Collective expert appraisal: summary of discussion with conclusions

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

On the evaluation of biomarkers of exposure and recommendation for biological limit values and biological reference values for cobalt 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 of exposure.

Presentation of the issue

On 12 June 2007, AFSSET, which became ANSES in July 2010, was requested by the Directorate General for Labour to carry out the necessary assessment for setting occupational exposure limits for cobalt and its compounds.

France currently has mean eight-hour occupational exposure limits for both cobalt carbonyl and cobalt hydrocarbonyl of 0.1 $mg.m^{-3}$ (in cobalt). These values were set by the Circular of 13 May 1987[1].

The Directorate General for Labour asked the ANSES to reassess this value and, if necessary, to propose new occupational exposure limit values based on health considerations for all cobalt compounds irrespective of their solubility.

This Request was entrusted to ANSES's OEL Committee which, in November 2011, submitted a report for consultation recommending the following measures for cobalt and its compounds with the exception of cobalt associated with tungsten carbide:

- to set a pragmatic 8-hour OEL of 2.5 $\mu g.m^{-3}$;
- that exposure over a 15 minute period should not exceed five times the value of the 8-hour OEL (i.e. 12.5 $\mu g.m^{-3}$);
- to assign a "skin" notation for soluble compounds[2].

The OEL Committee decided to supplement its appraisal by assessing the data concerning biological monitoring in the workplace for cobalt and its compounds with the exception of cobalt associated with tungsten carbide, in order to assess the suitability of recommending

[1] Completing and amending the Circular of 19 July 1982 relative to permitted values for concentrations of certain hazardous substances in the workplace atmosphere.

[2] For more details, see the report "Assessing the health effects and methods for measuring occupational exposure for cobalt and its compounds with the exception of cobalt associated with tungsten carbide"

monitoring one or more biomarkers in addition to an OEL, possibly including setting biological limit values for the biomarker(s) chosen.

Scientific background

Biological monitoring of exposure in the workplace has emerged as a complementary method to atmospheric exposure measurement 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 effective 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 authorises the use of biological monitoring of exposure and biological limit values.

OEL Committee definitions

Biomarker of exposure: 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 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 BME concentrations measured 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. 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 from this working group 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. An ANSES employee also contributed to this report.

The summary report on the BMEs for cobalt was based on 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 source 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 (term of office 2010-2013) on 30 May 2013.

The collective expert appraisal work and the summary report were submitted to public consultation from 01/10/2014 to 01/12/2014. 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 30 June 2015.

Result of the collective expert appraisal

Introduction

The scientific articles selected for evaluating biomonitoring data on cobalt were identified using the following keywords: “cobalt”, “biomarker”, “biomonitoring”, “urine”, “blood” and “occupational”, while limiting the search to human data.

Cobalt is a relatively rare element. It is found naturally, often in association with nickel, silver, lead, copper and iron ore. The compounds of cobalt responsible for occupational exposure can take several forms:

- insoluble compounds;
- soluble salts;
- a mixture of compounds of different solubility;
- cobalt in association with tungsten carbide, commonly known as “hard metals”.

The health effects observed can be very different depending on the type of exposure. For this reason it was decided to consider cobalt in soluble and/or insoluble forms separately from cobalt in association with tungsten carbide. Specific BLVs could then be recommended for each category if necessary.

This distinction was particularly appropriate because the International Agency for Research on Cancer (IARC) classifies cobalt compounds differently depending on their nature. Cobalt in association with tungsten carbide is classified as probably carcinogenic (2A), whereas metallic cobalt is classified as possibly carcinogenic (2B).

Toxicokinetics data

The literature contains little precise information concerning dermal absorption of cobalt, but it seems that except for soluble cobalt compounds, dermal absorption seems low in comparison with inhalation or ingestion. It should be noted that the American Conference of Industrial Hygienists (ACGIH) does not mention any significant absorption via the dermal route whereas the MAK Commission assigned a “skin” notation to cobalt and its compounds (ACGIH, 2012; Deutsche Forschungsgemeinschaft, 2012).

