.; Tankersley, W.G.; Wells, S.M.; Newman, L.S.; Maier, L.A. (2011a) Occupational and Environmental Medicine, 68, 842-848
Case control study	**occupational exposure** in nuclear workers	Human, 386 workers: 70 BeS, 61 CBD, and 255 control subjects	LTWA mean (median) concentration BeS: 0.25 (0.01) CBD: 0.64 (0.07) control: 0.15 (0.03)	glutamic acid at position 69 (E69) and beryllium exposure both contribute to the odds of CBD	Supporting study - uncon-strained regression model - mis-classifica-tion	van Dyke, M.V.; Martyny, J.W.; Mroz, M.M.; Silveira, L.J.; Strand, M.; Fingerlin, T.E.; Sato, H.; Newman, L.S.; Maier, L.A. (2011b) American Journal of Respiratory and Critical Care Medicine, 183, 1680-1688

5.6.3 Summary and discussion of repeated dose toxicity

The evidence on target organ toxicity through repeated exposure to beryllium was obtained from animal testing and epidemiological data. No repeated dose animal studies on inhalation exposure to beryllium metal exist. Instead the single dose studies in Table 21were assessed with regard to the delayed adverse effects on the respiratory tract after a recovery period of several days to one year. None of the animal tests was carried out in accordance with EU Regulation (EC) No 440/2008 or current OECD guidelines for the testing of chemicals. However, by means of a weight of evidence approach the information provided in the registration dossiers is sufficient to conclude that beryllium metal produces significant toxicity following exposure through inhalation. Due to the persistence of beryllium in the lung following a single inhalation exposure, long term exposure through persistent lung burden following the acute exposure event is evident.

Repeated chronic exposure is assumed to result in persistent lung lesions that are expected to be more severe, more extended compared to the chronic lesions following single exposures and which may occur in a shorter latency period.

Human data demonstrated that the incidence of chronic beryllium disease (CBD) can reliably be attributed to prolonged occupational exposure to any form of beryllium (ATSDR 2002, WHO 2001, EPA 1998, MAK 2003, Welch 2012). Overall, assumption of an **LOAEC for chronic beryllium disease of 0.2 µg/m³** as time weighted average derived from human exposure seems to be justified due to consistency of the effect levels throughout the studies in Table 23.

Based on the evidence from single dose animal studies it must be expected that a single inhalation exposure may also have the potential to cause CBD in humans.

Beryllium is classified as STOT RE 1, H372: "Causes damage to organs through prolonged or repeated exposure." According to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 and as T, R48/23: "Toxic: danger of serious damage to health by prolonged exposure through inhalation." according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008.

5.7 Mutagenicity

5.7.1 Non-human information

5.7.1.1 In vitro data

Table 24: Overview of experimental in vitro genotoxicity studies **according to registration dossier**

Method/ Guideline	Test system (Organism, strain)	Concentrations tested (give range)	Results		Remarks give information on cytotoxicity and other	Reference
			+ S9	– S9		
UDS test according to OECD TG 482 (Genetic Toxicology: DNA Damage and Repair, Unscheduled DNA Synthesis in Mammalian Cells In Vitro), GLP	Primary Hepatocytes of Male Wistar Rats	0, 50 % or 100 %[a] of Be metal extract in 2 ml cell culture medium (0.409 to 0.653 µg/l) with metabolic activation by cell line, positive control: 2-acetyl-aminofluorene	**negative**		Key study no cytotoxicity, the repair of pre-existing DNA damage induced by the positive control is decreased with 100 % Be extract	TL2, unpublished record 2010
Gene Mutation Assay in Chinese Hamster V79 Cells to OECD TG 476 (In vitro Mammalian Cell Gene Mutation Test), GLP	Chinese hamster lung fibroblasts (V79) HPRT locus	6.3, 12.5, 25, 50, 75, 100 %[b] (95 % with S9 mix) Be metal powder extract in MEM (3.120, 4.477, 14.02 µg/L)	**negative**	**negative**	Key study no cytotoxicity, but tested up to precipitating concentrations	TL2, unpublished record 2009a
Cell Transformation Assay (SHE Assay) according to EU Method B.21 (In Vitro Mammalian	Syrian hamster embryonic cells (SHE cells)	25 % to 100 %[c] of Be metal powder extract in cell culture medium with metabolic	**positive** (increase in number of transformed SHE colonies)		Key study no cytotoxicity, but tested up to precipitating concentrations	TL2, unpublished record 2009b

Method/ Guideline	Test system (Organism, strain)	Concentrations tested (give range)	Results		Remarks give information on cytotoxicity and other	Reference
			+ S9	– S9		
Cell Transformation Test), GLP		activation by SHE cells				
Chromosome Aberration Test according to OECD TG 473 (In vitro Mammalian Chromosome Aberration Test), GLP	Human Lympho-cytes from 2 healthy female donors	3.1, 6.3, 12.5, 25, 37.5, 50, 75, 100 %[d] (95 % with S9 mix) Be metal powder extract in cell culture medium (3.258, 20.27 ug/ml with fetal calf serum, 20.83, 4.434 ug/ml without fetal calf serum)	**nega-tive**	**nega-tive**	Key study no cytotoxicity, but tested up to precipitating concentrations	TL2, unpublished record 2009c
S. typhimurium and E. Coli Reverse Mutation Assay according to OECD TG 471 (Bacterial Reverse Mutation Assay), GLP	S. typhi-murium TA 1535, TA 1537, TA 98, TA 100 E. Coli WP2 uvrA	2.5, 10, 20, 40, 60, 80, 100 %[e] Be metal powder extract in 0.9 % saline (72 h, 37 °C)	**nega-tive**	**nega-tive**	Key study no cytotoxicity, but tested up to limit concentrations	TL2, unpublished record 2009d

Information available from Strupp 2011:

a) Analytical concentration in the 100% extract: 61 µg beryllium per liter = 6.8 µmol l^{-1} (not determined in the main experiment, but in a range-finding experiment).

b) Analytical concentration in the 100% extract: 4 µg beryllium per liter = 0.4 µmol l^{-1}.

c) Analytical concentration in the 100% extract: 22.95 µg beryllium per liter = 2.5 µmol l^{-1}.

d) Analytical concentration in the 100% extract: 21 µg beryllium per liter = 2.3 µmol l^{-1}.

e) Analytical concentration in the 100% extract: 734 µg beryllium per liter = 81 µmol l^{-1}.

5.7.1.2 In vivo data

This information is not available from the registration dossiers.

5.7.2 Human information

This information is not available from the registration dossiers.

5.7.3 Summary and discussion of mutagenicity

The data on the genotoxic potential of beryllium were obtained from in vitro testing. All of the five tests were carried out in accordance with EU Regulation (EC) No 440/2008 or current OECD guidelines for the testing of chemicals. Beryllium has the ability to induce morphological transformations in cultured mammalian cells (TL2, unpublished record 2009b) and exerts effects on the repair of pre-existing DNA damage (TL2, unpublished record 2010). These results are not supported by results obtained in tests for mutagenicity which are generally of higher significance (ECHA 2013b). Beryllium metal powder shows no genotoxicity regarding DNA damage, cytogenicity and gene mutation in Ames, HPRT, chromosome aberration or UDS test. Bacterial mutagenesis assays are frequently negative due to limited capacity for uptake of metal ions (ECHA 2013b). In mammalian cells secondary mechanisms instead of direct genotoxicity seem to be the processes underlying beryllium-induced indirect effects related to genotoxicity (IARC 2012). By

means of a weight of evidence approach it can be concluded from the available *in vitro* data that beryllium metal is unlikely to be able to induce heritable mutations in the germ cells of humans.

Data available for germ cell mutagenicity are conclusive but not sufficient for classification according to Regulation (EC) No. 1272/2008 and Directive 67/548/EEC.

5.8 Carcinogenicity

5.8.1 Non-human information

5.8.1.1 Carcinogenicity: oral

This information is not available from the registration dossiers.

