Collective expert appraisal: summary and conclusions

Regarding the "expert appraisal on recommending occupational exposure limits for chemical agents"

On the evaluation of biomarkers and recommendation for biological reference values for beryllium and its compounds

[CAS n°:7440-41-7]

This document summarises the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee) and the Working Group on biomarkers (biomarkers WG).

Presentation of the issue

On 12 June 2007, AFSSET, which became ANSES in July 2010, was requested by the Directorate General of Labour to carry out the necessary assessment for setting occupational exposure limits for beryllium and its compounds. Under a 1995 Circular[1], France has a time-weighted average exposure value for beryllium and its compounds of 0.002 $mg.m^{-3}$.

The Directorate General of Labour asked the ANSES to reassess this value and, if necessary, to propose new occupational exposure limit values based on health.

This request was entrusted to ANSES's OEL Committee which, in 2010, issued a report for recommending for beryllium and its compounds[2]:

- a pragmatic 8h-OEL of 0,01 $\mu g.m^{-3}$;
- assigning the "skin notation"

The OEL Committee decided to supplement its appraisal by assessing the data concerning biological monitoring in the workplace for beryllium and its compounds, in order to assess the suitability of recommending monitoring one or more biomarkers in addition to the atmospheric OEL, possibly including elaboration of biological limit values for the biomarker(s) chosen.

1 Circular of 12 January 1995 supplementing and amending the Circular of 19 July 1982 on the permissible values for concentrations of certain hazardous substances in workplace atmospheres

2 https://www.anses.fr/fr/system/files/VLEP-Ra-berylliumEN.pdf

Scientific background

Biological monitoring of exposure in the workplace has emerged as a complementary method to atmospheric metrology for assessing exposure to chemical agents. Biological monitoring assesses a worker's exposure by including all the routes by which a chemical penetrates the body (lung, skin, digestive tract). It is particularly worthwhile when a substance has a systemic effect, and:

- when routes other than inhalation contribute significantly to absorption,
- and/or when the pollutant has a cumulative effect,
- and/or when the working conditions (personal protection equipment, inter-individual differences in respiratory ventilation, etc.) determine large differences in internal dose that are not taken into account by atmospheric metrology.

With regard to prevention of chemical risk in the workplace, the French Labour Code provides for the use of biological monitoring of exposure and biological limit values.

OEL Committee definitions

Biomarker of exposure (BME): parent substance, or one of its metabolites, determined in a biological matrix, whose variation is associated with exposure to the agent targeted. Biomarkers of early and reversible effects are included in this definition when they can be specifically correlated to occupational exposure.

Biological limit value (BLV): this is the limit value for the relevant biomarkers.

Depending on the available data, the recommended biological limit values do not all have the same meaning:

- if the body of scientific evidence is sufficient to quantify a dose/response relationship with certainty, the biological limit values (BLVs) will be established on the basis of health data (no effect for threshold substances or risk levels for non-threshold carcinogens);
- in the absence of such data for substances with threshold effects, BLVs are calculated on the basis of the expected concentration of the biomarker of exposure (BME) when the worker is exposed to the 8-hour OEL. For carcinogens, in the absence of sufficient quantitative data, the biological limit value is calculated on the basis of another effect (pragmatic BLV). These last values do not guarantee the absence of health effects, but aim to limit exposure to these substances in the workplace.

Whenever possible, the OEL Committee also recommends biological reference values (BRVs). These correspond to concentrations found in a general population whose characteristics are similar to those of the French population (preferentially for biomarkers of exposure) or in a control population not occupationally exposed to the substance under study (preferentially for biomarkers of effects).

These BRVs cannot be considered to offer protection from the onset of health effects, but do allow a comparison with the concentrations of biomarkers assayed in exposed workers. These values are particularly useful in cases where it is not possible to establish a BLV.

Organisation of the expert appraisal

ANSES entrusted examination of this request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). The Agency also mandated the Working Group on biomarkers for this expert appraisal.

The methodological and scientific aspects of the work of this group were regularly submitted to the Expert Committee. The report produced by the working group takes account of observations and additional information provided by the Committee members.

This expert appraisal was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 “Quality in Expertise Activities”.

