# COLLECTIVE EXPERT APPRAISAL: summary and conclusions

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

on the evaluation of the effects on health and techniques for the measurement of exposure levels in workplace atmospheres for

**cobalt and cobalt compounds, excluding cobalt in association with tungsten carbide**

This document summarises and presents the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee)**.**

## 1. PRESENTATION OF THE ISSUE

ANSES received a formal request from the French Directorate General for Labour to conduct the scientific expert appraisal work required for setting occupational exposure limit values (OELVs) for cobalt and its compounds.

France currently uses a mean 8-hour exposure value for cobalt carbonyl and cobalt hydrocarbonyl of 0.1 mg.m$^{-3}$ (in cobalt). It was set by the Circular of 13 May 1987[1].

The Directorate General for Labour requested ANSES to re-assess this value and, if necessary, propose new occupational exposure limits based on health considerations for all cobalt compounds, whether soluble or not.

## 2. BACKGROUND

The French system for establishing OELVs has three clearly distinct phases:

- independent scientific expertise (the only phase entrusted to ANSES);
- proposal by the Ministry of Labour of a draft regulation for the establishment of limit values, which may be binding or indicative;
- stakeholder consultation during the presentation of the draft regulation to the French Steering Committee on Working Conditions (COCT). The aim of this phase is to discuss the effectiveness of the limit values and if necessary to determine a possible implementation timetable, depending on any technical and economic feasibility problems.

The OELs, as proposed by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee), are concentration levels of pollutants in workplace atmospheres that should not be exceeded over a determined reference period and

[1] Supplementing and amending the Circular of 19 July 1982 relative to permitted concentrations of certain hazardous substances in workplace atmospheres.

below which the risk of impaired health is negligible. Although reversible physiological changes are sometimes tolerated, no organic or functional damage of an irreversible or prolonged nature is accepted at this level of exposure for the large majority of workers. These concentration levels are determined by considering that the exposed population (the workers) is one that excludes both children and the elderly.

These concentration levels are determined by the OEL Committee experts based on information available from epidemiological, clinical and animal toxicology studies. Identifying concentrations that are safe for human health generally requires correction factors to be applied to the values identified directly by the studies. These factors take into account a number of uncertainties inherent to the extrapolation process conducted as part of an assessment of the health effects of chemicals on humans.

The Committee recommends the use of three types of values:

- an 8-hour occupational exposure limit value (8h-OEL): unless otherwise indicated, this corresponds to the limit of the time-weighted average (TWA) of the concentration of a chemical, in the air in the worker's breathing zone, over the course of an 8-hour working day.

In the current state of scientific knowledge (in toxicology, medicine and epidemiology), the 8h-OEL is designed to protect workers exposed regularly and for the duration of their working lives from the medium- and long-term health effects of the chemical in question.

- a short-term exposure limit (STEL): this is a limit corresponding to exposure measured over a 15-minute reference period (unless otherwise indicated) during the peak of exposure, irrespective of its duration. It aims to protect workers from adverse health effects (immediate or short-term toxic effects such as irritation phenomena) due to peaks of exposure.

- a ceiling value: this is an atmospheric concentration in workplace which should not be exceeded at any time during the day. This value is recommended for substances known to be highly irritating or corrosive or likely to cause serious potentially irreversible effects after a short period of exposure.

These three types of values are expressed:

- either in $mg.m^{-3}$, i.e. in milligrams of chemical per cubic metre of air and in ppm (parts per million), i.e. in cubic centimetres of chemical per cubic metre of air, for gases and vapours;

- or in $mg.m^{-3}$, only for liquid and solid aerosols;

- or in $f.cm^{-3}$, i.e. in fibres per cubic centimetre for fibrous materials.

The 8h-OELV may be exceeded for short periods during the working day provided that:

- the weighted average of values over the entire working day is not exceeded;

- the value of the short term limit value (STEL), when it exists, is not exceeded.

