Collective expert appraisal: summary of discussion with conclusions

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

Evaluation of biomarkers and recommendations for biological limit values and biological reference values for cadmium and its compounds

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 (biomarker WG).

Presentation of the issue

AFSSET, which became ANSES in July 2010, received a solicited request on 12 June 2007 from the French Directorate General for Labour to conduct the scientific expert appraisal work required for setting occupational exposure limit values (OELVs) for cadmium and its compounds. Under a 1992 Circular[1], France has an indicative eight-hour occupational exposure limit value (8h-OELV) for cadmium and its compounds of 0.05 $mg.m^{-3}$. Note that for cadmium oxide this circular sets an indicative 15-minute exposure limit of 0.05 $mg.m^{-3}$ of cadmium but no 8h-OELV.

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

Scientific background

Biological monitoring of exposure in workplaces 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 (wearing respiratory protection, inter-individual differences in respiratory ventilation, etc.) determine large differences in internal dose that are not taken into account by atmospheric metrology.

[1] Circular of 7 July 1992 amending and supplementing the Circular of 19 July 1982 as amended, on the acceptable values for *concentrations* of certain *hazardous substances* in workplace *atmospheres*

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: it is the 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 scope:

- 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 (critical dose for threshold effect substances or risk levels for non-threshold carcinogens);
- in the absence of such data for substances with threshold effects, the BLV will be calculated on the basis of the expected concentration of the biomarker of exposure when the worker is exposed to the 8h-OELV. For carcinogens, in the absence of sufficient quantitative data, the biological limit value is calculated on the basis of another type of effect (pragmatic BLV). These last values do not guarantee the absence of health effects, but aim to limit exposure to these substances in workplaces.

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 failing that, 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 of particular interest 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 (WG) on biomarkers for this expert appraisal.

The methodological and scientific aspects of this group's work were regularly submitted to the OEL 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 from the biomarker WG was mandated by the Agency to produce a summary report on biomarkers of exposure and the recommendation of biological limit values (BLVs) and biological reference values (BRVs) for the biomarkers(s) considered as relevant. An ANSES officer also contributed to this report.

The summary report on the biomarkers for cadmium results from bibliographical information taking into account the scientific literature published on this substance until 2012. 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 collective expert appraisal work and its conclusions and recommendations were adopted on 5 april 2013 by the OEL Committee (term of office 2010-2013).

The collective expert appraisal work and the summary report were submitted to public consultation from 10/12/2012 to 10/02/2014. The list of persons or organizations who contributed to the public consultation are listed in appendix 4 (French report). The comments received were reviewed by the OEL Committee (term of office 2014-2016) who adopted this version on 12 mai 2014.

Result of the collective expert appraisal

Introduction

The scientific articles selected for evaluating biomonitoring data on cadmium were identified from the following keywords: "cadmium", "biomarker", "biomonitoring", "biological monitoring" "urine", "blood" and "occupational", while limiting the search to human data.

Toxicokinetics data

Many elements of toxicokinetics reported here are taken from the report of the ATSDR (2012).

Inhalation is the primary route of exposure to cadmium (dust, smoke) for workers. In humans, the rate of pulmonary absorption varies from 40 to 60% and depends on the compound's physico-chemical properties (Prozialeck and Edwards, 2010). Cadmium can also enter the body by ingestion, and absorption by this route is not negligible (5% of the amount ingested). Conversely, percutaneous absorption of cadmium is not significant (0.5%) and has only been observed when the substance has been in contact with the skin for several hours.

Cadmium is distributed around the body by blood circulation. Cadmium is eliminated from blood with a half-life of about 80 to 100 days. In the body, cadmium binds to albumin, erythrocytes or metallothionein (MT) before being distributed to the tissues. Cadmium accumulates mainly in the kidneys (30% of the cadmium body burden) and liver, and to a lesser extent in the bones, muscles and skin. Because of its long half-lives (4 to 19 years in the liver and 10 to 20 years in

the kidney), the body burden of cadmium increases gradually with age. It is also released very slowly, resulting in significant blood concentrations long after exposure has ceased. Despite this, very few field studies have been conducted to describe the elimination kinetics of blood cadmium after cessation of exposure.

In the kidneys, because of the small size of the cadmium-MT complex the cadmium may be effectively reabsorbed from the glomeruli into the renal tubules. As it is absorbed, cadmium continues to accumulate (in non-toxic form) in the kidneys until renal MT is saturated (OEHHA, 2006).

In the absence of kidney damage, the cadmium excreted by the kidneys is only a small portion of the total amount of cadmium accumulated in the body. The cadmium that is filtered by the glomerulus is almost entirely reabsorbed by the proximal tubule epithelial cells; little or no cadmium is then excreted in the urine and its half-life may be between 10 and 20 years, or even 40 years according to some authors. Less than 1% of cadmium is excreted in the faeces.

Selection of biomarkers of exposure

The presence of cadmium and the cadmium-MT complex in urine is generally the result of natural renewal of proximal tubule epithelial cells. As described above, cadmium is not excreted to a great extent in the urine. It is only once the cadmium body burden becomes high enough, or when kidney damage begins to manifest itself, that the urinary excretion of cadmium increases significantly (Prozialeck and Edwards, 2010). However, in general, there is a relationship between the level of cadmium exposure (from data mainly on ingestion) and urinary cadmium concentrations (Kido *et al.*, 2004; Kobayashi *et al.*, 2005; Shimbo *et al.*, 2000).