5.8.1.2 Carcinogenicity: inhalation

Table 25: Overview of experimental studies on carcinogenicity **according to registration dossier**

Title/Method/ Guideline	**Route of exposure, duration**	**Species, Strain, Sex, No/ group**	**Dose levels, if available**	**Results Main effects/ Target organs/ Tumours**	**Remarks**	**Reference**
Blastomogenic Activities of various Beryllium compounds no guideline followed, non-GLP	**single** and chronic inhalation of **metallic beryllium**	Rat albino mongrel	Dose-effect depen-dence is esta-blished	lung cancer induced (no more details available)	Supporting study Publication in Russian, **short summary only**	Litvinov N.N., Kazenashev V.F., Bugryshev P.F., 1983, Eksp. Onkol., 5 (4): 23-26
Comparative Pulmonary Carcinogenicity of Beryllium no guideline followed, non-GLP	**Single**, nose-only inhalation of **Be metal** sacrifices 11 to 22 months	Mouse 6-8 w old A/J, C3H/HeJ 206 each strain controls, 50 each strain	Be lung burden: A/J 47µg (3.0 µg/g bw) C3H/HeJ 63 µg (3.4 µg/g bw)	Both strains: ↓ survival A/J: ↑ incidence of lung neoplasia (not typified) A/J more sensitive	Supporting study Be metal Clearance half-times A/J: 97 d C3H/HeJ: 108 d	Nikula K.J., Finch G.L. Hoover M.D. Belinsky S.A.; **Abstract**s of the 34th Annual Meeting (SOT) Vol 15, No 1, Abstr. 252, March 1995
Alterations in the K-ras and p53 Genes in Rat lung tumours no guideline followed, non-GLP	Induced pulmonary adeno-carcinomas, squamous cell carcinomas by **beryllium metal**	Rat	**beryllium metal**	No conclusive evidence of involvement of K-ras (activa-tion low inci-dence of 2/24) or p53 genes in Be lung car-cinogenicity	Supporting study, Mechanistic study with **little experimen-tal detail**	Belinsky S.A., Swafford D.S. , Finch G.L., Mitchell C.E., Kelly G., Hahn F.F., Anderson M.W. Nikula K.J., Environ Health Perspect 105 (Suppl 4): 901-906 (1997)
Lung Carcinogenicity from Inhaled Beryllium (Be) Metal, no guideline followed, non-GLP	**Single**, nose-only aerosol inhalation observation period at least 365 d	Rat Fischer 344/N total no. 936	lung burdens 0, 33, 84, 420 µg/rat	incidence of lung tumours: 2, 62, 89, 89 % (M) 0, 83, 96, 100 % (F) adeno-, squa-mous cell carcinomas	Supporting study **Abstract only metallic beryllium**, MMAD 1.4 µm, GSD 1.9	**Finch** G.L, F.F. Hahn, W.C. Griffith, M.D. Hoover, W.W. Carlton, A.H. Rebar, J.A. Mewhinney, R.G. Cuddihy; Toxicologist, Vol. 14, No 1, p 264, March 1994
Comparative	**Single**, nose-	**Rat**	lung	Substantial	Supporting	Finch G.L., Hoover

Title/Method/ Guideline	**Route of exposure, duration**	**Species, Strain, Sex, No/ group**	**Dose levels, if available**	**Results Main effects/ Target organs/ Tumours**	**Remarks**	**Reference**
Pulmonary Responses to Inhaled Be Metal in Rats versus Mice, no guideline followed, non-GLP	only inhalation of Be metal, lifespan observation period	Fischer 344/N **Mouse** A/J, C3H/HeJ	burdens: 0.2 – 450 µg/g lung in **rats** 1 – 300 µg/g lung in **mice**	neoplastic response at 17 µg Be/g **rat** lung, minimal at 300 µg Be/g **A/J** lung	study **Abstract only** type, location, incidence of neoplasia not reported	M.D., Nikula K.J., Belinsky S.A., Haley P.J. Hahn F.F., Abstracts of the VII International Congress of Toxicology, 7(1): 20-P-11, (July 1995)
Carcinogenic Responses to Inhaled Metallic Beryllium, equivalent or similar to other guideline: US NTP program, non-GLP	**single** nose-only aerosol inhalation 112 min, 3 daily exposures of 139 mins, lifespan observation	Mouse hetero-zygous TSG-p53 knockout mice (+/-) and (+/+) wildtype littermates (15 M/F)	Initial lung burdens: 12 +/- 4 µg, 54 +/-6 µg	Pulmonary neoplasms (mostly squamous cell carcinomas) in 4/28 (14 %) p53+/- mice 19 months post exposure at high dose	weight of evidence **Metallic Beryllium** MMAD 1.4µm	Finch G.L., March T.H., Hahn F.F., Barr E.B., Belinsky S.A., Hoover M.D. Lechner J.F. Nikula K. J. Hobbs C.H., Toxicologic Pathology, 26(4):484-491 (1998)
Dose-Response Relationships, no guideline followed, non-GLP	**single** nose-only aerosol inhalation (10.5-90 min), follow up 350 d	**Mouse** 11 w old C3H 34 F	0, 1.7, 2.6, 12, 34 µg Be/ mouse	No tumours reported (observation time maybe to short)	Weight of evidence Be metal Reference due to long observation period	G.L. Finch, K.J. Nikula, M.D. Hoover; Toxicological Sciences 42, 36-48 (1998)
Carcinogenicity of Beryllium Hydroxide and Alloys, no guideline followed, non-GLP	**Single Intra-tracheal** in 0.4 ml saline followed by 0.2 ml saline, up to 19 months	**Rat** Wistar 35 F	0.5, 2.5 mg Be metal (100 %)	Lung neo-plasms (adeno-carcinomas, adenomas): 0.5 mg 67 % 2.5 mg 100 % 16-19 months	Weight of evidence considered to have some relevance for humans	Groth D.H., Kommineni C., Mackay G.R., Environmental Research 21, 63-84 (1980)
Neoplasia Experimentally Induced by Beryllium Compounds no guideline followed, non-GLP	different routes Variable durations 2 – 40 months, variable post exposure period	mouse, rat, guinea pig, rabbit, dog, pig, monkey no data on sex/strain or number		Adenocarci-noma, epider-moid carcino-ma, mixed carcinoma, pleural meso-thelioma, alveolar cell carcinoma	Supporting study **Beryllium Com-pounds** percentage of tumour types not given	Schepers G.W., Progr. Exp. Tumor Res. 2:203-244 (1961)
Analysis of **K-ras, p53 and c-raf-1** mutations in rat lung tumours no guideline followed, non-GLP	**Single**, nose-only aerosol inhalation of Be metal 8-48 min, 14 months post exposure period	Rat Fischer 344/N 30 M 30 F	**410** (30 min) **500** (8 min) **830** (48 min) **980** (39 min) **mg/m³**	64 % lung tumour incidence, adenocarcino-mas, cuboidal or columnar cells growing over fine pa-pillary stroma.	Supporting study gene dys-functions associated with human lung cancer not involved	Nickell-Brady C., Hahn F.F., Finch G.L., Belinsky S.A., Carconogenesis 15 (2):257-262 (1994)
Animal models of Beryllium-induced Lung Disease no guideline	**Single** inhalation rats surviving <1 year	**Rat** Fischer 344/N M/F	Mean lung burden of 17 µg Be metal/g **rat** lung	50 % benign and/or malignant lung tumours	Supporting study **overview article**	**Finch** G.L., Hoover M.D., Fletcher F.H., Nikula K.J. Belinsky S.A. Haley P.J. Griffit W.C.,

Title/Method/ Guideline	Route of exposure, duration	Species, Strain, Sex, No/ group	Dose levels, if available	Results Main effects/ Target organs/ Tumours	Remarks	Reference
followed, non-GLP		**Mouse** A/J, C3H/HeJ	~ 60µg (~ 300µg Be/g **A/J** lung)	↑ lung tumour incidence and multiplicity in strain A/J mice		Environ Health Perspect 104 (Suppl 5) 973-979 (**1996**)

5.8.1.3 Carcinogenicity: dermal

This information is not available from the registration dossiers.