In addition to the OELs, the OEL Committee assesses the need to assign a "skin" notation, when significant penetration through the skin is possible. This notation indicates the need to consider the dermal route of exposure in the exposure assessment and, where necessary, to implement appropriate preventive measures (such as wearing protective gloves). Skin penetration of substances is not taken into account when determining the atmospheric limit levels, yet can potentially cause health effects even when the atmospheric levels are respected.

The OEL Committee also evaluates the applicable reference methods for the measurement of exposure levels in workplace atmospheres. The different protocols are classified according to the methods used. These methods are then assessed and ranked according to their compliance with the European Standard EN 482: 2006: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents".

## 3. 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). This body mandated:

- a working group on health effects to conduct the expert appraisal work on the health effects;
- a rapporteur from among the OEL Committee experts to assess the measurement techniques.

Three ANSES officers contributed to this work and were responsible for scientific coordination of the different expert groups.

The methodological and scientific aspects of the work of this group and rapporteur were regularly submitted to the OEL Committee. The final report takes account of all their observations.

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 - General Requirements of Competence for Expert Appraisals (May 2003)" to ensure compliance with the following points: competence, independence, transparency and traceability.

## 4. DESCRIPTION OF THE METHOD

<u>For the assessment of the health effects:</u>

A summary report was prepared by ANSES and submitted to the working group on health effects, which commented on and added to it.

The information in this summary report on the health effects of soluble and insoluble cobalt compounds is mostly taken from reports published by respected international organisations: ATSDR, 2004; NTP, 1998 and 2002, and IARC, 1997. New additions to the literature from 2004 to 2011 were taken from Medline and Toxline.

<u>For the assessment of the techniques for the measurement of exposure levels in workplace atmospheres</u>

The different protocols for measuring soluble and insoluble cobalt compounds in workplace atmospheres were identified and grouped according to the methods used. These methods were then assessed and ranked according to their compliance with the European Standard EN 482: 2006: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents". A list of the main sources consulted is detailed in the report.

These methods were classified into two categories:

- Category 1 for validated methods: these satisfy a majority of the validation criteria (range of measurements, uncertainties, sensitivity, storage of samples, etc.)
- Category 2 for indicative methods: here, the protocols do not specify or do not sufficiently explain the major validation criteria.

A detailed comparative study of the methods in Category 1 was carried out with respect to the various validation data and the technical feasibility, in order to recommend the most suitable method(s) for measuring concentrations for comparison with limit values.

The Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents adopted:

- the summary report for the assessment of the health effects, at its meeting on 9 September 2011;
- the summary report on the techniques for measuring exposure levels in workplace atmospheres, at its meeting on 11 June 2010.

The summary and conclusions of the collective expert appraisal were adopted by the Committee on expert appraisal for recommending occupational exposure limits for chemical agents on 17 November 2011.

This work was submitted to a public consultation from 18/10/2012 to 20/12/2012. The list of persons or organizations who contributed to the public consultation are listed in appendix. The comments received were reviewed by the OEL Committee who adopted this version on 4 April 2013.

## 5. RESULTS OF THE COLLECTIVE EXPERT APPRAISAL OF THE HEALTH EFFECTS OF METALLIC COBALT AND ITS INORGANIC COMPOUNDS, I.E. SALTS AND OXIDES

### 5-1 General information

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

- insoluble compounds,
- soluble salts,
- a mixture of compounds with different solubilities,
- cobalt associated with tungsten carbide, giving rise to what is commonly known as exposure to hard metals.

As the health effects observed can differ greatly depending on the type of exposure, the Committee chose to distinguish between exposure to cobalt in soluble and/or insoluble form and exposure to cobalt associated with tungsten carbide. A specific OEL for each case will be recommended if necessary.

Although there is little information available for assessing the chronic toxicity and carcinogenic potential by inhalation of insoluble cobalt compounds, it is important to pay particular attention to these substances, especially those in the form of dust, because, as with nickel, a difference in toxicity between soluble and insoluble metallic compounds cannot be ruled out. Whenever

possible, when describing studies, the form of the cobalt concerned is always specified in this report.