Inhaled cobalt particles may be deposit in the upper and lower respiratory tract. The transport and deposition of particles in the respiratory tracts depends upon particle diameter and their absorption depends on their solubility and permeability across biological barriers. The cobalt particles deposited in the respiratory tracts may also be transported mechanically into the gastrointestinal tract by mucociliary action and deglutition (ATSDR, 2004).

Absorption of cobalt via the digestive system varies considerably (18 to 97%) depending on the nature of the compound and the nutritional status (ATSDR, 2004). It seems that absorption is greater in women than in men and that anaemia promotes absorption of cobalt (vitamin B12, which contains cobalt, prevents anaemia). It is probable that compliance with hygiene’s rules at the workstation affects the digestive absorption of cobalt compounds, especially soluble compounds (hand-to-mouth transfer).

As one of the components of vitamin B12, cobalt is an essential biochemical element and can be found, once absorbed, in most bodily tissues. It accumulates in the liver, the lungs (inhalation) and the renal cortex (ATSDR, 2004; Franchini et al. 1994; Mosconi et al. 1994). If exposure ceases, concentrations of cobalt in the blood diminish by 9% (slightly exposed group) to 24% (highly exposed group) over two days and by 51% in one month (Alexandersson *et al*., 1988).

Cobalt can be excreted in the urine or the faeces (Lison et al. 1994). After exposure to soluble compounds, cobalt is excreted in the urine with a half life of 20 hours (Christensen 1995).

Elimination of cobalt after exposure via inhalation to insoluble compounds (metallic dusts whether or not associated with tungsten carbide, oxides and insoluble salts) is apparently affected by the duration of exposure and the size of the particles (cobalt is mostly evacuated mechanically to the gastrointestinal tract when the aerosol is composed of large particles)

(ATSDR, 2004; Foster et al. 1989). Following exposure to insoluble cobalt compounds, urine concentrations increase reaching a peak 5 to 10 hours after the start of exposure. There are three phases of urinary excretion, with respective half lives of 40 to 60 hours, 10 to 78 days and one year (ATSDR, 2004). However, this last phase is only found in cases of chronic exposure (Mosconi et al. 1994). Urinary concentrations reach a plateau after one month of daily exposure (Scansetti et al. 1985). Foster et al. (1989) report in a study on volunteers that approximately 40% of the lung burden of inhaled cobalt oxide was found six months after exposure.

Selection of biomarkers of exposure and effect

Some studies aimed to compare blood concentrations of cobalt with atmospheric concentrations. Varying correlations were found (r = 0.4 to 0.8), but no published study reported a regression equation between atmospheric and blood concentrations.

Furthermore, in addition to the fact that this BME requires invasive sampling, it does not seem to offer any advantages over urinary cobalt, in terms of either specificity or sensitivity. Nor were any relevant results found in the literature connecting blood concentrations of cobalt with potential health effects. It was therefore not deemed useful to recommend using this BME for monitoring occupational exposure.

Several studies have investigated biomonitoring of urine cobalt in the workplace. Considerable interindividual variations in concentrations of urine cobalt were found. This may be due to uncontrolled oral or dermal absorption (Scansetti et al. 1994; Linnaimaa et al. 1997).

Urine concentrations of cobalt seem to correlate well with atmospheric concentrations of cobalt, especially in the form of metals, salts and hard metals (Alexandersson et al. 1988; Ichikawa et al. 1985; Lison et al. 1994; Scansetti et al. 1985).

There is sufficient data in the literature to recommend monitoring urinary cobalt as a biomarker of exposure to cobalt.

The literature mentions certain effects related to exposure to cobalt compounds, such as haematotoxicity and thyroid effects but the heterogeneous nature of the results found makes it impossible to recommend or identify a biomarker of effect suitable for biomonitoring.