Blood cadmium is a biomarker of recent exposure to cadmium. It also partially reflects the accumulated body burden. However, when exposure levels change, it is the indicator that responds the fastest. As such, it partly reflects the rate of change in the cadmium body burden and can be used to verify that exposure to cadmium is adequately controlled in the short term. It can therefore be used as a biomarker of exposure as part of medical supervision for controlling exposure (taking into account all sources of exposure, including oral, which is often non-negligible in the case of metals).

The numerous publications analysed show that there is a correlation between urinary cadmium and increased urinary concentrations of some biomarkers of early stage of impairment of renal function.

Urinary cadmium was therefore selected as a biomarker of chronic exposure in order to prevent cadmium-induced tubular toxicity.

Selection of biomarkers of effect

Cadmium's nephrotoxicity has long been known and is generally used as the basis for determining biological limit values, because it is usually the best characterised effect resulting from chronic exposure to cadmium. A recent review by Prozialeck and Edwards (2010) described the mechanisms of cadmium's nephrotoxicity and the associated biomarkers reported in the literature. During chronic exposure to cadmium, the kidney is indeed a target organ of cadmium toxicity.

β2-microglobulin (β2M) is a widely studied protein for relating urinary concentrations of cadmium to the tubular cytotoxicity of cadmium in the absence of other renal diseases. However, its lack of stability in acidic medium could result in false results and underestimation of the actual excretion. Retinol binding protein (RBP) is increasingly studied because its stability in urine makes it an easier biomarker to use than β2M.

The literature describes many other biomarkers providing an early indication of tubular cytotoxicity that may be related to cadmium exposure (N-acetyl-β-D-glucosaminidase (NAG), α-glutathione S-transferase, 6-keto prostaglandin F1, sialic acid, transferrin and more recently Kim-1 protein being studied in rats). The data that can be used to relate urinary concentrations of cadmium to urinary concentrations of these markers are limited (reproducibility of assays, existence of field studies, etc.). As a result, only β2M and RBP were selected as biomarkers of effect. The data reported in the literature on urinary NAG are presented in Annex of the expert report.

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

Name	**URINARY CADMIUM**	
Other substances giving rise to this biomarker	None	
Concentrations found in exposed workers or volunteers	- Field studies: 1 to 200 µg.g^{-1} of creatinine (range) - Studies in volunteers: NS	
Conversion factor	Molecular weight: 112.41 1 µg.L^{-1} = 0.009 µmol.L^{-1} 1 µmol.L^{-1} = 112.41 µg.L^{-1} 1 µg.g^{-1} creat = 1.006 µmol.mol^{-1} creatinine 1 µmol.mol^{-1} creat = 0.993 µg.g^{-1} creat	
Concentrations in the general population	USA-NHANES (2543 people from the general population) - 95th percentile: 1.01 µg.g^{-1} creat (20 years and over) (CDC, 2012) Germany-GerES (4822 people from the general population) - 95th percentile: 0.91 µg.g^{-1} creat (smokers); 0.61 µg.g^{-1} creat (non-smokers) (Becker *et al.*, 2003) The German MAK Commission indicates a concentration of 0.8 µg.L^{-1} as the 95th percentile of the distribution of urinary concentrations in the general non-smoker population, not exposed occupationally and of working age (BAR[2] value) (Deutsche Forschungsgemeinschaft, 2012) France-ENNS (1939 people from the general population) - 95th percentile: 0.79 µg.g^{-1} creat (non-smokers); 1.00 µg.g^{-1} creat (smokers) (Fréry *et al.*, 2011)	
Recommended limit values for exposed workers (INRS, 2012)	USA - ACGIH (BEI)	5 µg.g^{-1} creatinine (ACGIH, 2001)
	USA - OSHA	3 µg.g^{-1} creatinine (OSHA, 2004)
	Quebec - IRSST (IBE)	5 µg.g^{-1} creatinine (IRSST, 2012)
	Finland - FIOH (BAL)	4.5 µg.L^{-1} (FIOH, 2010)

Name	**BLOOD CADMIUM**
Other substances giving rise to these biomarkers	None
Concentrations found in exposed workers or volunteers	- Field studies: 1 to 170 µg.L^{-1} (range) - Studies in volunteers: NS
Conversion factor	1 µg.L^{-1} = 0.009 µmol.L^{-1} 1 µmol.L^{-1} = 112.41 µg.L^{-1}
Concentrations in the general population	USA-NHANES (2543 people from the general population) - 95th percentile: 1.55 µg.L^{-1} (20 years and over) (CDC, 2012)

[2] Biologische Arbeitsstoff-Referenzwerte

	Germany-GerES (1998, 4822 people from the general population) - 95th percentile: 3.32 µg.L-1 (smokers); 0.71 µg.L-1 (non-smokers) (Becker *et al.*, 2002) The German MAK Commission indicates a concentration of 1 µg.L-1 as the 95th percentile of the distribution of blood concentrations in the general non-smoker population, not exposed occupationally and of working age (BAR value) (Deutsche Forschungsgemeinschaft, 2012)	
Recommended limit values for exposed workers (INRS, 2012)	USA - ACGIH (BEI)	5 µg.L-1 (ACGIH, 2001)
	USA - OSHA	5 µg.L-1 (OSHA, 2004)
	Quebec - IRSST (IBE)	5 µg.L-1 (IRSST, 2012)
	Finland - FIOH (BAL)	5.6 µg.L-1 (FIOH, 2010)