5.8.2 Human information

Table 26: Overview of data on carcinogenicity according to registration dossier

Method/ Guideline	Route of exposure, duration	Species, Sex, No	Results Main effects/ Target organs/ Tumours	Remarks	Reference
cohort study (retro-spective)	Beryllium Case Registry July 1952 – December 1975	Human, white, ≥ 15 a 421 M	Excess lung cancer risk in persons with previous acute beryllium disease	Supporting study Small number of cases short follow up times for workers enrolling later in the Registry	Infante P.F., J.K. Wagoner, N.L. Sprince, Environmental Research 21, 35-43 (1980)
cohort mortality study (retro-spective)	working in beryllium plants 1937 – 1948, follow up to 1966	Human, white, 15 – 65 a 3685 M	↑ (lung) tumour incidence, no conclusion of Be effects can be drawn due to limitations	Supporting study lack of Standard Mortality Ratios and consideration of confounding factors No exposure data	Mancuso T.F and A.A. El Attar, Journal of Occupational Medicine 11, (8), 422 – 434 (1969)
cohort mortality study (retro-spective)	Beryllium Case Registry July 1952 – 1988	Human, ≥ 15 a 689 M/F	↑ risk for pneumoconiosis* and lung cancer	Supporting study exposure not further specified except for having worked in beryllium industry	Steenland K. and Ward E., J Natl Cancer Inst 83, 1380-1385, 1991
cohort study (retro-spective)	Facility workers of 7 US Be plants 1940 – 1969, follow up to 1988	Human 16 – 65 a 9225 M	causal association of lung cancer and beryllium exposure not compatible	Supporting study weakness of the exposure side: no measurements, only crude estimates	Levy P.S., Roth H.D., Hwang P.M.T. Powers T.E., Inhalation Toxicology, 14: 1003-1015, 2002
cohort-nested case-control study	Workplace exposure of Be workers 1940 – 1970, follow up to 1988	Human, 3569 M/F	association between lung cancer and Be exposure not valid	Supporting study Partial re-assessment of a very complex study design (Sanderson 2001)	Deubner D.C., Roth H.D. Levy P.H, J Occup Environ Med. 2007; 49: 953-959
case control study (retro-spective)	Workplace exposure of Be workers 1940 – 1969, follow up to 1988	Human, 15 – 65 a 3569 M 142 cases 710 controls	association between (high) exposure to Be products and lung cancer challenged	Supporting study Re-examination of Findings From a Nested Case-Control Study (Ward 1992)	Levy P.S. Roth H.D. Deubner D.C. J Occup Environ Med. 2007; 49:96-101
Nested case	Workplace exposure of Be	Human, 15 – 65 a	↑ lung cancer among workers	Supporting study Significant findings	Sanderson W. T., Ward E.M., Steenland K. and

Method/ Guideline	Route of exposure, duration	Species, Sex, No	Results Main effects/ Target organs/ Tumours	Remarks	Reference
control study (retro-spective)	workers 1940 – 1969, follow up to 1988 and follow up from 1988 to 1992	3569 M 142 cases 710 controls	with higher lagged beryllium exposures	mainly based on log transformed exposure data and artificial exposure lagging over 10/20 a (Ward 1992)	Petersen M.R., Am. J. Ind. Med. 39:133-144 2001
cohort study (retro-spective)	working in beryllium plants Employment 1937-48, follow up to 1967	Human, white, 15 – 65 a 3685 M	Prior chemical respiratory illness seems to increase the subsequent development of lung cancer	Supporting study lack of Standard Mortality Ratios and consideration of confounding factors No exposure data	Mancuso T.F., Environmental Research 3, 251-275 (1970)
cohort study (retro-spective)	working in beryllium plants January 1942 – September 1968 employment, follow up to 1976	Human, white, ≥ 15 a 3055 M	statistically significant increase in neoplastic and non-neoplastic lung disease and heart disease	Supporting study duration of tenure (surrogate for exposure) not correlated to incidence and unclear exposure patterns	Wagoner J.K., P.F. Infante and D.L. Bayliss, Environmental Research 21, 15-34 (1980)
cohort study (retro-spective)	working in beryllium plants 1937 – 1948, follow up 1976	Human, white, ≥ 15 a 3685 M	In Be workforce the incidence of cancer was overall increased	Supporting study no correlation to the duration of employment	Mancuso T.F., Environmental Research 21, 48-55, (1980)
cohort study (retro-spective)	Facility workers of 7 US Be plants 1940 – 1969, follow up to December 1988	Human, 16 – 65 a 9225 M	↑ lung cancer among workers with a history of (primarily) acute beryllium disease	weight of evidence Little exposure data lung cancer due to high exposure not substantiated	Ward E., Okun A., Ruder A., Fingerhut M., and Steenland K., American Journal of Industrial Medicine 22:885-904 (1992)
clinical case study	unintentional, occupational Inhalation of Be containing dusts from sharpening tools (max 2 % Be) for 0.5 h/w 1970 to 1988	Human , 60 – 70 a 1 M	Lung tumour: adenocarcinoma, Stadium IV three years after his retirement	Supporting study Information on a single patient, only diagnoses and exposure estimates Other potential noxes: Asbestos, Smoking	Kampen V. van, J.Buenger, R. Merget, Bruening T., BGFA-Info 02/08, 6 – 9, (2008) Forschungsinstitut für Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung

* defined as chronic granulomatous lung disease

Table 27: Overview of data on carcinogenicity according to original publications (**not in registration dossiers**)

Method/ Guideline	Route of exposure, duration	Species, Sex, No	Results Main effects/ Target organs/ Tumours	Remarks	Reference
Nested case control study (retro-spective)	Workplace exposure of Be workers 1940 – 1969, follow up to 1992	Human, 15 – 65 a 3569 M 142 cases 710 controls	Average beryllium exposure was related to lung cancer risk after adjustment for birth cohort	weight of evidence reanalysis of data from a published case–control study of workers at a beryllium processing facility (Sanderson 2001)	Schubauer-Berigan, M.K.; Deddens, J.A.; Steenland, K.; Sanderson, W.T.; Petersen, M.R. (2008) Occup Environ Med., 65, 379-383
Cohort mortality	Facility workers of 7	Human, 16 – 65 a	Association between	weight of evidence follow-up of cause-	Schubauer-Berigan, M.K.; Couch, J.R.;

Method/ Guideline	Route of exposure, duration	Species, Sex, No	Results Main effects/ Target organs/ Tumours	Remarks	Reference
study	US Be plants 1940 – 1970, follow up to 2005	9199 M	maximum annual and cumulative beryllium exposure and lung cancer	specific mortality in workers of 7 plants (3 with quantitative Be exposure estimates) (Ward 1992)	Petersen, M.R.; Carreon, T.; Jin, Y.; Deddens, J.A. (2011) Occup Environ Med., 68, 345-353

5.8.3 Summary and discussion of carcinogenicity

The data on carcinogenicity of beryllium were obtained from animal testing and epidemiological studies. None of the tests on carcinogenicity was carried out in accordance with EU Regulation (EC) No 440/2008 or current OECD guidelines for the testing of chemicals. However, by means of a weight of evidence approach the available information is sufficient to support the conclusion that beryllium is likely to be a human carcinogen. Lung cancer occurred in rats and mice following single inhalation exposure of beryllium metal. Single intratracheal instillation of beryllium metal in rats induced lung tumours (Table 25). The available animal data are not suitable for risk quantification.

Epidemiologic studies have reported increases in lung-cancer risk in two worker cohorts exposed to beryllium. Due to co-exposure of beryllium metal and beryllium compounds at the workplace differentiation between elemental and other forms of beryllium is not possible (Table 27). Although beryllium exposure remains a plausible explanation for the increased lung cancer mortality experienced by these workers, alternative explanations cannot be excluded (Boffetta 2012). A meaningful cancer dose-response assessment cannot be conducted until more information is available on existing or new worker cohorts including complete work history, possible exposure to other carcinogens, and better exposure histories (McCleskey 2009).