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

Name	**BLOOD COBALT**	
Other substances giving rise to this BME	None	
Concentrations found in exposed workers or volunteers	- Field studies: All forms (hard metals, metal cobalt, salts, oxides)	EWES 1 µg.L^{-1} (Med) [< 0.5 – 32] SWES 11 µg.L^{-1} (Med) EWES 13 µg.L^{-1} (Med)
	- Studies in volunteers: Not specified	
Conversion factor	MW*: 59 1 µg.L^{-1} = 0.017 µmol.L^{-1} 1 µmol.L^{-1} = 59 µg.L^{-1}	
Concentrations in the general population[3]	Not specified	
Recommended limit values for exposed workers (INRS 2012)	USA - ACGIH	For exposure to cobalt and inorganic compounds: 1 µg.L^{-1} EWES (ACGIH, 2001)
	USA – OSHA	Not specified
	Quebec – IRSST	For exposure to cobalt and inorganic compounds: blood cobalt: 1 µg.L^{-1} after the shift and at the end of the week (IRSST 2012)
	Finland - FIOH	Not specified
	Germany - DFG	Not specified

* EWES: end of week and end of shift; SWES: start of week and end of shift; Med: median; cr: creatinine; MW: Molecular weight

Name	**URINARY COBALT**	
Other substances giving rise to these BMEs	None	
Concentrations found in exposed workers or volunteers	- Field studies: Hard metals	EWSS 2.4 µg.L^{-1} (GM) EWES 2.3 µg.L^{-1} (GM) MWES/EWES 37 µg.L^{-1} (AM) [1 – 392] MWES/EWES 7 µg.g^{-1} cr (AM) [0.7 – 27]
	Metallic cobalt	SWES 174 µg.g^{-1} cr (Med) [16 – 2 244] EWES 162 µg.g^{-1} cr (Med) [13 – 1 534]

[3] 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)

<table>
<tr><td></td><td colspan="3">All forms (hard metals, metallic cobalt, salts, oxides)</td><td>EWES 4 µg.g^{-1} cr (Med) [0.3 – 204]
SWES 175 µg.g^{-1} cr (Med) [16 – 2 244]
EWES 162 µg.g^{-1} cr (Med) [13 – 1.534]</td></tr>
<tr><td></td><td colspan="4">- <u>Studies on volunteers:</u> Not reported</td></tr>
<tr><td>Conversion factor</td><td colspan="4">MW: 59
1 µg.L^{-1} = 0.017 µmol.L^{-1}
1 µmol.L^{-1} = 59 µg.L^{-1}
1 µg.g^{-1} cr = 1.92 µmol.mol^{-1} cr
1 µmol.mol^{-1} = 0.52 µg.g^{-1} cr</td></tr>
<tr><td>Concentrations in the general population</td><td colspan="4">USA-NHANES[4] 2012 (1406 people from the general population)
- 95th percentile: 1.3 µg.L^{-1} or 1.2 µg.g^{-1} cr (total); 1 µg.L^{-1} or 0.8 µg.g^{-1} cr (men); 1.5 µg.L^{-1} or 1.5 µg.g^{-1} cr (women)
France ENNS[5] 2006-2007 (1991 people from the general population)
- 95th percentile: 1.4 µg.L^{-1} or 1.1 µg.g^{-1} cr (total); 0.7 µg.L^{-1} or 0.6 µg.g^{-1} cr (men); 2 µg.L^{-1} or 1.5 µg.g^{-1} cr (women)</td></tr>
<tr><td rowspan="10">Recommended limit values for exposed workers
(INRS, 2012)</td><td colspan="2">USA - ACGIH</td><td colspan="2">For exposure to cobalt and inorganic compounds, with the exception of oxides: 15 µg.L^{-1} EWES (ACGIH, 2001)</td></tr>
<tr><td colspan="2">USA – OSHA</td><td colspan="2">Not reported</td></tr>
<tr><td rowspan="7">Germany - DFG</td><td>For exposure to metal cobalt and compounds: atmospheric concentration (mg.m^{-3})</td><td>EKA*
Urine (µg.L^{-1})</td></tr>
<tr><td>0.01</td><td>6</td></tr>
<tr><td>0.025</td><td>15</td></tr>
<tr><td>0.05</td><td>30</td></tr>
<tr><td>0.1</td><td>60</td></tr>
<tr><td>0.5</td><td>300</td></tr>
<tr><td colspan="2">No precise time of sampling given (Angerer, 2012)</td></tr>
<tr><td colspan="2">Quebec - IRSST</td><td colspan="2">For exposure to cobalt and inorganic compounds: 15 µg.L^{-1} (255 nmol.L^{-1}) EWES (IRSST, 2012)</td></tr>
<tr><td colspan="2">Finland - FIOH[6]</td><td colspan="2">For exposure to cobalt and inorganic compounds: 35 µg.L^{-1} EWES (FIOH, 2010)</td></tr>
</table>