Information on biomarkers of effects identified as relevant for the biological monitoring of exposed workers

Name	**URINARY ß2-MICROGLOBULIN**	
Concentrations found in exposed workers or volunteers	- Field studies: on average from 45 to 300 µg.g-1 creatinine (from 4 to 136,000 µg.g-1 creatinine for the range) - Studies in volunteers: NS	
Conversion factor	MW: 11.8 kDa	
Concentrations in the general population	Belgium-Cadmibel (1699 people living in areas slightly and heavily polluted with cadmium) - 95th percentile: 283 µg.24h-1 (Buchet *et al.*, 1990) Belgium-PheeCad (593 people from the Cadmibel cohort) - 95th percentile: 250 µg.g-1 creat (2.36 nmol.mmol-1 creat) (Hotz *et al.*, 1999)	
Concentration found in non-exposed workers	Chaumont *et al.* (2010): 95th percentile = 276 µg.g-1 creat (n = 126) Roels *et al.* (1993): 95th percentile = 324 µg.L-1 (n = 50)	
Recommended limit values for exposed workers	USA – ACGIH	Not specified
	USA - OSHA	300 µg.g-1 cr (OSHA, 2004)
	Quebec – IRSST	Not specified
	Finland – FIOH	Not specified
	Germany – DFG	Not specified

Name	**URINARY RETINOL BINDING PROTEIN**
Concentrations found in exposed workers or volunteers	- Field studies: on average from 45 to 125 µg.g-1 creatinine (from 7 to 73,000 µg.g-1 creatinine for extreme values) - Studies in volunteers: NS
Conversion factor	MW: 21.4 kDa
Concentrations in the general population	Belgium-Cadmibel (1985-1989, 1699 people living in areas slightly and heavily polluted with cadmium) - 95th percentile: 338 µg.24h-1 (Buchet *et al.*, 1990) Belgium-PheeCad (1990-1995, 593 people from the Cadmibel cohort) - 95th percentile: 338 µg.24h-1 (Hotz *et al.*, 1999)
Concentration found in non-exposed workers	Chaumont *et al.* (2010): 95th percentile = 256 µg.g-1 creat (n = 177) Roels *et al.* (1993): 95th percentile = 190 µg.g-1 creat (n = 50)
Recommended limit values for exposed workers	None

Study of the relationship between concentrations of biomarkers of exposure and health effects

Although cadmium is regarded as a carcinogen according to IARC (1993), it was not possible to link this effect to the concentrations of biomarkers of exposure.

Renal toxicity

Until the 2000s, most field studies focused on reporting correlations between urinary cadmium concentrations and urinary concentrations of markers of tubular toxicity (β2M and RBP, or even NAG). The reference values for these tubular toxicity markers generally corresponded to usual laboratory values, at the 95th percentile of the distribution of concentrations in unexposed controls or exposed professionals. The authors then inferred the urinary concentrations of cadmium from the regression equations. Subsequently, authors have preferred to use the benchmark dose approach. This approach consists in identifying the cadmium concentration above which 5 to 10% of workers exposed to cadmium (in the study considered) have "abnormal"[3] urinary concentrations of tubular toxicity markers.

[3] 95th percentile of the concentration of these markers in a group of non-exposed controls as the "normal" reference concentration. Above this, concentrations are then regarded as "abnormal".

Table 1: Summary of results from studies reporting a dose-response relationship between the tubular function parameters and urinary concentrations of cadmium

Mode of evaluation	n	Critical value	U-Cd calculated $\mu g.g^{-1}$ creat	Reference
Urinary β2-microglobulin (β2M)				
Regression log[Uβ2M] ($mg.g^{-1}$ creat) = 1.4 log[UCd] ($\mu g.g^{-1}$ creat] + log(0.01) (determined graphically) r = 0.48	58	0.3 $mg.g^{-1}$ creat [a] (300 $\mu g.g^{-1}$ creat)	11	Bernard *et al.*, 1990
Regression [Uβ2M] ($mg.L^{-1}$) = 0.7 log[UCd] ($nmol.L^{-1}$) + 1.1 r = 0.42	34			Verschoor *et al.*, 1987
10 % probability of presenting an abnormal proteinuria value	90	324 $\mu g.L^{-1}$ [b]	11.5	Lauwerys *et al.*, 1994
All workers	599	276 $\mu g.g^{-1}$ creat [c]		Chaumont *et al.*, 2011
BMD_5 (L_{95})			9.6 (5.9)	
Excluding smokers				
BMD_5 (L_{95})			12.2 (5.5)	
Logarithmic regression log[Uβ2M] ($mg.mmol^{-1}$ creat) = 0.08 [UCd] ($nmol.mmol^{-1}$ creat) + log(0.008) r = NS but significant	60	0.034 $mg.mmol^{-1}$ creat [d] (300 $\mu g.g^{-1}$ creat)	7.8	Elinder *et al.*, 1985
Caucasian population	NS	300 $\mu g.g^{-1}$ creat[e]		EFSA, 2009
BMD_{10} (L_{90})			1.35 (1.15)	
BMD_5 (L_{95})			1.2 (1)	
All the population				
BMD_{10} (L_{90})			1.2 (0.6)	
BMD_5 (L_{95})			0.3 (0.2)	
Workers < 60 years old	561	34 $\mu g.mmol^{-1}$ creat [f] (300 $\mu g.g^{-1}$ creat)		Jarup and Elinder, 1994
BMD_{10}			5	
Workers > 60 years old				
BMD_{10}			1.5	
Urinary retinol binding protein (RBP)				
10 % probability of presenting an abnormal proteinuria value	90	190 $\mu g.g^{-1}$ creat [b]	10.4	Lauwerys *et al.*, 1994
All workers	599	256 $\mu g.g^{-1}$ creat [c]		Chaumont *et al.*, 2011
BMD_5 (L_{95})			5.1 (3)	
Excluding smokers				
BMD_5 (L_{95})			12.6 (6.6)	