Preventing risks of conflicts of interest

ANSES analyses interests declared by the experts before they are appointed and throughout their work in order to prevent potential conflicts of interest in relation to the points addressed in expert appraisals.

The experts’ declarations of interests are made public on ANSES's website (www.anses.fr).

Description of the method

A rapporteur of the biomarkers WG was appointed by the Agency to produce a summary report on biomarkers of exposure and the recommendation of biological limit values (BLVs) and biological reference values for the BME(s) considered relevant. Two ANSES employees also contributed to this report.

The summary report on the BMEs for beryllium was based on bibliographical information taking into account the scientific literature published on this substance until 2015.

The bibliographical research was conducted in the following databases: Medline, Toxline, HSDB, ToxNet (CCRIS, GENE-TOX, IRIS), ScienceDirect. The rapporteur reassessed the original articles or reports cited as references whenever he considered it necessary, or whenever the Committee requested it.

The report, the summary and conclusions of the collective expert appraisal work were adopted by the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents on 11 October 2016.

The collective expert appraisal work and the summary report were submitted to public consultation from 31/03/2017 to 31/05/2017. The people or organizations who contributed to the public consultation are listed in appendix of the report (only available in French). The comments received were reviewed by the OEL Committee (term of office 2014-2017) who adopted this version on 03 July 2017.

Result of the collective expert appraisal

Introduction

The scientific articles selected for evaluating biomonitoring data on beryllium were identified using the following keywords: “beryllium”, “biomarker”, “biomonitoring”, “biological monitoring”, “urine”, “blood”, “occupational”, “beryllium lymphocyte proliferation test”, “analysis method”, while limiting the search to human data.

Toxicokinetics data

Although inhalation is the primary route of occupational exposure, no quantitative data on the absorption fraction were found in the literature consulted (ATSDR, 2002; IARC, 1993; IARC, 2012; US EPA, 1998).
However, some parameters such as particle size, shape and solubility influence pulmonary absorption. The solubility of particles of beryllium and its compounds is influenced by their own chemical composition and by the properties of the airway lining fluid. In animals, the pulmonary clearance of insoluble compounds seems slower than that of soluble compounds (see Section 2.4 of the French full report).

The finest beryllium particles can cross through the skin and mucous membranes and cause sensitisation, but the role of dermal exposure in the occurrence of lung damage is not clear.

The IRSST (2012a) reported that gastrointestinal absorption of beryllium is very low. The quantity absorbed, which depends on the dose and solubility of compounds, is limited by the formation of insoluble beryllium phosphates in the intestines. Following the inhalation of beryllium, part of the inhaled compound is transported to the digestive tract by the mucociliary system and/or by deglutition of the insoluble part deposited in the upper airways.

Absorbed beryllium is distributed through the body by plasma proteins in the form of colloidal phosphate. Beryllium can thus be adsorbed on plasma proteins (prealbumin or immunoglobins in humans) or bind to the lymphocyte membranes. In the short term, beryllium accumulates in the liver, particularly following significant exposure. In the long term, beryllium is primarily found in the lymph nodes and bones (beryllium's final storage site). The most soluble compounds are distributed in the liver, abdominal lymph nodes, spleen, heart, muscles, skin and kidneys. The least soluble compounds remain in the lungs and pulmonary lymph nodes.

Beryllium and its compounds are not metabolised. In the lungs, only soluble beryllium salts are partially converted into less soluble forms (IRSST, 2012a; INRS, 2006; IPCS, 2001) such as beryllium phosphate (ATSDR, 2002; OEHHA, 2003). Insoluble beryllium compounds are assimilated by phagocytes and can be ionised by myeloperoxidase (IPCS, 2001).

There are few data on the elimination of beryllium following exposure by inhalation in humans.

Experimental data in animals (rats and hamsters) show that the elimination of beryllium oxide is biphasic with a first slow phase (a few months) and a second even slower phase (several years) (Sanders et al. 1975; Rhoads and Sanders, 1985). This elimination also depends on the physical form of beryllium oxide, which influences its solubility (which decreases when the calcination temperature increases) according to the results of a study in dogs (Finch et al. 1990). The least soluble beryllium compounds are eliminated more slowly than soluble compounds.