* EWSS: end of week and start of shift; EWES : end of week and end of shift; MWES: middle of week and end of shift; AM: arithmetic mean; EKA: Expositionsäquivalente für Krebserzeugende Arbeitsstoffe (Exposure equivalents for carcinogenic agents)

[4] National Health and Nutrition Examination Survey
[5] Etude nationale nutrition santé (National Health and Nutrition Survey)
[6] Following a change, the value recommended by FIOH is 130 nmol.L^{-1} or 7,7 µg.L^{-1} (2015)

Study of the relationship between concentrations of BMEs for cobalt and certain health effects

Finley *et al*. (2012) carried out a comprehensive review of systemic effects of cobalt reported in the scientific literature, considering effects common to both humans and animals. The effects documented for humans are summarised in the following tables. It should be noted that the authors did not describe toxicological mechanisms. On the other hand, the authors consider that these are specific effects of cobalt insofar as they have been observed in animals, under controlled exposure, and in humans during specific treatments using cobalt.

Table 1: Summary of cobalt concentrations measured simultaneously with haematotoxicity values

Blood cobalt		
All values are below 2 µg.L^{-1} (n = 82) Reference group (non-exposed workers) Exposure to cobalt dust (metal, oxides or salts)	SWES: Geometric mean: 11 µg.L^{-1} (n = 82) - (2.0 to 120.0) EWES: Geometric mean: 12.7 µg.L^{-1} (n = 82) – (2.0 to 120.0) Anomalies in the blood formula in exposed workers compared to the reference group: - significant increase in concentrations of white blood cells; - significant decrease in concentrations of erythrocytes and in haemoglobin and haematocrit. No modification of mean corpusclar volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentrations or platelet concentrations	Swennen *et al*. (1993)
Mean: 0.5 µg.L^{-1} (n = 51) (0.1 to 1.3) Reference group (workers returning from holiday) Exposure to cobalt blue dye	Mean: 2 µg.L^{-1} (n = 46) - (0.2 to 24) Significant decrease in haematocrit and mean corpuscular volume compared to the reference group. Lower haemoglobin and erythrocyte concentrations than for the reference group, but the difference was not significant	Raffn *et al*. (1988)
Not reported Exposure to a mixture of various cobalt salts, oxides and fine cobalt metal powders	Median: 1.0 µg.L^{-1} (n = 249) – (< 0.5 to 32.0) No correlation between blood count and blood cobalt concentrations. According to the authors, the concentration levels reached were not associated to haematotoxicity in exposed workers either in the short or the long term	Lantin *et al*. (2011)
Urine cobalt		
Mean: 5 µg.g^{-1} creat. (n = 51) (0.9 to 34) Reference group (workers returning from holiday) Exposure to cobalt blue dye	Mean: 73 µg.g^{-1} cr (n = 46) - (2 to 1450) Significant decrease in haematocrit and mean corpuscular volume compared to the reference group. Lower haemoglobin and erythrocyte concentrations than for the reference group, but the difference was not significant	Raffn *et al.* (1988)