NS: not specified; U-Cd: urinary cadmium
[a] *Laboratory reference value*
[b] *95th percentile of the distribution in a population of non-occupationally exposed controls (n = 50) in another study (Roels, 1993)*
[c] *95th percentile of the distribution of concentrations in workers regarded as "subject to low exposure, with urinary Cd concentrations < 1µg/g-1 cr" (n = 126 for ß2M and 177 for RBP).*
[d] *95th percentile of the distribution of concentrations in the population of non-occupationally exposed controls from another study (Buchet et al., 1980)*
[e] *Cut-off value*
[f] *According to the authors, value commonly used in the studies*

Bone toxicity

Most studies dealing with the osteotoxic potential of cadmium have been conducted in the general population. These studies have established a causal link between cadmium exposure and an increased risk of fracture or osteoporosis, and are reported in the Annex of the report. Only two studies, by the same team, were carried out on the bone toxicity of cadmium in an occupational environment (Alfven *et al.*, 2000; Alfven *et al.*, 2004). This lack of data makes it impossible to quantify with certainty the relationship between the concentrations of biomarkers of exposure and bone toxicity markers or clinical factors (osteoporosis, fractures) specifically for the population of interest (workers).

Study of the relationship between concentrations of biomarkers of exposure and cadmium exposure

Toxicity of cadmium has been studied in relation to urinary concentrations of cadmium. It therefore seems possible to identify a critical concentration for urinary cadmium, although not for blood cadmium. However, blood concentrations of cadmium can be linked to urine concentrations.

Nordberg and Kjellström (1979) published a multi-compartment toxicokinenic model that simulates the absorption, accumulation and excretion of cadmium. It includes the modelling of the transfer of cadmium from the respiratory tract into the blood and target organs. Some studies also report correlations calculated from field data (Table 2).

Table 2: Summary of correlation equations reported in field studies

Verschoor *et al.* (1987)	Average age (years)	Average duration of employment (years)	U-Cd (µg.L^{-1})	Bl-Cd (µg.L^{-1})
			Geometric mean (min – max)	
Factory 1	39	8.7	2.6 (1.2 - 5.4)	1.26 (0.37 - 4.3)
Factory 2	41	10.3	12.5 (3.4 - 46)	5.8 (2.1 - 14.7)
Log [Bl-Cd] (nmol.L^{-1}) = log [U-Cd] (nmol.L^{-1}) - 0.3				r = 0.76; n = 34
Jakubowski *et al.* (1987)	Average age (years)	Air-Cd µg.m^{-3}	U-Cd (µg.g^{-1} creat)	Bl-Cd (µg.L^{-1})
			Geometric mean (min - max)	
Chemistry		570 (10 - 2540)	27 (4 - 200)	40 (10 - 164)
Production	41	190 (10 - 4300)	36 (11 - 120)	49 (11 - 120)
Assembly		60 (20 - 890)	10 (0 - 110)	18 (5 - 110)
Log [Bl-Cd] (µg.L^{-1}) = 0.7 log [UCd] (µg.g^{-1} cr) + 1.2				r = 0.85; n = 100
Kawada *et al.* (1990)	Average age (years)	Average duration of employment (years)	U-Cd (µg.g^{-1} creat)	Bl-Cd (µg.L^{-1})
			Arithmetic mean (± standard deviation)	
Production	30.8	10.4	0.87 (± 1.67)	1.71 (± 1.29)
Production	33.1	11.3	0.86 (± 2.29)	1.21 (± 1.76)
Control	37.4	14.6	2.00 (± 3.40)	2.44 (± 2.32)
Log [Bl-Cd] (µg.L^{-1}) = 0.4 log [UCd] (µg.g^{-1} cr) +0.1 (with non-exposed subjects)				r = 0.4; n = 79
Borjesson *et al.* (1997)	Average age (years)	U-Cd (µg.g^{-1} creat)	Bl-Cd (µg.L^{-1})	
		Median (min - max)		
Nickel-cadmium batteries	64	3.2 (0.5 - 10.7)	3.9 (0.6 - 11.2)	
[Bl-Cd] (µg.L^{-1}) = [U-Cd] (µg.g^{-1} cr) + 0.4 (excluding retired workers)				r = 0.51; n = 15