For animals, on the other hand, the available data for soluble cobalt comes mainly from the NTP document on the toxicity of cobalt sulfate heptahydrate.

The general information collected on these substances indicates that the classifications are identical at the European level and that their registration in French tables of occupational diseases[2] are also identical, irrespective of the cobalt derivative concerned.

In 2006, the IARC reassessed the carcinogenic potential of cobalt compounds and classified metallic cobalt without coexposure with tungsten carbide and soluble salts of cobalt in Group 2B (*possibly carcinogenic to humans*).

The lowest 8h-OELV for cobalt and its compounds is currently 0.02 $mg.m^{-3}$, recommended by ACGIH and applied in Spain and Quebec. There is no corresponding STEL.

It is worth noting that in October 2011, the NTP published a new report online assessing the health effects of cobalt. This comprehensive report studied the health effects of cobalt in dust form on two animal species (rats and mice) over a period of two years.

The OEL Committee examined the graphs and tables available as well as the caution that the data supplied had not been finalised and are subject to modification. As with any report in draft form, it is not possible either to use it or to cite it.

As a result, and despite the quality of the data provided in the NTP report of 2011, it was not possible to use them to establish OELs. The OEL Committee reserves the right to amend this report once the new NTP document on cobalt dusts has been validated.

### 5-2 Toxicokinetics – Metabolism

Physico-chemical characteristics play an important role in the toxicokinetics and toxicity of cobalt compounds.

For example, cobalt in particle form can be inhaled and deposited in the respiratory tract. Large particles (diameter between 1 and 5 µm) tend to be deposited in the upper respiratory tract where they undergo impaction and sedimentation. Smaller particles continue their progress into the lower respiratory tract where they can undergo sedimentation, diffusion and electrostatic precipitation. The deposited fraction varies according to the age and size of the subject and on respiratory volume.

Fractional deposition of inhaled cobalt oxide particles in humans varied from approximately 50% of the inhaled dose for particles with a geometric mean diameter of 0.8 µm to approximately 75% of the inhaled dose for particles with a geometric mean diameter of 1.7 µm (Foster et al. 1989).

The particles of cobalt deposited in the respiratory tract can be absorbed into the blood after dissolution or transported mechanically to the gastro-intestinal tract by mucociliary action of the respiratory tract and swallowing action.

Data on the retention of cobalt oxide ($^{57}Co$ used as a tracer) in the respiratory tracts of humans and of several animal species show considerable variation between species. In humans, almost half of the original pulmonary burden persisted 6 months after exposure, whereas in rats, pulmonary clearance regarding cobalt was almost complete after 6 months.

As a component of vitamin B12, cobalt is an essential biochemical element and is consequently found in most tissues. It has been identified in the liver, muscles, lungs, lymph nodes, heart,

[2] French tables of occupational diseases 65 and 70 include all cobalt derivatives, and the disorders listed concern allergies. However, Tables 70 *bis* and *ter* only take account of dust from sintered or fused metallic carbides containing cobalt, which are not dealt with in this report.

skin, bones, hair, stomach, brain, kidneys, plasma and bladder of non-exposed subjects, with the highest concentration of cobalt being found in the liver (Collecchi et al., 1986; Forbes et al., 1954; Hewitt, 1988; Ishihara et al., 1987; Muramatsu and Parr, 1988; Teraoka, 1981; Yamagata et al., 1962; Yukawa et al., 1980).

A greater concentration of cobalt has been found in the lungs of workers in the metallurgy sector and of coal miners occupationally exposed to cobalt (Gerhardsson et al., 1984; Hewitt, 1988; Hillerdal and Hartung, 1983; Teraoka, 1981).

Rats exposed to metallic cobalt (from 0.001 to 0.5 $mg.m^{-3}$, 24 hours/day for 3 months) had accumulated cobalt in the thyroid, spleen, liver and kidneys. An accumulation of cobalt was also found in the lungs when exposure had exceeded 0.001 $mg.m^{-3}$.