All values are below 2 µg.g^{-1} cr (n = 82) Reference group (non-exposed workers) Exposure to cobalt dust (metal, oxides or salts)	SWES: Geometric mean: 53 µg.g^{-1} cr (n = 82) – (2.7 to 2245) EWES: Geometric mean: 70 µg.g^{-1} cr (n = 82) – (1.6 to 2038) Anomalies in the blood formula in exposed workers compared to the reference group: - significant increase in concentration of white blood cells; - significant decrease in concentrations of erythrocytes and in haemoglobin and haematocrit. No modification of mean corpusclar volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentrations or platelet concentrations	Swennen *et al*. (1993)
Not reported Exposure to a mixture of various cobalt salts, oxides and fine cobalt metal powders	Median: 4 µg.g^{-1} cr (n = 249) – (0.3 to 204.3) No correlation between blood count and urine cobalt concentrations. According to the authors, the concentration levels reached were not associated to haematotoxicity in exposed workers either in the short or the long term	Lantin *et al*. (2011)

Table 2: Summary of cobalt concentrations measured simultaneously with thyroid toxicity values

Blood cobalt		
All values are below 2 µg.L^{-1} (n = 82) Reference group (non-exposed workers) Exposure to cobalt dust (metal, oxides or salts)	SWES: Geometric mean: 11 µg.L^{-1} (n = 82) - (2.0 to 120.0) EWES: Geometric mean: 12.7 µg.L^{-1} (n = 82) – (2.0 to 120.0)	Swennen *et al.* (1993)
	Reduced serum T3 levels No other changes (T3 uptake, serum T4 and TSH concentrations)	
Not reported Exposure to a mixture of various cobalt salts, oxides and fine cobalt metal powders	Mean: 1.0 µg.L^{-1} (n = 249) – (< 0.5 to 32.0)	Lantin *et al.* (2011)
	No correlation between thyroid parameters and blood cobalt concentrations. According to the authors, the concentration levels reached were not associated to thyrotoxicity in exposed workers either in the short or the long term	
Urine cobalt		

All values are below 2 µg.g^{-1} cr (n = 82) Reference group (non-exposed workers) Exposure to cobalt dust (metal, oxides or salts)	SWES: Geometric mean: 53 µg.g^{-1} cr (n = 82) - (2.7 to 2245) EWES: Geometric mean: 70 µg.g^{-1} cr (n = 82) – (1.6 to 2038) Reduced levels of serum T3 No other changes (T3 uptake, serum T4 and TSH concentrations)	Swennen *et al.* (1993)
Not reported Exposure to a mixture of various cobalt salts, oxides and fine cobalt metal powders	Median: 4 µg.g^{-1} cr (n = 249) – (0.3 to 204.3) No correlation between thyroid parameters and blood cobalt concentrations. According to the authors, the concentration levels reached were not associated to thyrotoxicity in exposed workers either in the short or the long term.	Lantin *et al*. (2011)

Study of correlations between urine cobalt concentrations and atmospheric concentrations

The literature reports correlations between atmospheric concentrations and urine cobalt concentrations. On the other hand, no regression equation between atmospheric concentrations and blood concentrations was found in the literature. It should be noted that field studies usually involve biomonitoring of exposure to hard metals (cobalt and tungsten carbide).