Zwennis and Franssen (1992)	U-Cd (µg.g^{-1} creat) Median (min - max)	Bl-Cd (µg.L^{-1})
Recycling (metal)	-	0.5 (0.1 - 3.9)
Soil depollution	0.5 (0.1 - 0.8)	0.4 (0 - 2.9)
Welding	0.7 (0.1 - 1.9)	0.5 (0.3 - 2.2)
Recycling (cables)	0.5 (0.3 - 2.5)	0.8 (0 - 2.2)
Printing	0.7 (0 - 2.5)	1.1 (0.2 - 3.4)
Enamelling	1.5 (0.2 - 2.9)	-
Pigmented plastic	1.0 (0.1 - 3.4)	2.0 (0.1 - 6.0)
Glass	0.7 (0 - 3.7)	1.4 (0.1 - 1.9)
Incineration	1.2 (0.1 - 3.9)	0.5 (0 - 4.2)
Pigment	0.5 (0 - 4.9)	1.6 (0 - 4.3)
Cathode tubes	0.4 (0 - 5.5)	0.5 (0.1 - 1.9)
Paint	0.5 (0 - 6.5)	1.5 (0.6 - 3.8)
Gilding	0.8 (0 - 7.8)	1.5 (0 - 11.9)
Cd stabilisers	1.1 (0.1 - 9.8)	1.6 (0 - 9.8)
Enamelling	1.1 (0 - 17.9)	0.9 (0.1 - 7.7)
Welding	2.3 (0.2 - 60.4)	12.9 (2.7 - 48.4)
	[Bl-Cd] (µg.L^{-1}) = 0.6 [U-Cd] (µg.g^{-1} cr) +0.8	r = 0.84; n = 598

Bl-Cd: blood cadmium; air-Cd: airborne cadmium

Establishment of BLVs and choice of biological reference values

Urinary cadmium

The literature data established a potential causal link between exposure to cadmium and long-term bone toxicity, but were unable to identify with certainty a critical concentration for either blood or urinary cadmium for the population of interest (exposed workers). In fact, the only studies available on the bone toxicity of cadmium in the workplace are the two by Alfven *et al.*, which cannot be used to quantify the dose-response relationship. The decision was instead taken to establish a BLV for urinary cadmium using data on cadmium's renal toxicity, which are much more abundant in the literature.

It is accepted in the different studies that an increase in urinary concentrations of β2M or RBP above 1000 µg.g^{-1} creatinine is related to irreversible tubular cytotoxicity. It is also recognised that urinary concentration above 300 µg.g^{-1} creatinine is related to the first signs of tubular cytotoxicity that should be prevented (Prozialeck and Edwards, 2010; Hotz *et al.*, 1999; Bernard, 2008; Jarup *et al.*, 1998). This is why a urinary concentration for RBP or β2M of 300 µg.g^{-1} creatinine is often used as the threshold for cadmium toxicity.

Recent studies propose benchmark doses based on large samples and are therefore more relevant for determining reference values. The three studies proposing benchmark doses are those by Jarup and Elinder (1994), EFSA (2009) and Chaumont *et al.* (2011). It was not considered appropriate to use the results presented in the EFSA report since the target population was the general population, and the studied data came from a very heterogeneous population of which only 1% were workers.

The BMD_{10} calculated by Jarup and Elinder (1994) corresponding to a critical concentration of β2M of 300 µg.g^{-1} creatinine is 5 µg.g^{-1} creatinine in workers over 60 years of age. It should be noted that the confidence interval at 90 or 95% of this value is not specified in the publication.

The recent study by Chaumont *et al.* (2011) is the only one to provide a robust calculation of a benchmark dose (and the calculation of uncertainty) in a large population (n = 599) of French, European and American workers, using the response of the β2M and RBP biomarkers. This

study has certain methodological advantages, such as the exclusion of smokers from the studied group (influence of smoking).

The lowest concentration (5.5 µg.g^{-1}) rounded to the lower value was chosen and a BLV equal to 5 µg.g^{-1} creatinine was proposed on the basis of an increase in the prevalence of abnormal urinary concentrations of RBP or β2M.

As the average age of workers in the study by Chaumont *et al.* (2011) was 45 years (± 10 years), using this study to establish a BLV could mean that this value offers less protection to young workers. Ideally, it would be prudent to apply a safety factor. The scientific literature does not confirm this assumption with certainty, nor is it possible to assess the value to be assigned to such a factor. Jarup and Elinder (1994) calculate a BMD_{10} at 1.5 µg.g^{-1} creatinine in workers over 60 years of age. It should be noted that this study's methodology was criticised by Bernard and Lauwerys (1997) who indicate that the urinary β2M threshold values used were not relevant for people over the age of 60 (changes in renal physiology). The scientific literature does not provide adequate justification for this assumption, nor any way of assessing such a factor. Nevertheless, given the cumulative nature of cadmium in the body due to its very long half-life, it seems relevant to combine verification of compliance with the BLV and additional monitoring to ensure that the integrity of renal function is preserved. This monitoring should be initiated at a lower urinary concentration of cadmium than the BLV.

Despite the methodological uncertainties of the study by Jarup and Elinder (1994), the experts proposed to use it to identify a threshold value for the setting of additional occupational medicine measures. Accordingly, the value of 1.5 µg.g^{-1} creatinine identified in workers over 60 years of age, rounded to 2 µg.g^{-1} creatinine of urinary cadmium, is recommended as the threshold for initiating monitoring of renal function biomarkers such as β2M and RBP (in urine). Its purpose is to take into account the risk assessment parameters that cannot be fully integrated into the proposed BLV; these mainly include the age of the workers, the highly cumulative nature of the cadmium renal burden due to its very long half-life, and smoking.

The French ENNS study, in the general population (2000 people, differentiated according to smoking status), can be used to define a biological reference value (Fréry *et al.*, 2009). The BRVs selected for urinary cadmium are 0.80 µg.g^{-1} creatinine in non-smokers and 1.00 µg.g^{-1} creatinine in smokers.