Following exposure of humans to physiologically insoluble cobalt compounds (cobalt metal, cobalt oxides), clearance from the body, assessed by both urinary/fecal clearance and a reduction in whole-body retention, appears to follow three-phase kinetics.

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- The first phase, likely representing mucociliary clearance of particles deposited in the tracheobronchial region, has a half-time on the order of 2–44 hours (Apostoli et al. 1994; Mosconi et al. 1994b).
- The second phase, with a half-time on the order of 10–78 days, may represent macrophage-mediated clearance of cobalt particles from the lung (Beleznay and Osvay 1994; Mosconi et al. 1994b).
- The third clearance phase, representing long-term clearance from the lungs, has a half-time on the order of years (Bailey et al. 1989; Beleznay and Osvay 1994; Mosconi et al. 1994b; Newton and Rundo 1971).

The elimination of cobalt following inhalation exposure was affected by the time after exposure (urinary excretion increases as time increases) and particle size (more cobalt is initially mechanically cleared to the gastrointestinal tract when the aerosol consists of bigger particles) (Bailey et al. 1989; Foster et al. 1989).

The rate of urinary excretion appears to correlate with the rate of translocation of cobalt from the lungs to the blood, and the rate of fecal clearance with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1986, 1989; Patrick et al. 1989; Talbot and Morgan 1989).

Elimination occurs according to the following gradient, depending on species (from highest to lowest) rat> mouse> hamster> guinea pig> baboon> human> dog.

### 5-3 General toxicity

*In humans, other effects apart from carcinogenicity*

Inflammation of the nasopharynx is one of the typical acute effect of inhalation of dust containing cobalt. However, it is not clear whether this inflammation is the result of an irritant effect or of an immune-mediated allergic reaction (e.g. allergic rhinitis) (Lison, 1996). Contact dermatitis is often reported following acute dermal exposure to metallic cobalt (Fischer and Rystedt, 1983).

Cobalt is an allergen that in some cases is capable of producing contact dermatitis, rhinitis, asthma and possibly allergic alveolitis.

It seems that the allergenic properties of cobalt mostly come from exposure to the metal itself, rather than to its salts. Nielsen et al. (2000) showed that repeated daily exposure of the hands to a solution of cobalt salts did not lead to eczema in patients known to be allergic to cobalt.

In workers subjected to chronic exposure to metallic cobalt, the two main target organs are the skin and the respiratory tract (Lauwerys, 1994).

Chronic exposure to cobalt in the form of metal, fumes or dust causes respiratory disorders. Symptoms range from coughing to permanent invalidity. Hypersensitivity of the respiratory tract, progressive dyspnea, impaired pulmonary function, loss of weight and dermatitis have also been reported (Dorsit, 1970 [quoted by NTP, 2002]; NIOSH, 2001).

Chronic bronchitis and allergic sensitisation can also result from prolonged exposure to cobalt powder. Some cases (but poorly documented) of interstitial pneumopathy have been reported following exposure to cobalt alone.

The following table describes the principal epidemiological studies of workers exposed to cobalt; only those that included measurements of atmospheric sampling have been taken into account.

| | Type of study | Effects observed | Form of cobalt | NOAEL $mg.m^{-3}$ | LOAEL $mg.m^{-3}$ | Reference |
|---|---|---|---|---|---|---|
| Number of workers | | Respiratory | Metal | 0.0175 | | Deng et al., 1991 |
| 194 | Transversal | Resp. (reduced FEV, FVC, increased coughing and irritation of the upper respiratory tracts) | Metal | 0.0053 | 0.0151 | Nemery et al., 1992 |
| 82 | Transversal (mean duration: 8 years) | Resp. (dyspnea)<br>Haemato. (5% reduction in erythrocytes)<br>Endocr. (7% reduction in T3 cells)<br>Skin (eczema and erythema) | Metal and soluble salts | | 0.125 | Swennen et al., 1993 |
| 48 | Transversal | Resp. (10% reduction in FEV, FVC, increased coughing and dyspnea) | Diamond polishers (metal) | | 0.0152-0.1355 | Gennart and Lauwerys, 1990 |
| 122 | Longitudinal (followed for 13 years) | Significant reduction in FEV | Fine metallic powder | | 0.04 | Verougstraete et al., 2004 |
| 224 | Transversal (6-8 years of employment) | Asthma and chronic bronchitis | Cobalt chloride associated with zinc | | 0.1 | Roto et al., 1980 |