Beryllium is classified as Carc. 1B, H350i:"May cause cancer by inhalation." according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 as a minimum classification and as Carc. Cat. 2, R49: "May cause cancer by inhalation." according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008. The eMSCA considers this classification as justified.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.1.1 Non-human information

This information is not available from the registration dossiers.

5.9.1.2 Human information

This information is not available from the registration dossiers.

5.9.2 Developmental toxicity

5.9.2.1 Non-human information

This information is not available from the registration dossiers.

5.9.2.2 Human information

This information is not available from the registration dossiers.

5.9.3 Summary and discussion of reproductive toxicity

There are only limited data available regarding the reproductive and developmental toxicity of **beryllium compounds** in animals by routes of exposure that are relevant to humans. No animal experiments of the reproductive or developmental toxicity of inhaled beryllium are available (WHO 2001). Many of the animal studies may have been conducted at doses that result in maternal toxicity (Welch 2012).

Based on the available data a conclusion on the classification of beryllium for reproductive toxicity according to Regulation (EC) No. 1272/2008 and Directive 67/548/EEC is not possible. Beryllium is a known carcinogen (classified as Carc. 1B, H350i). A classification to possible reproductive effects would not change risk management measures for a substance already classified as Carc. 1B, thus the eMSCA is currently not planning to request further information for this endpoint.

5.10 Endocrine disrupting properties

This information is not available from the registration dossiers.

5.11 Other effects

5.11.1 Non-human information

5.11.1.1 Neurotoxicity

This information is not available from the registration dossiers.

5.11.1.2 Immunotoxicity

Table 28: Overview of experimental studies on immunotoxicity **according to registration dossier**

Method/ Guideline	Route of exposure Duration	Species	Dose levels	Results Main effects	Remarks	Reference
Pulmonary Toxicity of Beryllium Metal and Beryllium Oxyde, no guideline followed, non-GLP	intratracheal instillation 1 ml in anaesthetized monkey via lung catheter in deep part of specified lobe	Monkey Cyno-mologus (Macaca fascicularis)	1, 50, 150 µg Be metal: MMAD 1.4 µm, GSD 1.4, suspended and diluted in 1 ml of saline	↑ No. of lung lymphocytes, > 50 µg: granuloma formation and marked Type II cell (pneumo-cytes) hyperplasia and variable lymphocyte	Sup-porting study	Haley P.J. K.F. Pavia, D.S. Swafford, D.R. Davila, M.D. Hoover, G.L. Finch, Immunopharmacology and Immuno-toxicology, 16(4),

Method/ Guideline	Route of exposure Duration	Species	Dose levels	Results Main effects	Remarks	Reference
			(vehicle: water)	infiltration		627 – 644 (1994)
Immuno-toxicity of Be Metal and Beryllium Oxide in Cynomolgus Monkeys	as above	as above	as above	as above	Sup-porting study **Sum-mary only**	Haley P.J., G.L. Finch, D. Davilla, M.D. Hoover, The Toxicologist, Vol 12, (1) 31st meeting, February 1992

5.11.1.3 Specific investigations: other studies

Table 29: Experimental in vitro cytotoxicity study according to registration dossier

Method/ Guideline	Test system (Organism, strain)	Concentrations tested	Results	Remarks	Reference
Cytotoxicity Assay In vitro: Evaluation of Bioavaila-bility (XTT-Test) according to Guideline ISO 10993: "Biological Evaluation of Medical Devices" Part 5: "Tests for cytotoxicity: In vitro methods", Chapter 8.2.: "Tests on extracts", 1999 and Part 12: "Sample preparation and reference materials", 2002, GLP	mouse cell line L929	2.05 g extracted for 24 h at 37 ± 1.5 °C in 20.5 ml phosphate buffer (pH 4.5), supplemented with 10 % (v/v) FCS 3, 10, 30, 100 % of the extract	No cytotoxic effects were observed following incubation with an extract of Be Metal Powder up to the highest tested concentration.	Supporting study Beryllium Metal Powder	TL3, unpublished record 2008

5.11.2 Human information

This information is not available from the registration dossiers.

5.11.3 Summary and discussion of specific investigations

The data for immunotoxicity of beryllium were obtained from animal testing. A study published as abstract and peer-reviewed article was intended to cover the endpoint immunotoxicity. The observed lung effects are consistent with those seen in man and rodents. However, the significance of the observed beryllium specific immune response for human safety evaluation is not clear with regard to the dose-response-relationship, as the exposure route is not relevant for humans and the results have not been confirmed in inhalation experiments in monkeys (chapter 5.5.3).

5.12 Combined effects

This information is not available from the registration dossiers.

5.13 Derivation of DNEL(s) / DMEL(s)

The process of DNEL/DMEL derivation is outlined in Section R.8.4 of the REACH Guidance (ECHA, 2012). According to this guideline, a DNEL for the leading health effect needs to be derived for every relevant human population and every relevant route, duration and frequency of exposure, if feasible.

For carcinogenic substances, two types of effect levels can be established: derived no effect level (DNEL) for carcinogens with a threshold and derived minimal effect level (DMEL) for carcinogens without a threshold. If it is not possible to identify a DNEL/DMEL, this shall be clearly stated and fully justified.

According to REACH, the derivation of a DNEL/DMEL is required only for substances that are classified and registered in quantities of ≥10 tonnes per year. Since all current beryllium registrations are for marketed quantities of less than 10 t/a, no Chemical Safety Reports and DNEL/DMEL calculations are provided within the registration dossiers. Nevertheless, for quantitative risk assessment a guidance value (i.e., OEL, DNEL/DMEL etc.) is needed in order to assess the available exposure data. Thus, DNEL/DMEL values for beryllium were calculated by the eMSCA according to the REACH provisions despite its low marketed tonnage.

5.13.1 Overview of typical dose descriptors for all endpoints

No dose-descriptors are available from the registration dossiers. The dose-descriptors have therefore been gathered from available and relevant epidemiological data published in the open literature. Out of this database together with the information published in reviews of international bodies/regulatory programs (ATSDR 2002, WHO 2001, EPA 1998, MAK 2003) suitable studies and typical dose descriptors for derivation of DNEL values are selected.

A review of all available dose descriptors per each toxicity endpoint indicates that the major concern associated with acute and chronic exposures to beryllium is lung cancer and chronic beryllium disease.

Endpoint carcinogenicity

Available animal studies show severe limitations (i.e., single dose treatment, short duration, limited animal numbers etc.) that do not allow the quantitative interpretation of their results (Section 5.8.3).

Several epidemiologic studies investigate the relationship between occupational exposures to beryllium and development of lung cancer in exposed workers (reviewed in Table 26 and Table 27). The most of them are seriously questioned by industry and scientific community (i.e., Boffetta et al., 2012), and are not considered as a reliable basis for cancer risk quantification. Major criticism is focused on the high uncertainties associated with exposure assessment and selection of the most appropriate exposure metrics (e.g. role of particle size and surface area concentrations, peak versus cumulative exposures, breathing zone concentrations), the handling of confounding factors such as smoking and health status, and the lack of plausible MOA for lung cancer development that can be reliably tested in an animal model.

Overall, the available animal and human studies are considered not suitable for evaluation of the dose response for lung cancer development and thus they cannot provide a reliable starting point for quantitative risk assessment.

Endpoint chronic beryllium disease

This is the most prominent effect observed at the lowest exposure levels in epidemiological studies. The three studies which were used for derivation of the long-term systemic DNELs are summarized below. An **LOAEC for chronic beryllium disease of 0.2 µg/m³** as time weighted average is obtained from human exposure in all three studies.