Selection of biomarkers of exposure and effect

Biomarkers of exposure

For beryllium and its compounds, several BMEs have been identified in the literature, in particular blood beryllium and urinary beryllium.

Beryllium assays in lung tissue are also described but cannot be considered a suitable BME to be used for the biological monitoring of occupational exposure due to its invasive nature.

Beryllium in exhaled breath condensate (EBC) is a BME, but there are very few available data. In a recent "exposed-unexposed" study by Hulo et al. 2016, beryllium was measured in the EBC of workers in the aluminium sector (n=30). The authors reported that beryllium concentrations in EBC were correlated with the cumulative beryllium exposure index (CEI)[3]. Future studies are necessary to confirm these results. This biomarker will not be discussed here.

Regarding blood beryllium, no information was found in the literature establishing a link between blood concentrations of beryllium and atmospheric concentrations, let alone the occurrence of health effects. It was therefore not deemed relevant to recommend using this BME for the biological monitoring of occupational exposure to beryllium.

Several studies describe the relationship between urinary concentrations and atmospheric concentrations of beryllium. Furthermore, some field studies report only qualitative information. An increase in urinary concentrations of beryllium associated with an increase in its atmospheric concentration has been observed at the workplace. **Thus, at this time, urinary beryllium seems to be a suitable BME for the biological monitoring of occupational exposure to beryllium.**

Biomarkers of effect

Historically, demonstration of the health effects of beryllium has relied on performance of the beryllium lymphocyte proliferation test (Be-LPT).

The blood Be-LPT is an *in vitro* test used as an indicator of sensitisation to beryllium. Despite its potential advantages for the screening, diagnosis and prevention of berylliosis, the issue of this test's validity has been addressed by several authors. Results on the sensitivity of the Be-LPT are highly variable (ranging from 38% to 100%), and there are no data establishing its specificity. Its positive predictive value does not seem very high and could be estimated at approximately 50% for sensitisation to beryllium but 25% for chronic beryllium disease (CBD) (INSPQ, 2004b). Several studies have reported significant intra- and inter-laboratory variability for the test. Moreover, this type of test can produce false-negative results (Kreiss et al., 1997; Deubner et al. 2001b; Maier, 2001; Stange et al. 2004; Pott et al. 2005; Schuler et al. 2005). There are no sensitisation confirmation tests other than successive Be-LPTs or the conversion of sensitisation into CBD (INRS, 2005).

The BAL-Be-LPT is a lymphocyte proliferation test undertaken with bronchoalveolar lavage fluid. Given its invasive nature, this test is generally used only in patients who have had two positive blood Be-LPT results or who have abnormal chest x-rays. Combined with the implementation of other diagnostic techniques such as clinical evaluation, pulmonary function tests, scintigraphy or lung biopsy, BAL-Be-LPT is used to confirm the diagnosis of CBD (INSPQ, 2004b).

[3] Obtained by summing the results of the number of years in a task multiplied by average beryllium exposure for the task

In conclusion, given the lack of data establishing its specificity, the variability of results regarding its sensitivity, its low positive predictive value, and intra- and inter-laboratory variability, the blood Be-LPT cannot be recommended as a biomarker for the biological monitoring of occupational exposure to beryllium.

Information on biomarkers of exposure identified as relevant for the biomonitoring of exposed workers