n	Atmospheric concentration (µg.m^{-3}) **Median** Mean [min – max]	Urine concentration **Median** Mean [min – max]		Concentration of urine Co for 2.5 µg.m^{-3}	Reference
Hard metals only					
26	-	-	SWES: [UCo] (µg.L^{-1}) = 0.29 [ACo] (µg.m^{-3}) + 0.83 r = 0.831	1.5 µg.L^{-1} [a]	Scansetti *et al*. (1985)
	-	-	EWES: [UCo] (µg.L^{-1}) = 0.70 [ACo] (µg.m^{-3}) + 0.80 r = 0.805	2.6 µg.L^{-1} [a]	
150	(AM) 98.2 [3 – 1 203]	MWES/EWES (AM) 37.5 µg.L^{-1} [1 – 392]	EWES: [UCo] (µg.L^{-1}) = 0.67 [ACo] (µg.m^{-3}) + 0.9 r = 0.99 Calculated on the basis of mean levels per sector	2.6 (µg.L^{-1})	Ichikawa *et al*. (1985)
70	(AM) 50	-	Time not specified [UCo] (µg.L^{-1}) = 0.70 [ACo] (µg.m^{-3}) + 0.70 r = 0.81	2.5 µg.L^{-1} [a]	Alexandersson *et al*. (1988)
50	[0.05 – 0.19]	Time not specified [2.6 – 38] µg.L^{-1}	-	-	Stebbins *et al.* (1992)
81	(AM) 140	-	Time not specified [UCo] (µg.L^{-1}) = 0.61 [ACo] (µg.m^{-3}) + 19.99 r = 0.69	21.5 µg.L^{-1} [a]	Scansetti *et al.* (1994)

131	-	Time not specified **8.9** µg.L^{-1} (AM) 14 [0.5 – 160]	-	3 µg.L^{-1} [b]	Linnainmaa *et al.* (1997)
36	(AM) 1.6	EWSS (GM) 5.3 µg.L^{-1} EWES (GM) 6.1 µg.L^{-1}	-	-	De Palma *et al*. (2010)
13	(AM) 0.03	EWSS (GM) 2.4 µg.L^{-1} EWES (GM) 2.3 µg.L^{-1}			
Metallic powders					
60	(AM) 5 [0.2 – 11]	MWES/EWES (AM) 7 µg.g^{-1} cr [0.7 – 27]	-	5 µg.g^{-1} cr [b]	Nemery *et al.* (1992)
77	(AM) 15 [0.7 – 43]	MWES/EWES (AM) 21 µg.g^{-1} cr [2.3 – 75]			
Metallic powders including hard metals and salts					
72	SW **68** [2 – 7 700] EW **89** [1 – 4 690] Sels	SWES **32** µg.g^{-1} cr [0.8 – 1000] EWES **46** µg.g^{-1} cr [1.6 – 666]	Time : end of week and end of shift Log[UCo] (µg.g^{-1} cr) = 0.63 log[ACo] (µg.m^{-3}) + 0.44 r = 0.6 to 0.8	4.9 µg.g^{-1} cr	Lison *et al.* (1994)
35	SW **433** [13 – 6 819] EW **383** [17 – 10 767] Metal	SWES **175** µg.g^{-1} cr [15.7 – 2244] EWES **162** µg.g^{-1} cr [13.1 – 1534]			
10	SW **9** [2 – 127] EW **19** [1 – 203] Hard metals	SWES **13** µg.g^{-1} cr [3.1 – 87.5] EWES **18** µg.g^{-1} cr [3.0 – 85.6]			
Metallic powders, salts and oxides					
82	SW **84** [2 – 7700]	SWSS **23** µg.g^{-1} cr SWES **44** µg.g^{-1} cr	-	-	Swennen *et al.* (1993)
	EW **110** [1 – 7772]	EWSS **45** µg.g^{-1} cr EWES **72** µg.g^{-1} cr			

15	SW **210** [5 – 3 652] EW **467** [23 – 7 772] Oxides	SWES **62** µg.g^{-1} cr [21 – 491] EWES **70** µg.g^{-1} cr [13 – 2037]	-		Lison *et al.* (1994)
20	Not specified	Not specified	Time not specified [UCo] (µg.g^{-1} cr) = 1.05 [ACo] (µg.m^{-3}) + 3.02 r = 0.76 (if atmospheric concentrations are lower than 30 µg.m^{-3}) Oxides only	5.6 µg.g^{-1} cr	Fujio *et al.* (2009)