Table 30: Overview of studies and dose descriptors per endpoint used for DNEL derivation

Endpoint	Study used	Dose descriptor	Remarks on study*
Repeated dose toxicity: sub-acute / sub-chronic / chronic	A population-based **cross-sectional** health survey in a small collective of workers daily exposed to airborne beryllium full-shift or 8 hours (Schuler 2005)	LOAEC: 0.2 µg/m³ beryllium air levels	Historical airborne beryllium measurements (personal full-shift samples) indicated that beryllium sensitization and chronic beryllium disease were associated with an area in which beryllium air levels exceeded 0.2 µg/m³, and not with areas where this level was rarely exceeded.
Repeated dose toxicity: sub-acute / sub-chronic / chronic	**Exposure response analysis** for beryllium-sensitized or CBD diagnosed workers exposed to airborne beryllium over an 8-hour workday not routinely using respiratory protection (Madl 2007)	LOAEC: 0.2 µg/m³ beryllium air levels	Historical airborne beryllium measurements (personal 8 h samples) showed that beryllium-sensitized workers and workers diagnosed with chronic beryllium disease were exposed to beryllium concentrations greater than 0.2 µg/m³ (95th percentile), and 90 % were exposed to beryllium concentrations greater than 0.4 µg/m³ (95th percentile) within given year of there working history.
Repeated dose toxicity: sub-acute / sub-chronic / chronic	**Exposure response relations** for beryllium sensitization and CBD among short-term workers exposed to airborne beryllium over an 8-hour workday (Schuler 2012)	LOAEC: 0.20 µg/m³ (total beryllium mass concentration) LOAEC: 0.17 µg/m³ (respirable beryllium mass concentration) beryllium air levels	Historical personal exposure estimates of average, cumulative, and highest-job-worked exposure for airborne total, respirable, and submicron mass concentration beryllium (8 h full-shift personal samples) for the entire duration of onsite work history of six years or less indicated that chronic beryllium disease was associated with cumulative exposure.

* It has to be noted that U.S. workplace dust sampling methods that measure „total dust" are different to European dust sampling methods measuring „inhalable dust". According to Getschman (2013) it is difficult to compare the measurement results of these sampling methods.

5.13.2 Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptor for critical health effects

Beryllium metal is not produced in Europe but it is imported for use in a range of industries such as aerospace, automotive, energy, medicine, defence and electronics. Considering its physicochemical properties and industrial use, exposures to beryllium in the workplaces occur primarily via the inhalation route.

Lung cancer and beryllium sensitization (BeS) with subsequent development of chronic beryllium disease (CBD) are considered the critical health effects associated with occupational exposure to beryllium and its compounds. Consequently, two types of effect levels are required to control exposure at the workplace: (1) a health-based long-term systemic DNEL (inhalation) for protection of CBD development, and (2) a risk-based DMEL for assessment of the cancer risks associated with beryllium exposure. As discussed earlier (chapter 5.8.3), the available animal studies and epidemiologic data do not provide a reliable base for DMEL calculation. Therefore, cancer risks associated with occupational exposure to beryllium cannot be quantitatively assessed within this

evaluation. With respect to the risks of developing a CBD, a long-term systemic DNEL for inhalation was calculated according to the provisions of the REACH Guidance and compared with the exposure data.

It should be noted that CBD is still a significant occupational problem. In Germany, CBD is recognized as an occupational disease and is listed under Nr. 1110 in Annex 1 of the Occupational Diseases Ordinance (BKV, 2009). The recognized cases of CBD over the last few years have remained quite steady at 2-3 new cases per year (BMAS/BAuA, 2013; Reports are available for download at www.baua.de/suga).

Endpoint carcinogenicity

The carcinogenic properties of beryllium and its compound have been subject to evaluation by, several national authorities and regulatory agencies. These are briefly reviewed for information purposes.

In Germany, beryllium and its inorganic compounds have been classified as carcinogenic Category 1 (Substances which cause cancer and make a considerable contribution to the risk of cancer) (DFG 2013). As for the majority of carcinogenic substances, no health-based workplace exposure limit for beryllium could be established at this point. For carcinogens without a threshold, the concept of risk-based limit values developed by the Committee on Hazardous Substances (AGS) is currently applied (Announcement 910, published in 2008 and still in a testing phase; http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/Announcement-910.html). These risk-based values should be considered when performing a risk assessment, however they are not legally binding yet (legal basis expected for 2015). At present, the AGS is working on the development of an exposure-risk relationship for beryllium.

Outside the EU, the US EPA (1998) has classified beryllium as a Group B1, probable human carcinogen, and derived an inhalation Unit Risk estimate of 0.0024 per μg/m^3. This value is the geometric mean of eight estimates ranging from 0.00016 to 0.0072 per μg/m^3. Base for the calculation are dose-response data from an occupational study by Wagoner et al. (1980) and exposure estimates from industrial hygiene reviews by NIOSH (1972) and Eisenbud and Lisson (1983). After adjustments for differences in smoking habits and vital statistics, EPA calculated elevated, but not statistically significant, SMR of 1.36 to 1.44. For Unit Risk calculations, two median exposure levels of 100 and 1000 μg/m^3 and relative risks of 1.98 and 2.09 were used as the 95% upper-bound estimate of the above risk figures.

The study by Wagoner et al. (1980) has been criticized for underestimating the expected lung cancer rates, for not adjusting for latency or smoking status, and for including workers who never worked at the plant (EPA 1998). Further, no quantification of individual worker exposures was available or attempted in this study, and duration of employment was used as a surrogate measure. Beryllium assessment is currently under review and the latest draft can be found at the IRIS website.

NRC (2008) (http://www.nap.edu/catalog.php?record_id=12464) considered the available human and animal data on beryllium exposure inadequate for a meaningful dose-response assessment and cancer risk calculations. The authors suggested that additional information is necessary regarding the most relevant dose metrics (e.g. peak or cumulative exposure) and the mode of action for tumour induction, influence of beryllium physicochemical characteristics, potential co-exposure to other lung carcinogens at the workplace, and identification of an animal model representing most closely cancer development in humans.

Endpoint chronic beryllium disease

Guidance values for OEL for beryllium and its compounds have been developed by several national authorities and regulatory agencies.

The American Conference of Governmental Industrial Hygienist (ACGIH) adopted recently a threshold limit value time-weighted average (TLV-TWA) of 0.05 µg/m³ based on prevention of BeS and CBD (ACGIH, 2009). Development of this standard was based on studies by Kelleher et al. (2001) and Madl et al. (2007) indicating that incidences of BeS and disease development are very low at this level. Specifically, a total of 27 beryllium-sensitized and CBD workers have been identified that included 9 cases with BeS, 16 cases with subclinical CBD, and 2 cases with CBD (Madl et al., 2007). From the 27 cases, 10 individuals had lifetime weighted (LTW) average exposures of less than 0.2 µg/m^3 while the rest (17 workers) had exposures above 0.2 µg/m³. For three of the cases LTW was between 0.05 and 0.1 µg/m^3, and 7 cases had LTW in the range 0.1 to 0.2 µg/m³. ACGIH points out that this TLW-TWA is based on long-term average concentrations, and peak exposures may also play an important role for BeS.

Within this evaluation, the LOAEC of 200 ng/m³ identified in several epidemiologic studies (chapter 5.13.1) is considered as a starting point for long-term systemic DNEL calculation. Applying a factor of 3 for the use of LOAEC instead of NOAEC as a point of departure (POD), a DNEL of 66 ng/m³ (rounded to 60 ng/m³) is calculated (Table 31). The REACH methodology suggests the use of additional factor of 5 to account for intraspecies variability (especially if data originates from small collectives), however this can be omitted since CBD is observed among already sensitive individuals. No further assessment factors are required for this calculation. The long-term systemic DNEL of 60 ng/m³ should be protective for beryllium sensitization and development of CBD.