NAME	URINARY BERYLLIUM
Concentrations found in exposed workers or volunteers	- Field studies: Stiefel et al. 1980 Atmospheric exposure <8 ng.m^{-3} (beryllium chloride dust) Urinary beryllium ≈ 3.6 ng.g^{-1} i.e. 3.6 µg.L^{-1} Wegner *et al.*, 2000 Atmospheric exposure <0.4-20 µg.m^{-3} Urinary beryllium: Mean 0.13 ± 0.12 µg.L^{-1} (Median 0.09 µg.L^{-1}) Start of shift Urinary beryllium Mean: 0.08 ± 0.07 µg.L^{-1} (Median 0.03 µg.L^{-1}) End of shift Apostoli et Schaller 2001 Steel plant exposure (furnace): 0.11 (Median) [0.03-0.18] µg.m^{-3} Urinary beryllium: Median (range): 0.09 µg.L^{-1} [<0.03-0.45] µg.L^{-1} (End of shift) Steel plant exposure (foundry): 0.025 (Median) [0.02-0.05] µg.m^{-3} Urinary beryllium: Median (range): 0.06 µg.L^{-1} [<0.03-0.40] µg.L^{-1} (End of shift) Cu-Be alloy exposure (foundry): 0.2 (Median) [0.1-0.9] µg.m^{-3} Urinary beryllium: Median (range): 0.125 µg.L^{-1} [<0.03-0.54] µg.L^{-1} (End of shift) Cu-Be alloy exposure (furnace): 0.4 (Median) [0.04-0.8] µg.m^{-3} Urinary beryllium: Median (range): 0.25 µg.L^{-1} [<0.03-0.49] µg.L^{-1} (End of shift)
Conversion factor	Beryllium molecular weight = 9.012 g.mol^{-1} Creatinine molecular weight = 113.12 g.mol^{-1} 1 µg.L^{-1} = 0.111 µmol.L^{-1} 1 µmol.L^{-1} = 9.012 µg.L^{-1} 1 µg.g^{-1} creatinine = 12.55 µmol.mol^{-1} creatinine
Concentrations in the general population[4]	Quebec (n=318 people from the general population): ○ Median: <0.05 µmol.L^{-1} i.e. 0.45 µg.L^{-1} (adjusted based on the urinary density of 1.024 g.mL^{-1} (INSPQ 2004a). USA ○ NHANES[5] (n=2848 people from the general population) P95[6] <0.072 µg.L^{-1}, from 2009 to 2010 (CDC 2015). SCOEL ○ BGV: 0.04 µg.L^{-1} (sampling time not critical) (draft document of 2016) Germany ○ The MAK Commission in Germany gives a concentration of 0.05 µg.L^{-1} as the BAR value[7] (DFG 2016). ○ 100% < Limit of quantification (LOQ) (LOQ = 0.009 µg.L^{-1}), P95 <0.009 µg.L^{-1}; (n=87) adults (Heitland et al. 2006a). ○ Mean <0.06 µg.L^{-1} (limit of detection), (n=34) (Wegner et al. 2000).

[4] Or failing that, in a non-occupationally exposed control population; 95th percentile, or failing that the median or the mean (number of people in the study if this information is available)

5 National Health and Nutrition Examination Survey

6 95th percentile

[7] Biologische Arbeitsstoff-Referenzwerte; Reference value in the working-age population not occupationally exposed.

	United Kingdom ○ Mean 0.0116 µg.L^{-1} (0.20 µmol.mol^{-1} creatinine), P90[8] 0.02 µg.L^{-1} (0.35 µmol.mol^{-1} creatinine), (n=62) (Morton et al. 2011) ○ P95 = 0.0116 µg.L^{-1}, (n= 132) (Morton et al. 2014) Italy: ○ Mean <0,03 µg.L^{-1} (limit of detection), (n=30) (Apostoli et Schaller 2001) ○ Mean 0.4 µg.L^{-1} (<0.02-0.82), (n = 579) (Minoia et al. 1990) Belgium: ○ P95 < 0.007 µg.L^{-1} (limit of detection), (n=1022 adults) (Hoet et al. 2013) Finland ○ URL (Upper Reference Limit) 15 nmol/l (0.13 µg.L^{-1}) (FIOH, 2015)	
Recommended limit values for exposed workers	USA – ACGIH (BEI)	Not determined (ND)
	Quebec – IRSST	ND (IRSST 2012b)
	Finland – FIOH	BAL: End of shift, end of week with no defined value
	Germany – DFG	Beryllium and its inorganic compounds: EKA[9]: The German commission recommends that urinary beryllium be measured at the end of the work shift, or after several work shifts in the event of long-term exposure, but does not establish a quantified vEKA value (for exposure to beryllium and its inorganic compounds) (DFG 2016). BAT: ND
	Other value(s) (Swiss, etc.)	France: ND (INRS 2003, revised in 2015). Switzerland (VBT): ND UK (BMGV): ND (HSE 2005) SCOEL: ND.

Study of the relationship between concentrations of BME and health effects

Although beryllium is considered a carcinogenic agent (Group 1) by the IARC (IARC, 2012), it was not possible to link this effect to biomarkers of exposure.