**Table 1: Effects of chronic exposure to cobalt compounds in the workplace**

Other effects were observed during occupational exposure to insoluble or soluble cobalt insoluble or soluble, including: cardiomyopathy, characterised by functional effects on the ventricles, haematotoxicity, liver congestion, and endocrine and neurological effects. However, the levels of exposure to cobalt by inhalation associated with these effects were not determined.

*In humans, both carcinogenic and genotoxic effects*

There are few epidemiological studies of the risk of cancer in workers exposed to cobalt (Jensen and Tüchsen, 1990). A high incidence of lung cancer was observed in English cobalt miners but the aetiology is unknown (Lauwerys et al., 2007). Epidemiological studies carried out on cobalt miners in the USA, Canada, the Democratic Republic of the Congo and other countries were unable to detect a relationship between exposure to cobalt and the presence of tumours (exposure time longer than 8 years and undetermined concentration of cobalt). On the other hand, cobalt has been clearly identified as the cause of respiratory diseases, especially when in metallic form.

Lison et al. (2001) showed *in vitro* that certain biological activities of particles of metallic cobalt might not be explained by the presence of soluble species of cobalt. Particles of cobalt might therefore affect the integrity of DNA both by producing oxygen-activated species (a process independent of the production of cobalt cations) and by inhibiting the excision repair system (a process based on the transformation of particles into soluble cobalt (II) ions).

*In animals*

There are many studies on animals and readers are invited to consult the original documents for their description.

In this summary, only the NTP study has been detailed.

**In the subchronic study,** F334/N rats (10 males and 10 females) and $B6C3F_1$ mice (10 males and 10 females) were exposed to cobalt sulfate heptahydrate at concentrations of 0; 0.3; 1; 3; 10 and 30 $mg.m^{-3}$, for 6 hours/day and 5 days/week for 13 weeks; these concentrations correspond respectively to 0; 0.11; 0.38; 1.14; 3.8 and 11.4 mg $cobalt.m^{-3}$.

At the end of the study, the principal consequences identified were necrosis and inflammation of the respiratory tract epithelium (nasal cavities, larynx, trachea and bronchioles) observed in rats exposed to 19 mg $cobalt.m^{-3}$ and mice exposed to 1.9 mg $cobalt.m^{-3}$ (cobalt sulfate) for more than 16 days. Exposure of rats and mice to cobalt sulfate for 13 weeks led to adverse effects in all parts of the respiratory system, with the larynx proving to be the most sensitive. At concentrations of cobalt ≥ 0.11 $mg.m^{-3}$, the rats and mice developed metaplasia of the larynx as well as histiocytic infiltration of the lungs. In rats, chronic inflammation of the larynx was observed at concentrations ≥ 0.38 mg $cobalt.m^{-3}$, with more severe effects on the nose, larynx and lungs at higher exposure levels. In mice, acute inflammation of the nose was observed at concentrations ≥ 1.14 mg $cobalt.m^{-3}$, with more severe effects on the nose, larynx and lungs at higher levels (Bucher et al., 1990; NTP, 1991).

Furthermore, non-respiratory effects (on the heart, blood, liver and kidneys) were observed at the highest doses.

In the chronic toxicity study carried out by the NTP, groups of 50 male and 50 female rats were exposed to aerosols containing 0, 0.3, 1.0 or 3.0 $mg.m^{-3}$ of cobalt sulfate heptahydrate, 6 hours/day, 5 days/week, for 105 weeks.