Blood cadmium

Jakubowski *et al.* (1987) studied the relationship between blood and urinary cadmium, on the one hand, and markers of renal toxicity, i.e. RBP and β2M, on the other hand. The study was undertaken in 102 exposed workers and 85 controls. They reported a probability of nephrotoxicity markers increasing in 10% of the subjects when the cumulative exposure index exceeded 300 to 400 µg.year.L^{-1}. For a work life of 30 to 40 years, this represents a blood cadmium concentration of 10 µg.L^{-1}. Note however that this is not a no-effect concentration but rather a value similar to a BMD_{10}. Moreover, the mean (geometric) concentration found in the controls was high at 4.8 µg.L^{-1} whereas the corresponding values in the exposed population ranged from 7.5 to 49 µg.L^{-1} depending on the industrial sector.

Chia *et al.* (1989) studied certain parameters of renal dysfunction in a group of 65 women exposed to cadmium compared to nine controls. The exposed women had a mean concentration of blood cadmium (range) of 7.6 (1 - 26) µg.L^{-1} whereas the corresponding values for the controls were 0.8 (0.2 – 1.4) µg.L^{-1}. For urinary cadmium, the concentrations were 1.73 (0.05 – 21) µg.L^{-1} in the exposed population and 0.09 (0.02 – 0.2) µg.L^{-1} in the controls. The authors noted a correlation between blood cadmium and NAG excretion on the one hand and β2M excretion on the other hand. Urinary NAG excretion increased in subjects from 1 µg.L^{-1} of

blood cadmium. It then reached a plateau and rose again from 10 µg.L^{-1} of blood cadmium. As for β2M excretion, it only increased for blood cadmium concentrations above 10 µg.L^{-1}.

Bernard *et al.* (1990) examined several parameters of nephrotoxicity in 58 workers in a non-ferrous smelter compared to the same number of controls. The geometric means (range) for cadmium blood concentrations were respectively 0.89 (0.3 – 2.9) and 6.54 (1.6 – 51) µg.L^{-1} in the control workers and exposed workers. When grouping together all of these subjects to study the prevalence of abnormal values for nephrotoxicity parameters as a function of blood cadmium (<2; 2-5; 5-10 and >10 µg.L^{-1}), the authors observed a statistically significant increase in abnormal values only in the >10 µg.L^{-1} group for all of the nephrotoxicity parameters, suggesting a NOAEL between 5 to 10 µg.L^{-1}. Note that the thresholds for abnormal values used by the authors were respectively 324 and 240 µg.g^{-1} creatinine for β2M and RBP.

Jarup *et al.* (1988) examined the relationship between an index of cumulative exposure to cadmium corresponding to the weighted average blood concentration of cadmium times the exposure time and urinary excretion of β2M in 440 workers (326 men, 114 women) in a battery plant. The authors showed that there was a correlation between this blood index of cumulative exposure and the other atmospheric index of cumulative exposure expressed in µg-years.m^{-3}. They also showed a dose-response relationship between abnormal tubular proteinuria, defined as a β2M value above 311 µg.g^{-1} creatinine, and the blood index of cumulative exposure. By interpolating from the graph in Figure 3b of the article, a 10% increase in abnormal proteinuria corresponds to approximately 12,500 nmol.months.L^{-1}. For a work life of 30 to 40 years, this value corresponds to an average blood cadmium concentration of 2.9 to 3.9 µg.L^{-1}.

Roels *et al.* (1991) examined the glomerular filtration rate in workers who were exposed to cadmium or retired at the time of the study in addition to a control group. Of the 36 exposed subjects under the age of 50 years, none showed abnormal proteinuria defined as β2M > 300 µg.g^{-1} creatinine, RBP > 300 µg.g^{-1} creatinine or albumin > 15 mg.g^{-1} creatinine. Their average blood cadmium concentration was 4.3 µg.L^{-1}. In subjects over the age of 50 years, 31 exposed workers did not show abnormal proteinuria and their average blood cadmium concentration was 3.2 µg.L^{-1}. Twelve exposed workers over the age of 50 years had abnormal proteinuria and an average blood concentration of 7.5 µg.L^{-1}.

Jarup and Elinder (Jarup *et al.*, 1995) examined the relationship between glomerular filtration and blood cadmium concentrations in 42 welders exposed to cadmium for at least five years. The authors reported a drop of 20% or more in glomerular filtration versus the normal expected value in 3.4%, 33% and 100% of subjects having a blood cadmium concentration below 5.6 µg/L, between 5.6 and 8.4 µg.L^{-1} and above 8.4 µg.L^{-1}, respectively. Note that this decrease in glomerular filtration was considered an irreversible phenomenon.

The toxicokinetic model published by Nordberg and Kjellström (1979) was not used since it has not been validated for blood levels and occupational exposure.