Atmospheric concentrations of beryllium are usually determined using a traditional occupational hygiene method, while beryllium testing in urine or blood is not commonly used for the evaluation of exposure to beryllium. This is because until around ten years ago, there were no analytical methods with sufficient sensitivity to detect beryllium in biological matrices.

According to the ATSDR (2002) report, the variability of the data on urinary excretion of beryllium makes it a little useful test. More recently, the IRSST (2012b) indicated that in the current state of knowledge, it is not possible to clearly establish relationships between urine or

[8] *P90: 90th percentile*

[9] EKA = Expositionsäquivalente für krebserzeugende Arbeitsstoffe (Exposure equivalents for carcinogenic substances at the workplace)

blood concentrations of beryllium and atmospheric levels of beryllium or health effects. The studies undertaken over the last fifteen years have primarily used the Be-LPT to assess health effects and have established relationships between this biomarker of effect and environmental exposure.

Study of correlations between urinary beryllium concentrations and atmospheric beryllium concentrations

n	Ambient atmospheric concentration ($\mu g.m^{-3}$)	Urinary concentration (LOD)	Correlation equation	Urinary beryllium concentration for exposure to the 8h-OEL (10 $ng.m^{-3}$)	Reference
8	< 8 $ng.m^{-3}$ (beryllium chloride dust)	3.6 $ng.g^{-1}$ i.e. 3.6 $\mu g.L^{-1}$ (8 subjects)[10] i.e. 3.6 $\mu g.L^{-1}$ (LOD: 0.05 $\mu g.L^{-1}$)	- Graph characterising the relationship between concentrations of beryllium in air and in urine prepared by ATSDR, 2002. No value reported $y = 0.3988 x + 0.8318$ $R^2 = 0.9859$	~ 5 $ng.g^{-1}$	Stiefel et al. (1980)
	Not reported (NR) (beryllium dust)	NR	$y = 0.0943 x + 0.58$ $R^2 = 0.9417$	~ 1.5 $ng.g^{-1}$	Zorn et al. (1986)
24	**Median** [min – max] **0.11** [0.03-0.18] and **0.025** [0.02-0.05] $\mu g.m^{-3}$ in steel plants	**Median** [min – max] **0.09** [<0.03-0.45] and **0.06** [<0.03-0.40] $\mu g.m^{-3}$ in steel plants (end of shift) (14 and 10 subjects)	$y = 0.000513 x + 0.036$ $R^2 = 0.991$[11]	~ 0.04 $ng.g^{-1}$	Apostoli et Schaller 2001
21	**Median** [min – max] **0.4** [0.04-0.8] and **0.2** [0.1-0.9] $\mu g.m^{-3}$ in beryllium and copper alloy plants (Cu-Be alloy)	**Median** [min – max] **0.25** [<0.03-0.49] **0.125** [<0.03-0.54] $\mu g.L^{-1}$ in beryllium and copper alloy plants (end of shift) (12 and 9 subjects) (LOD: 0.03 $\mu g.L^{-1}$)			

[10] 8 subjects exposed to quantities below 8 ng $Be.m^{-3}$ of $BeCl_2$, for 4-6 hours per day for 10 days

[11] From the median values for 4 work zones

27	<0.4-20 µg.m^{-3} for >4 hours/day/week, long-term exposure (beryllium)	**Median** Mean Standard deviation **0.09** 0.13±0.12 µg.L^{-1} (start of shift) (27 subjects) **0.03** 0.08±0.07 µg.L^{-1} (end of shift) (27 subjects) (LOD: 0.06 µg.L^{-1})	-	-	Wegner et al., 2000

Establishment of BLVs and choice of biological reference values

The collective expert appraisal report of the OEL Committee on beryllium and its compounds proposes a pragmatic 8h-OEL of 0.01 µg.m^{-3}. This pragmatic OEL is based on an effect other than lung cancer, CBD (since the scientific data currently available on the carcinogenicity of beryllium and its compounds were insufficient to undertake a quantitative health risk assessment).

No occupational studies in humans have found a relationship between urinary concentrations of beryllium and the occurrence of health effects (in particular carcinogenic effects and CBD).