Table 31: Overview of information considered during DNEL derivation for workers

Exposure pattern	Route	Descriptor	Value	Remarks
Long-term systemic effect	Inhalation	Relevant dose descriptor for development of chronic beryllium disease	LOAEC: 200 ng/m^3	A time weighted average obtained from epidemiologic studies with occupationally exposed workers
		Modification of the relevant dose descriptor	--	Not needed since data originate from occupational studies
		Assessment factor (AF)	AF Value	Remarks
		Dose response	3	Extrapolation from LOAEC to NOAEC
		Intraspecies	1	For workers, the default factor of 5 is replaced with 1 since CBD is observed among already sensitive individuals
		Exposure duration	1	Not needed since data originate from occupational studies
		Quality of database	1	
		DNEL	200 / 3 = 66 ng/m^3 (rounded to 60 ng/m³)	

5.14 Conclusions of the human health hazard assessment and related classification and labelling

Evaluation of the existing information on the toxicity of beryllium indicated that the legal classification for acute oral toxicity as "Acute Tox. 3*; H301: Toxic if swallowed", for irritation as "Eye Irrit. 2; H319: Causes serious eye irritation" and "Skin Irrit. 2; H315: Causes skin irritation", might have been based on a combined evaluation of beryllium and its compounds.

Following the requirements set down in Annex I of Regulation (EC) No 1272/2008 (CLP) and the data available, beryllium metal does not appear to fulfil the criteria for classification as "Acute Tox. 3*; H301", "Eye Irrit. 2; H319" or "Skin Irrit. 2; H315".

The legal classification of beryllium for acute inhalation toxicity is "Acute Tox. 2*, H330: Fatal if inhaled", meaning that it is a minimum classification following Annex VI 1.2.1 of Regulation (EC) No 1272/2008 (CLP). This (minimum) classification appears to be appropriate as the acute toxicity estimate of 170 mg/m³ is in the category 2 range. Therefore the asterisk can be deleted, when classification and labelling is harmonised.

The legal classification of beryllium for specific target organ toxicity repeated exposure has been translated from classification as "T; R48/23: Toxic: danger of serious damage to health by prolonged exposure through inhalation" under 67/548/EEC (DSD) indicating inhalation as the route of exposure into the corresponding class and category according to Regulation (EC) No 1272/2008 (CLP), but with a general hazard statement not specifying the route of exposure. **It is conclusively proven from human data on chronic beryllium disease (CBD) that no other route of exposure can cause the lung damage in accordance to the criteria in Annex I.** Therefore the route of exposure should be indicated in the hazard statement as "STOT RE 1; H372: Causes damage to lungs through prolonged or repeated exposure by inhalation."

Based on the extensive data regarding beryllium exposure via inhalation resulting in development of chronic beryllium disease (CBD) sufficient evidence on respiratory sensitisation in humans is available that indicated classification as respiratory sensitizer category 1, H334: "May cause allergy or asthma symptoms or breathing difficulties if inhaled." according to Regulation (EC) No. 1272/2008 (CLP) is appropriate. As such a classification would not change risk management measures for a substance already classified as Carc. 1B, the eMSCA is currently not planning to harmonise classification and labeling for this endpoint.

Beryllium is classified as Carc. 1B, H350i:"May cause cancer by inhalation." according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 as a minimum classification and as Carc. Cat. 2, R49: "May cause cancer by inhalation." according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008. The eMSCA considers this classification as justified.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

not assessed.

7 ENVIRONMENTAL HAZARD ASSESSMENT

not assessed

8 PBT AND VPVB ASSESSMENT

not assessed

9 EXPOSURE ASSESSMENT

9.1 Human Health

9.1.1 Exposure assessment for worker

9.1.1.1 Overview of uses and exposure scenarios

Production

Beryllium is not produced in Europe. The needed semi-finished products, like panels and profiles, are imported, mainly from the USA. In 2007, the USA exported 19.6 tons of beryllium into the EU and Switzerland.

World production of beryllium has been reported to be about 200 t/a [ACGIH, 2009] resp. approximately 280 t in 2010 [Beryllium Science and Technology Association, BeST, 2012]. The beryllium market review 2010 [Merchant Research and Consulting Ltd., 2010] assumes that the use of beryllium will grow at a yearly rate of about 2 %. BeST (2012) assumes an annual consumption of 320 t in 2020 and 435 t in 2030.

Beryllium is provided in its metallic form, as copper-alloy, and as beryllium oxide for ceramic parts.

Chemical Safety Reports were not available during substance evaluation. Instead of exposure scenarios with detailed information on uses, registrants provided a tabular list of use descriptors (see

Table 8).

Processing, use, and disposal

For the major part, beryllium is used as a component of **alloys** in a content of less than 2 %

- as master alloy in thermal processes (for production of low concentration alloys), or as
- an additive to prevent oxidation processes in the melt.

Alloys with a beryllium content significantly *above* 2 % occur in special applications, like

- construction of scientific equipment,
- nuclear technology, and
- aerospace industry.

To a large extent (about 75 %), beryllium containing **articles** are used in electrical and electronic parts, in switches, springs, connectors, etc. Usually, these components are very small and are installed in the final equipment in a way that they cannot be accessed directly.

Beryllium containing **metal scrap** is usually collected by converters and led to metal recycling. **Filter dust** from exhaust installations of metal-using companies that also use beryllium alloys of low beryllium concentrations are disposed off on land-fills.

In summary, it can be stated that because of its various uses, beryllium can be contained in many products.

Table 7 contains a list of industry branches and articles in which beryllium containing parts are used [Darby, A. and Fishwick, D., 2011].

9.1.1.2 Scope and type of exposure

Exposure to beryllium containing **articles** (electrical / electronic parts, etc.) is unlikely as, usually, they are small, non-switched and not directly accessible in the final product, except for **repair and recycling**. Metal scrap and filter residues may expose workers of recycling and maintenance companies.

Concerning the pathway, occupational exposure to beryllium is expected to occur mainly through inhalation of dust (No. of occupational disease (BK-No.) 1110). Skin contact is possible as well. Ingestion as exposure pathway will be neglected according to the assumption that standard occupational hygiene measures are implemented at typical workplaces.

According to Cherrie [Cherrie, J. et al., 2011], 65,971 workers are potentially exposed in the EU to beryllium. Foundries that work with Cu-Be alloy are of particular concern as workers in these foundries may have beryllium exposures exceeding the occupational exposure limit. Cherrie gives an estimate of 1,239 foundry workers.

The American Conference of Governmental Industrial Hygienists [ACGIH 2009] estimated 134,000 workers to be potentially exposed to beryllium in the United States. The production of beryllium is limited to two beryllium mines employing approximately 200 workers. Exposure to beryllium may primarily be expected in

- the production of beryllium, (not relevant for Europe)
- the thermal handling or machining of beryllium products and in
- recycling of beryllium and its alloys (and minerals).

9.1.1.2.1 Monitoring data

<u>French study</u>

In a socioeconomic study for the protection of workers who use beryllium and beryllium compounds [Cherrie, J. et al., 2011], about 65,000 workers in 16 branches of industry are indicated (Table 32). This set of data describes the situation in France in 2009.

Processes with the assumed highest exposures are

- melting,
- pouring, and
- hot work, as well as
- mechanical grinding and machining of beryllium alloys.

Therefore, the industry branch “manufacture of basic metals” (NACE 27) with 1,239 employees belongs to the areas with the highest exposure. A more detailed look at this specific part of the

study on beryllium exposure in the French industry is also given in Table 32 and confirms this statement [Vincent, R. et al., 2009]. In all activity sectors, except NACE 27.52 (“casting of steel”) and 27.53 (”casting of light metals”), the median exceeds the ACGIH limit of 0.05 µg/m^3 [ACGIH, 2009]. The highest exposure exists for manufacture of basic metals, casting of other non-ferrous metals, primary copper transformation, casting of steel and manufacture of radio, television and communication equipment and apparatus.