[UCo]: urinary cobalt concentration; [ACo]: atmospheric cobalt concentration ; AM: arithmetic mean ;GM: geometric mean; EW: end of week; SW: start of week
a value calculated from the regression equation reported in the publication
b value calculated from a graph in the publication

Establishing BLVs and choosing biological reference values

The collective expert appraisal by the OEL Committee on cobalt compounds recommended a pragmatic 8h-OEL for cobalt compounds, excluding hard metals, of 2.5 µg.m^{-3}. The expert Committee considered that there was limited proof of the carcinogenic nature of cobalt compounds (with the exception of cobalt associated with tungsten carbide) and that dose-response relationships for this effect were unreliable. The OEL Committee therefore decided to establish a pragmatic 8h-OEL for a non-carcinogenic effect (damage to the respiratory system).

Regarding the relationship between biological effects and concentrations of cobalt BMEs, the Committee chose to study haematology disorders (changes to the blood count), endocrine disorders (thyroid function) and lung disorders.

The causal relationship between changes to the blood count and cobalt is far from obvious as they can also be observed in non-exposed subjects. Furthermore, experimental studies have shown a tendency to polycythaemia. Changes to the blood count related to cobalt can therefore not be used to establish a BLV. Studies on thyrotoxicity also give different results, making it impossible to establish a BLV on this type of effect. According to Finley *et al*. (2012), some authors report that thyroid disorders are observed in patients treated with cobalt (onset of goitres) and experimental data have shown a reduction in the uptake of iodine by the thyroid and changes to thyroid tissues.

Certain studies mention an effect on respiratory function, but co-exposure to the dust of other metals can cause same effects.

Lastly, other biological effects have been observed in workers exposed to cobalt, but the studies did not report results on BME measurements and can therefore not be used to establish a BLV. According to Finley *et al*. (2012), the disorders observed include cardiomyopathies, neurological effects, etc.

Some studies established relationships between atmospheric concentrations and blood or urine cobalt concentrations. Concerning the link between urine cobalt concentrations and atmospheric concentrations of cobalt with the exception of cobalt in association with hard metals, only the publications by Nemery *et al*. (1992) and Lison *et al*. (1994) could be used. The study of Nemery et al. (1992) enables to graphically determine urinary concentration of cobalt at end of week and end of shift of about 5 µg.g^{-1} of creatinine corresponding to metallic cobalt exposure at the 8-hour OELV of 2.5 µg.m^{-3} proposed by the OEL Committee. This result is confirmed by the work of Lison et al. (1994) for estimating the urinary concentrations

of cobalt using the regression equation derived for exposure to a range of cobalt compounds (salts, metals and hard metals[7]).

According to Lison *et al*. (1994), there is only a slight correlation between urine cobalt concentrations measured at end of shift and atmospheric concentrations in workers exposed to cobalt oxides. This was contradicted by the study by Fujio *et al*. (2009), who showed a fairly strong correlation (r = 0.76) when the atmospheric concentration did not exceed 30 $\mu g.m^{-3}$. The urine cobalt concentration calculated for exposure at an 8h-OEL, based on the regression equation, is 5.6 $\mu g.g^{-1}$ of creatinine.

In view of the limited number of studies describing exposure to cobalt compounds excluding association with hard metals, and the limitations of the studies (atmospheric concentration levels often higher than the OEL), the Committee decided to try and estimate urine concentrations for exposures to cobalt compounds in association with tungsten carbide for comparison purposes.

For a given exposure, urine concentrations calculated from regression equations for exposure to cobalt in the form of hard metals (at end of week and end of shift) are lower than those calculated for exposure to cobalt alone (Alexandersson et al. 1988; Ichikawa *et al.* 1995; Linnainmaa et al. 1997; Scansetti et al. 1985)[8]. It should be noted that at start of week and end of shift the concentration calculated is lower (Scansetti *et al.* 1985), which suggests that concentrations increase in the course of the working week.