An increase in the incidence of alveolar/bronchiolar neoplasia was observed in male rats following exposure to 1.14 mg cobalt.m$^{-3}$ and in female rats exposed to 0.38 mg cobalt.m$^{-3}$. Statistical analysis showed that tumours occur to a significant extent in both genders of rat; the same was true in mice for both genders when exposed to 1.14 mg cobalt.m$^{-3}$.

The IARC analysed all these data. It considered that in mice, the proliferative alveolar/bronchiolar lesions observed in the lungs were all similar to those occurring spontaneously. It noted that cobalt did not cause any increase in the incidence of tumours in tissues apart from the lung (IARC, 2006).

In rats, on the other hand, the IARC noted that exposure to cobalt sulfate heptahydrate caused an increase in the incidence of both benign and malignant alveolar/bronchiolar neoplasms and of benign and malignant pheochromocytomas.

In its report, the IARC states that it can be difficult to interpret the available elements of proof concerning the carcinogenicity of cobalt in laboratory animals, as reports (and particularly the NTP report on cobalt sulfate heptahydrate) do not contain enough details to allow a proper statistical analysis of the results; this especially concerns the survival rate of exposed subjects relative to the control groups (IARC, 2006).

Furthermore, a careful analysis of the results of the NTP study, whether for the experiment carried out on 10 animals of each gender for 13 weeks or the experiment carried out on 50 animals of each gender for 104 weeks, shows that the dose-response curve is of poor quality for most of the effects observed.

Lastly, the NTP also uses a qualitative classification for the carcinogenic potential of the substances it studies. This classification divides substances into two categories: those known to be carcinogenic for humans, and those reasonably suspected of being carcinogenic for humans. Cobalt is placed in the second NTP category.

### 5-4 Establishment of occupational exposure limit values

Choice of the critical effect

There have only been a limited number of studies investigating the carcinogenicity of cobalt in humans. In its document, the IARC notes that in the NTP study, where rats were exposed to cobalt sulfate heptahydrate by inhalation, although a broad spectrum of inflammatory and proliferative symptoms as well as pulmonary lesions were observed, many of the cellular tumours were morphologically similar to those occurring spontaneously. The principal difference between mice and rats lies in the mainly fibrous, scaly nature of the alveolar/bronchiolar affections in rats.

**The Committee states that there is only limited evidence of the carcinogenicity of cobalt and its compounds, that the dose/response relationships for this effect are uncertain and that it has decided to establish a pragmatic 8hr-OEL for a different effect than cancer.**

However, and in line with current knowledge, the Committee states that cancer is a stochastic effect for which a linear dose-response relationship to the origin is admitted ; it is therefore possible that such an effect may occur at lower doses than those with non-carcinogenic effects. The purpose of the recommended OEL is therefore not to avoid possible carcinogenic effects but rather to serve as a means for reducing exposure.

During exposure to cobalt and its compounds by inhalation, effects on the respiratory tracts appear at lower doses than for other effects, such as myocardial toxicity and, as shown by the epidemiological studies examined, the first symptoms observed in workers exposed to cobalt compounds are respiratory in nature.

The OEL Committee **therefore decided to choose impairment of the respiratory system as the critical effect for establishing a pragmatic 8h-OEL for cobalt and its compounds.**

Choice of the key study

In the cohorts of workers exposed to cobalt in the workplace that were studied, the risk of respiratory system disorders seems to increase with the level and/or duration of the exposure. The absence of precise data reduces the reliability of all these studies.

The Committee decided that the NTP study in rats over two years was the most relevant, for the following reasons:

- It is a two-year study (i.e. full-life for rats) with an exposure scenario close to that for workers: 6 hours/day, 5 days/week.
- A 13-week pre-study enabled the authors to choose a balanced range of exposure levels: 0, 0.11, 0.38 and 1.14 mg cobalt.$m^{-3}$.
- Exposure was properly controlled, administered through inhalation with cobalt in aerosol form.
- A dose/response relationship was found for certain respiratory effects and a benchmark dose was established for each of these effects.