Finally, concerning relationships between blood and urinary concentrations, the correlations reported in field studies calculate blood cadmium concentrations of 3 to 50 µg.L^{-1} for a urine concentration of 5 µg.g^{-1} creatinine. Some studies were not used because they had methodological limitations or uncertainties in their results (Kawada *et al.*, 1990; Jakubowsi *et al.*, 1987). The study by Zwennis and Franssen (1992) is particularly interesting in terms of the process of establishing a BLV for blood cadmium, as it was carried out in more than 900 workers and the correlation between blood and urinary levels of cadmium was studied in around 600 workers exposed to cadmium in 16 different industries. Based on the equation reported, for a urinary concentration of cadmium of 5 µg.g^{-1} creatinine, the calculated blood concentration is 4 µg.L^{-1}. It is true that in the range of low concentrations, there is a broad spread of points on the graph in Figure 1 of the article. Nevertheless, these results suggest that over the long term and on average, routine exposure corresponding to a blood cadmium concentration of 4 µg.L^{-1} would produce a urinary concentration of 5 µg.g^{-1} creatinine.

All of these observations are summarised in Table 3..

Table 3: Summary of blood cadmium concentrations related to concentrations of tubular toxicity markers reported in field studies

Urinary criterion	Parameter	Blood cadmium (µg/L)	Reference
β2M, RBP	10% increase in abnormal values	10	(Jakubowski *et al.*, 1987)
NAG, β2M	Threshold for an increase in abnormal values	1 (NAG) 10 (β2M)	(Chia *et al.*, 1989)
β2M, RBP	Threshold for an increase in abnormal values	10	(Bernard *et al.*, 1990)
β2M	10% increase in abnormal values	2.9 to 3.9	(Jarup *et al.*, 1988)
β2M, RBP, Albumin	No abnormalities Abnormalities	3.2 7.5	(Roels *et al.*, 1991)
Glomerular filtration	3.4% abnormalities 33% abnormalities 100% abnormalities	<5.6 5.6 to 8.4 >8.4	(Jarup *et al.*, 1995)
Urinary cadmium	BLV of 5 µg/g creatinine	4	(Zwennis and Franssen, 1992)

According to all of these data, a BLV for blood cadmium of 4 $\mu g.L^{-1}$ appears both cautious and reasonable.

In the absence of data in France, the German GerES study, in the general population (4000 people, differentiated according to smoking status), can be used to define a biological reference value for blood cadmium (Becker *et al.*, 2002). It should be noted that the national US NHANES survey was conducted more recently but does not report results based on smoking status (CDC, 2012). The BRVs selected for blood cadmium were 0.7 $\mu g.L^{-1}$ for non-smokers and 3 $\mu g.L^{-1}$ for smokers.

β2-microglobulin and retinol binding protein in urine

Should the data in the general population be used primarily to build biological reference values for biomarkers of exposure, it is mainly to indicate concentrations in the absence of any occupational exposure to the chemical concerned. It is therefore necessary to confirm the absence of exposure, which cannot be guaranteed and/or verified in field studies, even if professionals are regarded as non-exposed to the substance concerned. On the other hand, for biomarkers of effect it is more important to ensure that the population in which these biomarkers are measured has similar physiological characteristics to the target population (adults of working age), which is not the case with studies in the general population.

The literature search only identified two field studies reporting urinary concentrations of these two biomarkers in workers not occupationally exposed to cadmium. The study by Chaumont *et al.* (2010) reported a 95th percentile of urinary concentrations of RBP of 256 $\mu g.g^{-1}$ creat (177 workers considered non-exposed to cadmium; UCd < 1 $\mu g.g^{-1}$ creat) and of β2M equal to 276 $\mu g.g^{-1}$ creat (126 workers considered non-exposed to cadmium; UCd < 1 $\mu g.g^{-1}$ creat). The study by Roels reported 95th percentiles of urinary concentrations of RBP and β2M of respectively 190 $\mu g.g^{-1}$ creat and 324 $\mu g.L^{-1}$ in 50 workers non-exposed to cadmium. By taking a default value for the urinary creatinine concentration equal to 1.4 $g.L^{-1}$ (Cocker *et al.*, 2011; Bader *et al.*, 2012), the 95th percentile of the urinary concentration of β2M would be 231 $\mu g.g^{-1}$ creat.

Thus, for β2M, the urinary concentration of 250 µg.g^{-1} creatinine is proposed as the biological reference value (95th percentile in non-exposed workers between 230 and 280 µg.g^{-1} creatinine approximately).

For RBP, the urinary concentration of 250 µg.g^{-1} creatinine is proposed as the biological reference value (95th percentile in non-exposed workers between 190 and 260 µg.g^{-1} creatinine approximately).

The available data on the general population are reported, to provide further information. From 1985 to 1991, a large Belgian cohort was monitored (the Cadmibel cohort of 1700 people and the PheeCad sub-cohort of 600 people, 5 years later) (Buchet *et al.*, 1990; Buchet *et al.*, 1996; Hotz *et al.*, 1999). The 95th percentile of urinary concentrations of β2M was between 190 and 250 µg.g^{-1} creatinine, and around 225 µg.g^{-1} creatinine for RBP[4].

Conclusions of the collective expert appraisal

It was not possible to establish one or more biological limit values on the basis of cadmium's carcinogenicity. As a result, the renal effect was chosen for establishing BLVs for urinary cadmium, and more indirectly, for blood cadmium (pragmatic BLVs).