Table 32: Exposure monitoring data from [Cherrie, J., 2011; Vincent, R. et al., 2009]

NACE Code		N	Mean	Median	GM	GSD	Range	Percentiles		
								25th	75th	90th
			(µg/m³)	(µg/m³)	(µg/m³)		(µg/m³)	(µg/m³)	(µg/m³)	(µg/m³)
24	Manufacture of chemicals and chemical products	2	-	-	-*	-	0.5 - 2.3	-	-	-
26.1	Manufacture of glass and glass products	4	-	-	0.707	-**	0.25 - 1	-	-	-
27	Manufacture of basic metals	159	5.366	0.422	0.494	13.0	0.005 - 95.4	0.06	4.21	16.1
27.42	Aluminium production	32	0.388	0.191	0.147	5.4	0.05 - 2.53	0.05	0.55	0.95
27.44	Copper primary transformation	13	2.532	1.9	0.968	11.0	0.005 - 7	1.17	3.62	5.56
27.52	Casting of steel	53	3.444	0.1	0.238	9.1	0.005 - 51.9	0.05	1.31	7.72
27.53	Casting of light metals	12	0.017	0.015	0.016	1.3	0.01 - 0.03	0.015	0.018	0.023
27.54	Casting of other non-ferrous metals	48	13.023	6.69	5.249	5.0	0.062 - 95.4	2.93	16	29.36
28	Manufacture of fabricated metal products, except machinery and equipment	76	0.185	0.015	0.023	6.8	0.001 - 1.84	0.007	0.11	0.6
32	Manufacture of radio, television and communication equipment and apparatus	29	2.4	0.01	0.036	31.5	0.004 - 19.24	0.004	1.04	10.44
33	Manufacture of medical, precision and optical instruments, watches and clocks	74	0.16	0.03	0.032	7.3	0.001 - 2.23	0.005	0.14	0.5
35	Manufacture of transport equipment other than motor vehicles	14	0.008	0.005	0.007	1.6	0.005 - 0.15	0.005	0.01	0.015

* Mean, Median, GM and GSD not available

** GSD not available

German Monitoring data (IFA)

The German worker exposure data were provided by the IFA-'Institute for Occupational Safety and Health of the German Social Accident Insurance' (formerly BGIA; German: Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) in a special report [IFA, 2013].

Data source characteristics
The new data provided by IFA were measured in industry for the years 2000 to 2011. The data are differentiated into

- personal sampling data taken while the individual was carrying out all activities (i.e. active plant work, control room work and break periods) and
- data from stationary sampling in the different workplaces.

The identification and documentation of the following evaluated data from exposures in the workplace are based on the criteria of the MGU [BGIA, 2009] - measuring hazard identification of accident insurance carrier (formerly BGMG). A quality management system which essentially implements the requirements of DIN EN ISO 9001 ensures the standard of MGU. The testing laboratories operated in accordance with DIN EN ISO 17025.

All data collected will be merged into the exposure database MEGA (measurement data to exposure to hazardous substances at work). The MEGA exposure database is maintained and evaluated for the Institutions for Statutory Accident Insurance and Prevention by IFA.

The limit of quantification (LoQ) is given in Table 33.

Table 33: Determination of the limits of quantification according to EN 13890

Method of sampling	**personal sampling**		**stationary**	
Diameter of sampling device [mm]	37		70	150
Flow rate [L/min]	3.5	10	66.67	375
Period of sampling [h]	2			
LoQ [µg/m³]	**0.48**	**0.17**	**0.050**	**0.018**
Sampling system	Total dust (GSP)		PM4G	Total dust (VC25G)

If individual measurements are below the limit of quantification (LoQ) of the applied analytical method, half of this value is taken into account within the statistical evaluation. The MEGAPRO software, developed by IFA, allows the statistical analysis of the data of the exposure database MEGA according to different selection criteria and evaluation strategies. As the LoQ is partially higher than the DNEL of 0.060 µg/m³, more sensitive analysis methods will have to be developed.

Criteria for the inclusion of data in the evaluation

- measurements related to exposure
- sampling duration
- exposure time ≥ 6 hours.
- Exclusion of data collectives
  - consisting of less than 10 measurements or

- data from less than three different German Social Accident Insurances or
- data from less than five different companies[2].

In order to achieve a better comparability to the DNEL of 0.060 µg/m³, the MEGA measurement data given in mg/m³ were converted into µg/m³ by multiplying by the factor of 1000.

Evaluation strategy and selection criteria
The evaluation is made in the form of

- industry (branch groups) and
- activity groups, and further differentiated by the
- sampling strategy (static or on the person) and the
- presence of a LEV (Local Exhaust Ventilation).

A general overview of the branch groups handling beryllium, identified in the German IFA-report, (correlating with the main uses mentioned at the beginning of chapter No. 2, "Manufacture and Uses"), is given in Table 34 below.

Table 34: Branch groups adjusted by according numbers of measurements **(IFA 2013, chapter 7.1, table 1 and 2, page 9f.**

Branch group groups	Number of measurements (sampling >6 h)
Disposal, recycling	116
Building trade	10
Foundry	101
Glas	16
Engine building	14
Metal working	79
Other branch groups	33
Overall result:	**369**

A deeper analysis of the exposure of workers in the main work area group separated into exposure relevant processes is considered separately in the same way in Table 35.

Legend of symbols		
*	=	Measurement data below quantification limit are considered by half of the quantification limit-value
**	=	Data of less than 5 facilities which might possibly be a too small number of sites for characterization of a whole branche
!	=	Number of measurements below quantification limit is larger than number of positive detections. Therefore, no value is given.
+	=	the value is *below* the detecion limit (subject to sampling period, sampling value, etc.)
LoQ	=	Quantification limit

Below, in Table 35, for each branch groups, the measurement results for a sampling time of > 6 h are given as 90 %- and 95 %-percentile (enhanced by number of evaluated data, number of

[2] Management agreement between the German Social Accident Insurances and the German Statutory Accident Insurance for the purpose of data protection.

facilities, number of data below the according detection limit, and the highest detection limit during the measurements).

Table 35: Statistical analysis concerning branch groups, sampling > 6 h **(IFA 2013, chap.4, table 1)**

Data collective No. / **branch group**	No. of measure-ments	No. of facilities	Frequency below LoQ		Max. LoQ	Exposure concentration [µg/m³]					
						50 % value		**90 % value**		**95 % value**	
			number	%	[µg/m³]**						
No.7 (no restriction)	369	117	309	83 %	7.6	!	LoQ	+	0.462	+	0.767
No.13 disposal, recycling	116	31	110	94.8	7.6	!	LoQ	!	LoQ	+	0.19
No.14 construction	10	5	8	80	2.1	!	LoQ	+	1.05	**2.52**	
No.16 foundry	101	16	68	67.3	2.7	!	LoQ	+	0.697	+	**1.05**
No.17 glass production	16	3**	13	81.3	1.4	!	LoQ	+	0.98	**2.78**	
No.19 engineering	14	9	12	85.7	2	!	LoQ	0.358		0.554	
No.20 metalworking	79	33	70	88.6	2.8	!	LoQ	+	0.18	+	0.228
No.22 other industries	33	20	28	84.8	0.81	!	LoQ	+	0.375	+	0.512

All industries mentioned in Table 35, show high exposures to beryllium. But the highest exposure levels have been observed in construction and in foundries (95 % percentile). The high exposure to beryllium in glass production is probably attributable to the use of beryllium oxide. However no information is given on this in the IFA documentation.

In Table 36 below, the branches are subdivided showing the exposure for single activities (sampling time: > 6 h).