Identification of the Point of Departure (POD)

After analysing the results, the Committee chose the data from the 2-year chronic study, with the proteinosis observed in male rats as the critical effect. This is defined as a “pulmonary disorder characterised by the accumulation of lipid/proteinaceous matter in the distal airways. The principal symptoms include difficulty in breathing with coughing and wheezing on inhalation”. (Inserm, 2004) These clinical signs are similar to those found in workers exposed to cobalt.

The one-stage model correlates most closely with the experimental results. It was used to establish a BMD in rats by inhalation of 0.083 mg of cobalt.$m^{-3}$ and a BMDL at 10% of 0.07 mg of cobalt.$m^{-3}$.

Establishing an 8h-OEL – applying safety factors

Using a Point of Departure in the form of a BMDL at 10% of 0.07 mg.$m^{-3}$, the following safety factors are proposed:

- An inter-species extrapolation factor of 10, related to the transposition of data from rats to humans.

  It should be remembered that the OEL proposed concerns all cobalt compounds, irrespective of their solubility. Studies show a species-dependent gradient of elimination for insoluble compounds; it was observed that rats eliminate cobalt from the lungs much more rapidly than humans, indicating greater sensitivity in the human species and fully justifying this safety factor.
- A safety factor related to inter-individual variability. This factor takes into account the low inter-individual variability in laboratory animals. For a value established for a population of workers (healthy adults) a degree of homogeneity is assumed, so the Committee proposes a safety factor of 3.

8h-OEL = 0.07/(10 x 3) ≈ 2.5 µg.$m^{-3}$

Establishing a 15 min-STEL

No dose-response relationship could be identified on which to establish an STEL.

As a result, the OEL Committee, in accordance with the methodology adopted, recommends that workers not be exposed for 15 min at values higher than 5 x 8h-OEL, or 12.5 µg of cobalt.$m^{-3}$.

Assigning a skin notation

According to Palmen (2005), Wahlberg (original document not available) found an absorption rate for cobalt of 38 nmol.$cm^{-2}h^{-1}$ (2.2 mg Co.$cm^{-2}.h^{-1}$) following *in vitro* application of a 0.085 M solution of cobalt chloride for 4 hours on the skin of a human abdomen (autopsy material, washed with soap and water and frozen before use) (Wahlberg, 1965). If the ECETOC criteria are applied (ECETOC 1998) for skin notation, the dose absorbed is 4.48 mg of cobalt. This is 120 times the quantity absorbed during 8 hours of exposure to the proposed OEL.

Based on these elements, it may be concluded that dermal exposure to soluble cobalt compounds can lead to significant systemic absorption, and that a skin notation should be assigned to soluble (but not to insoluble) cobalt compounds.

## 6. RESULTS OF THE COLLECTIVE EXPERT APPRAISAL ON THE EVALUATION OF THE TECHNIQUES FOR THE MEASUREMENT OF EXPOSURE LEVELS IN THE WORKPLACE

There are five methods available for sampling and analysing cobalt dust.

A study of all five methods revealed general problems related more particularly to sampling (standardisation of the inhalable fraction, etc.) and to solution preparation than to the analytical techniques.

Only the method involving filter sampling, dissolution of dust samples and analysis by ICP-MS is suitable for the OEL values suggested by the Committee.

## 7. CONCLUSIONS

**Recommended limit values:**

Pragmatic 8h-OEL = 2.5 µg.$m^{-3}$

15min-STEL / (recommendation not to exceed 5 times the 8h-OEL) = 12.5 µg.$m^{-3}$

Skin notation: Yes, for soluble compounds

**Recommended sampling and measurement techniques**

The method involving filter sampling, dissolution of dust samples and analysis by ICP-MS is the only one recommended for assessing occupational exposure for purposes of comparison with limit values.

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Maisons-Alfort, 04.04.13

On behalf of the Committee Experts

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