The question of the solubility of the compounds to which workers are exposed may arise in the calculation of these urinary concentrations.

The field data of Nemery *et al*. (1992) and Lison *et al*. (1994) thus enabled to recommend a BLV of 5 $\mu g.g^{-1}$ of creatinine on the basis of exposure to cobalt compounds, excluding hard metals, at 2.5 $\mu g.m^{-3}$ (8h-OEL recommended by the OEL Committee).This value must not be applied to exposure to cobalt when associated with tungsten carbide.

The French ENNS study of the general population can be used to establish a biological reference value. The urine cobalt concentration corresponding to the 95th percentile of the distribution of values in this study is 1.1 $\mu g.g^{-1}$ of creatinine with no distinction of gender, 1.45 $\mu g.g^{-1}$ of creatinine or 1.95 $\mu g.L^{-1}$, in women and 0.6 $\mu g.g^{-1}$ of creatinine or 0.7 $\mu g.L^{-1}$ in men (Fréry et al. 2011). These concentrations, rounded up to 1.5 $\mu g.g^{-1}$ of creatinine or 2 $\mu g.L^{-1}$ in women and 0.6 $\mu g.g^{-1}$ of creatinine or 0.7 $\mu g.L^{-1}$ in men, are adopted as biological reference values.

Conclusions of the collective expert appraisal

The biological values recommended for monitoring exposure to cobalt are:

Urine cobalt at end of week and end of shift

BLV based on exposure to the 8h-OEL (2.5 $\mu g.m^{-3}$): **5 $\mu g.g^{-1}$ of creatinine**

This value applies to cobalt in the form of metallic powders, salts and oxides.
It does not apply to exposure to cobalt associated with tungsten carbide.

[7] It should be noted that in the study by Lison et al. (1994), only 8% of the results concerned workers exposed to hard metals (10 out of a total of 117), which had little influence on the results for the other exposures (metallic cobalt and salts).

[8] Apart from this study by Scansetti et al. (1994) which suggests high dermal or oral absorption, the y-intercept of the equation reported is very high when compared with those in other studies.

Biological reference values:

- 1.5 µg.g^{-1} of creatinine or 2 µg.L^{-1} (women)
- 0.6 µg.g^{-1} of creatinine or 0.7 µg.L^{-1} (men)

Sampling methods and factors liable to affect the interpretation of results

Cobalt levels measured in urine samples taken at end of shift and end of week reflect the mean exposure for the week. According to certain authors, as the equilibrium concentration is reached after 30 days of exposure, samples should not be taken after long periods of absence.

No specific equipment is required for sampling (polyethylene or polypropylene flasks). Samples should also be taken away from the workplace, ideally after a shower or at the very least after handwashing, in order to reduce the risk of contaminating the samples.

For cobalt measurement, no preserving agent should be added to the samples. They can be kept at 4°C until analysis but this should be carried out within two weeks.

The analysis of the results should take into account influential factors such as the wearing of certain types of prosthetics and the differences between men and women.

Biometrology

Urine cobalt			
Interlaboratory quality control	Faculty of Health and Medical Sciences, University of Surrey (UK): TEQUAS Scientific Institute for Public Health (Belgium): Quality Control Belgium Institute and Out-patient Clinic for Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg (Germany): G-EQUAS National Institute of Public Health of Quebec, Toxicology Centre: PCI		
	Method 1	**Method 2**	**Method 3**
Analytical technique	Electrothermal atomic absorption spectrometry	Inductively coupled plasma mass spectrometry	Differential pulse anodic stripping voltammetry
Detection limit	0.1 µg.L^{-1}	0.02 µg.L^{-1}	0.2 µg.L^{-1}
Quantification limit	Not specified	0.06 µg.L^{-1}	Not specified
Reliability	Not specified		
Precision	Not specified		
Benchmark	Commercial standard		Not specified
References		Goullé et al. 2005	Heinrich et al. 1984

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