Biomarkers of exposure	
Urinary cadmium	
Pragmatic BLV (tubular toxicity)	**5 µg.g^{-1} creatinine**
Threshold value for additional medical monitoring	**2 µg.g^{-1} creatinine**
Biological reference values:	0.8 µg.g^{-1} creatinine (non-smokers)
	1 µg.g^{-1} creatinine (smokers)
Blood cadmium	
Pragmatic BLV (tubular toxicity)	**4 µg.L^{-1}**
Biological reference values:	0.7 µg.L^{-1} (non-smokers)
	3 µg.L^{-1} (smokers)
Biomarkers of early stage of effects	
Urinary retinol binding protein	
Biological reference value	250 µg.g^{-1} creatinine
Urinary beta-2-microglobulin	
Biological reference value	250 µg.g^{-1} creatinine

Components of biological monitoring

At the time of employment (baseline): blood cadmium, urinary cadmium and tubulopathy markers (full examination of renal function).

During exposure (periodic examinations):

[4] Values calculated from the average creatinine level of around 1.5 g.24 h^{-1} (rounded) considering the mean of the rates reported in men and women, reported in the publications by Buchet *et al.* (1990), Buchet *et al.* (1996), and Hotz *et al.* (1999).

Blood cadmium (measurement of changes in concentrations over time: reflects recent exposure and exposure via ingestion that is often non-negligible in the case of occupational exposure to metals).

Urinary cadmium:

- if the concentration is less than 2 µg.g^{-1} creatinine, measurement of early markers of tubulopathy (RBP and β2M) is unnecessary;
- if the concentration is greater than 2 µg.g^{-1} creatinine and less than 5 µg.g^{-1} creatinine, periodic monitoring of urinary and blood concentrations of cadmium should be supplemented by periodic monitoring of early urinary markers of tubulopathy (RBP and β2M) comparing the results obtained with the biological reference values recommended.

Sampling method and factors that may affect the interpretation of results

All urine specimens can be taken with the usual equipment. To simplify the monitoring procedures, all urine specimens can be taken in the morning before starting the shift (this avoids the risk of contaminating samples), regardless of the day of the working week. When measuring β2M it is important to note that urine specimens should be taken from the second morning micturition and must be buffered to pH 7 immediately after collection.

When measuring urinary cadmium, no preservative should be added to samples.

Urine specimens may be stored at 4°C for analysis of all urinary markers (cadmium, β2M and RBP) provided that the analysis is performed as soon as possible, and no later than 15 days after sampling (Anouar *et al.*, 2011; FIOH, 2010; INRS, 2012; Perret *et al.*, 1994; UCL, 2010). Urine specimens for analysis of β2M can be kept longer at -20°C.

It is recommended that blood samples be taken before the shift begins to avoid the risk of contaminating samples, regardless of the day of the working week. It is also recommended that they not be taken just after a prolonged work stoppage. Samples should be stored in tubes containing anticoagulant (sodium heparin or EDTA) and no preservative should be added. They can be stored at 4°C before analysis, which must be done as quickly as possible, no later than 5 days after collection (FIOH, 2010; INRS, 2012; UCL, 2007).

Cadmium concentrations, especially in the blood, are influenced by tobacco consumption and to a lesser extent by diet. The excretion of RBP and β2M is influenced by age, diseases or exposure to nephrotoxic substances. These biomarkers are not specific to cadmium effect.

Biometrology

β2M can be measured in urine using the enzyme immunoassay (Kawada *et al.*, 1990; Chaumont *et al.*, 2011), by radioimmunoassay (Roels *et al.*, 1978), by simple immunodiffusion test (Garçon *et al.*, 2004 and 2007) or by immunonephelometry (Bernard *et al.*, 1981). RBP can be measured in urine by simple immunodiffusion test (Nogawa *et al.*, 1979), by the automated immunonephelometry technique (Roels *et al.*, 1978) or using the enzyme immunoassay (Garçon *et al.*, 2004 and 2007; Chaumont *et al.*, 2011).

URINARY CADMIUM					
Interlaboratory quality control	Scientific Institute of Public Health (Belgium): Quality Control Belgium University of Erlangen-Nuremberg (Germany): G-EQUAS National Public Health Institute of Quebec (Canada): PCI and QMEQAS				
Analytical technique	Limit of detection Limit of quantification	Precision	Trueness	Reference standard	Bibliographic reference
Electrothermal atomic absorption spectroscopy	0.07 $\mu g.L^{-1}$	Not specified		Commercial standard	Komarek *et al.*, 1991; Moreira *et al.*, 1995
High-frequency inductively coupled plasma mass spectrometry	0.01 $\mu g.L^{-1}$ 0.02 $\mu g.L^{-1}$				Lu *et al.*, 1993; Subramanian *et al.*, 1983; Goulle *et al.*, 2004; Chaumont *et al.*, 2011
BLOOD CADMIUM					
Interlaboratory quality control	Scientific Institute of Public Health (Belgium): Quality Control Belgium National Public Health Institute of Quebec (Canada): PCI and QMEQAS				
Atomic absorption spectrometry	1 $\mu g.L^{-1}$ -	Not specified		Commercial standard (highly purified Cd)	Sharma *et al.*, 1982
Electrothermal atomic absorption spectrophotometry	0.1 - 0.4 $\mu g.L^{-1}$ -			Commercial standard	Roberts and Clark, 1986
High-frequency inductively coupled plasma mass spectrometry	0.01 - 0.04 $\mu g.L^{-1}$ -			Multi-element commercial standard	Stroh, 1993
Flame atomic absorption/flow injection system	0.15 $\mu g.L^{-1}$ -			Commercial standard	Welz *et al.*, 1991
Potentiometric stripping analysis	0.1 $\mu g.L^{-1}$ -			Not specified	Ostapczuk, 1993

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