Urinary beryllium

Relationships have been observed between urinary beryllium concentrations and atmospheric beryllium concentrations. However, due to their limited number and significant discrepancies between studies, they cannot be used to establish a biological limit value. Future studies are necessary to better define these relationships.

Moreover, no studies since 2001 have assessed the relationship between atmospheric concentrations and urinary concentrations of beryllium in the workplace. Although methods for the detection of urinary beryllium have improved, it is not currently possible to recommend a biological limit value due to the lack of epidemiological data.

Therefore, since a biological limit value cannot be recommended, a biological reference value can be proposed.

Proposed biological reference values

There are no French data reporting urinary levels of beryllium for large numbers of people from the general population[12].

In the Belgian study by Hoet et al. 2013 undertaken with 1022 subjects, the 95th percentile of the distribution of urinary concentrations for the subjects was below the limit of detection of 7 ng.L^{-1}.

Recent data have reported lower limits of detection. A study by Devoy et al. 2013 describes an assay method (analysis by inductively coupled plasma mass spectrometry) achieving a limit of detection of 0.6 ng.L^{-1}. However, the data in this article do not provide information about urinary beryllium values in the general population.

Using the same assay method, Morton et al. 2014 undertook a study with 132 adult subjects living in the United Kingdom who were not occupationally exposed to beryllium. The authors reported a limit of quantification of 0.6 ng.L^{-1} and estimated a 95th percentile of 11.6 ng.L^{-1}. The usefulness of this study is limited by the fact that the authors did not consider the sample to be representative of the general population.

The OEL Committee recommends as BRV a value below 7 ng.L^{-1} , the value of 7 ng.L^{-1} corresponding to the limit of detection of the analytical method used in the study of Hoet et al 2013, only study considered as representative for the French general population.

Conclusions of the collective expert appraisal

The biological values recommended for monitoring exposure to beryllium and its compounds are:

Urinary beryllium:

BLV based on a health effect	None
BLV based on exposure to the 8h-OEL	None
Biological reference value	Below 7 ng.L^{-1}

Sampling method and factors that may affect the interpretation of results

Morton et al. (2011) observed that urinary concentrations of beryllium in urine samples taken at the end of the shift and end of the week from workers in an aluminium foundry were 47% higher than at the beginning of the week, with mean values increasing from 4.1 ng.L^{-1} to 6.1 ng.L^{-1}.

Due to the uncertainty of the toxicokinetic data, no sampling time can be recommended. However, the FIOH and DFG recommend sampling at the end of the shift and end of the week.

To avoid contamination, sampling outside of the workplace, after taking a shower or washing hands and the urinary meatus and changing clothes, is generally recommended (FIOH, 2015; INRS 2003, rev. 2015).

According to good practices for the storage of biological samples, samples should be refrigerated.

Smoking increases urinary concentrations of beryllium (IRSST 2012b; INRS 2003, rev. 2015). A study by Morton et al. (2011) showed that workers who smoked had levels of urinary beryllium

[12] No results regarding BME assays for beryllium in French national surveys (ENNS and Esteban).

that were 37% higher than those who did not smoke. The authors noted that this effect could be due to the hand-mouth transfer of beryllium or the fact that cigarettes may contain beryllium.

As reported by ATSDR (2002), Reeves et al. (1986) measured 0.47-0.74 µg of beryllium per cigarette in three packs of cigarettes of different German brands and 2-10% beryllium in cigarette smoke.

Biometrology

URINARY BERYLLIUM					
Existence of an interlaboratory quality control program	University Erlangen-Nuremberg (Germany) : G-EQUAS				
Analytical technique	Limit of detection Limit of quantification	Fidelity	Precision	Reference standard	References
Inductively coupled plasma mass spectrometry (ICP-MS)	0.007 µg.L^{-1} 0.05 µg.L^{-1}	C_v<10%	Not reported		UCL, 2013
	0.002 µg.L^{-1} 0.006 µg.L^{-1}			Yttrium and germanium	Morton et al. 2011
	0.0006 µg.L^{-1}	Not reported		germanium	Morton et al. 2014*
	0.009				Heitland et al. 2006a
	0.03				Apostoli et Schaller 2001

C_v : coefficient of variation

* Participation in interlaboratory quality control program (G-EQUAS)

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