Table 36: Statistical analysis for single activites of work, sampling > 6 h **(IFA 2013, chap.5, tab.1)**

Data collective No. / **work activity groups**	No. of measure-ments	No. of facilities	Frequency below LoQ		Max. LoQ	Exposure concentration [µg/m³]					
						50 % value		**90 % value**		**95 % value**	
			number	%	[µg/m³]**						
No.7 (no restriction)	369	117	309	83.7	7.6	!		+	0.462	+	0.767
No.24 lathe, planing, CNC-machine	23	14	19	82.6	4	!		+	0.124	+	0.143
No.23 recycling of electronic scrap, picture tubes	26	10	24	92.3	7.6	!		!	LoQ	+	0.057
No.34 recycling of electronic scrap, degrading	49	16	49	100	2.7	!		!	LoQ	!	LoQ
No.57 recycling of electronic scrap, shredding	19	5	15	78.9	2.2	!		+	0.106	+	0.11
No.25 glas, mould production, repair, general	12	2**	10	83.3	1.4	!		+	**1.26**	**4.16**	
No.58 foundry, moulding shop	21	2**	21	100	0.16	!		!	LoQ	!	LoQ
No.59 foundry, casting	27	9	17	63	0.47	!		0.521		0.878	
No.60 foundry, fettling shop	17	3**	12	70.6	2.3	!		+	**1.08**	+	**1.16**
No.30 foundry, smelter	31	9	14	45.2	0.17	0.0995		0.417		0.469	
No.28 sawing, milling, blanking	14	7	12	85.7	0.25	!		+	0.2	**1.83**	
No.29 polish, buffing	18	12	15	83.3	0.44	!		+	0.254	0.571	
No.31 welding	22	13	19	86.4	1.5	!		+	0.173	+	0.694
No.32 other fields	75	38	69	92	2.1	!		!	LoQ	+	0.481
No.33 separation system, machining process	15	8	13	86.7	2.8	!		+	**1.33**	+	**1.36**

According to Table 36, the most noticeable exposure levels are observed in fettling shops of foundries (No.60), during sawing, milling, blanking (No.28), in separation and machining processes (No.33) due to building of aerosols, as well as mould production, repair, and general work in glass production (No.25) due to high temperatures.

Exposures to beryllium *below* the according LoQ or below 0.06 µg/l were received for the following work activities: degrading of electronic scrap (No.34), recycling of picture tubes (No.23), and moulding shop of foundries (No.58).

9.1.1.2.2 Modelled data

None

9.1.1.2.3 Comparison of monitoring and modelled data

None

9.1.2 Exposure assessment for consumer

No consumer uses resulting in consumer exposure to beryllium were identified. However, consumers use articles comprising parts containing beryllium. The registration data (ECHA 2013a) refers the article categories "AC 01: Other (non intended to be released): electronic articles" and "AC 1: Vehicles". The beryllium containing articles in electrical and electronic parts are usually very small and installed within the final equipment in a way that they can not be reached directly. During normal and foreseeable usage this will only result in negligible consumer exposure, if any as the beryllium containing parts will generally be alloys with low beryllium content. This also holds true for contacts during do-it-yourself or recreational activities, which could involve both article categories mentioned.

Further information on the exposure assessment for consumers is given in the confidential part.

9.2 Environmental exposure assessment

not assessed

9.3 Combined exposure assessment

not assessed

10 RISK CHARACTERISATION

10.1 Human Health

10.1.1 Workers

Exposure to beryllium and its compounds at the workplace occurs mainly via inhalation; the contribution of the dermal exposure pathway is not regarded as relevant to the inhalation risk considered in this report. For risk characterization, the inhalation exposure data is compared to the long-term systemic DNEL (inhalation) of 0.06 µg/m^3. The DNEL value is based on epidemiologic studies with occupationally exposed collectives where BeS und CBD were identified as critical systemic effects resulting from beryllium exposure (see chapter 5.13.2 for details).

Comparison of the DNEL of 0.06 µg/m^3 and publicly available exposure data (see exposure information described in chapter 9.1.1) indicates that the risks associated with the use of beryllium are not sufficiently controlled. It should be noted, however, that the exposure data considered in this report were collected in only two European countries – Germany and France. Therefore, a general conclusion about the risks associated with the use of beryllium and its compounds throughout Europe might be associated with uncertainties. Nevertheless, in both cases exposure data significantly exceed the calculated DNELs, and similar exposure situations are also expected in other countries.

With respect to the exposure data provided by Cherrie et al., 2011, the highest exposure exists for manufacture of basic metals, casting of other non-ferrous metals, primary copper transformation, casting of steel and manufacture of radio, television and communication equipment and apparatus. As shown in Table 32, in all activity sectors except NACE 27.53 (”casting of light metals”), already the 75th percentile of the exposure data significantly exceed the long-term systemic DNEL (inhalation) of 0.06 µg/m^3. Manufacturing of parts and equipment products is also associated with elevated risks, although the excess is not as high as those for NACE 27 activities. Manufacturing of transport equipment other than motor vehicles (NACE 35, Table 32) is the only branch where exposures can be regarded as safe.

Considering the German monitoring data provided by the IFA institute (Table 35), exposure to beryllium in industry sectors such as building trade (Nr. 14), foundry (Nr. 16), and glass production (Nr. 17) exceed significantly the calculated DNEL . For the remaining industry sectors exposure values are also clearly above the calculated DNEL. Work activities such as glass, mould production, and repair (No. 25), welding (Nr. 31), casting (Nr. 59) and machining (Nr. 33) belong to the areas where the exceedance of the DNEL is the highest (Table 36). It has to be noted that the high exposure to Beryllium in glass production is probably attributable to the use of beryllium oxide. However no information is given on this in the IFA documentation.

Overall, the publicly available exposure monitoring data for beryllium from both the French and the evaluating MSCA indicates that there are practically no industry sectors/ work areas where exposure is sufficiently controlled below the DNEL of 0.06 µg/m^3.

10.1.2 Consumers

No risk characterisation for consumers was performed as no consumer uses resulting in consumer exposure to beryllium have been identified.

10.1.3 Indirect exposure of humans via the environment

not assessed

10.2 Environment

not assessed

10.3 Overall risk characterisation

not assessed

10.3.1 Human health (combined for all exposure routes)

not assessed

10.3.2 Environment (combined for all exposure routes)

not assessed

11 OTHER INFORMATION

The evaluation of the toxicity of beryllium has been based on the registration dossiers as well as on reviews by a variety of international bodies/regulatory programs and original publications. Available data for all endpoints have been assessed. Beryllium has been evaluated by the International Programme on Chemical Safety (WHO 2001), the U.S. Department of Health and Human Services (ATSDR 2002), the German Senate Commission for the Testing of Harmful Working Materials (MAK 2002, 2003), and the U.S. Environmental Protection Agency (EPA, 1998). Where relevant, the original publications were reviewed and evaluated as indicated in the text. In addition literature was searched in the on-line databases DIMDI, ToxNet (HSDB, Toxline incl. PubMed), ISI Web of Knowledge, and Scopus, latest search September 2013.

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TL1	2009d	Beryllium Metal Powder - Primary Eye Irritation Study in Rabbits	Unpublished study record, confidential
TL1	2009e	Beryllium Metal Powder - Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test	Unpublished study record, confidential
TL2	2009a	Gene Mutation Assay in Chinese Hamster V79 Cells In Vitro (V79 / HPRT) with Beryllium Metal Powder	Unpublished study record, confidential
TL2	2009b	Cell Transformation Assay in Syrian Hamster Embryo Cells (SHE Assay) with Beryllium Metal Powder	Unpublished study record, confidential
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13 ABBREVIATIONS

Table 37: List of abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATE	Acute toxicity estimate
BeS	beryllium sensitization
BOEL	Binding occupational exposure limit
bw	Body weight
CBD	Chronic beryllium disease
C&L	Classification and Labelling
d	day(s)
DWA	Daily Weighted Average
EC	Effective Concentration
F	Female
FAP	fused aluminosilicate particles
FCS	Fetal calf serum
GLP	Good laboratory praxis
GSD	Geometric standard deviation
h	hour(s)
IFA	Institute for Occupational Safety and Health of the German Social Accident Insurance (formerly BGIA; German: Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung)
i.v.	intravenous
LoQ	limit of quantification
LTW(A)	Lifetime-weighted average
M	Male
MAK	Maximale Arbeitsplatz-Konzentration
MEGA	Database of measurements of exposure to hazardous substances at work of German IFA
MMAD	Mass median aerodynamic diameter
MEM	minimum essential medium
OEL	Occupational exposure limit
PEG	polyethylene glycol
PROC	Process category
RMO	Risk management options
SCOEL	Scientific Committee on Occupational Exposure Limits
SMR	Standardized mortality ratio
SU	Sectors of end-use
SVHC	Substances of very high concern
TWA	Time weighted average
w	week
WHO	World Health Organization

ANNEX: CONFIDENTIAL INFORMATION