



# *MANAGEMENT OF THE RISK RELATED TO CHRONIC OCCUPATIONAL EXPOSURE TO CADMIUM AND ITS COMPOUNDS*

This file has been realized within the framework of the European cadmium risk reduction strategy, as a proposal put forward by the ICdA as a risk management measure for the protection of workers from chronic effects from cadmium exposure. The basis of this document relies on the work conducted in 1996 by industrial associations "Association Française Interprofessionnelle du Cadmium (AFIC, Paris)" and "Cadmium Industry and Environment (CIE, Brussels)" by a working party from the Belgian and French non-ferrous metals industries. The work was further reviewed and endorsed by EUROMETAUX (the Association representing the European Non-Ferrous Metals industries) and its member National Federations, for presentation to Directorate-General V of the European Commission.

EUROMETAUX

Management of the risk related to chronic occupational exposure to cadmium and its compounds
Brussels, 31 May 1996

The working party from the Belgian and French non-ferrous metals industries comprised of the following people :

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The work was then updated and modified in 2005 to consider the most recent information on effects related to occupational exposure to cadmium. This review was conducted by a working group composed of experts within the European cadmium producing and users sectors including:

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Special thanks to Dr Spång, occupational doctor at Saft in Sweden, and to Dr. P Linnett, previous occupational doctor at Johnson Matthey in the UK, for their input.

Brussels, March 2006

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# PART I – Background and Literature review

## 1. Scope and purpose of the document

This file presents a management scheme for the risk related to the chronic exposure to cadmium and cadmium compounds(1) in the occupational environment. It is relevant to all cadmium-related industrial processes in a broad sense, including the production of Cd metal from ore (primary production) or recycling (secondary production), the transformation of metallic Cd into Cd- compounds (e.g. CdO, $CdSO_4$, CdS,...) and the manufacture of Cd-containing products (Nickel-cadmium accumulators, Cd-alloys, Cd-stabilisers, Cd-pigments,...).

The risks related to chronic occupational Cd-exposure are well known. The risk management scheme presented in Part II of this file is based on the extensive present scientific data and industrial experience. It is aimed at the prevention of the major risk related to Cd at the present conditions encountered at the workplace, i.e. the development of Cd-nephropathy. According to current knowledge, the kidney is the most sensitive target organ of chronic Cd exposure and protecting against effects to the kidney should also offer protection against potential risks of lung cancer or any risks to the bone.
However, for the latter, recommendations are made for conducting a study to evaluate whether there is any potential direct effect on bone for workers exposed to cadmium.

The purpose of this file is to provide guidance to all people involved in the management of Cd-risk at the workplace : medical doctors, industrial hygienists, production managers,...This file is also intended to give guidance to regulatory bodies concerned with management of cadmium at the workplace.

## 2. Introduction and background

### 2-1 Health risks related to Cd at the workplace

The health risks related to acute and chronic exposure to Cd at the workplace are well known. The IPCS document "Environmental Health Criteria n° 134, which examined the available evidence in the nineties, has often been used as a starting-point for reviewing hazard and risks associated with Cd exposure (IPCS 1992).
More recently, the European risk assessment on cadmium and cadmium oxide, human health reviewed the available and updated literature on human health effects of Cd (Cd RAR, 2004).

#### *2-1-1 Effects related to acute and chronic exposure to cadmium in the past*

2-1-1-1 Trends in occupational exposure to Cd

In the past, pyrometallurgical operations with Cd have been associated with high concentrations of Cd dusts and fumes. Airborne Cd concentrations were very variable according to the plant-specific working conditions, but markedly elevated values, in the mg/m³ range, were observed regularly in the 1940s to 1960s (IPCS 1992). Considerable improvements in occupational

(1) *In the rest of the text, the word "cadmium" will replace "cadmium and its compounds".*

hygiene have been installed since then, and present air Cd concentrations are usually of the order of tens of microgram/m³ and lower. In assessing the health risks associated with present-day working conditions, this marked positive trend should be taken into account.

#### 2-1-1-2 Acute effects

In the past, acute effects of Cd on the lungs (chemical pneumonia and pulmonary oedema) have been reported in a few cases of extremely high exposure by inhalation. For an 8 hr-exposure period, the threshold effect levels in the lung for cadmium oxide fumes and respirable dust have been estimated to be around 5 mg/m³ (Friberg et al., 1986).

Acute gastro-enteritis can be caused by ingestion of large quantities of Cd, but the amount of Cd absorbed is probably limited due to vomiting.

#### 2-1-1-3 Chronic effects related to elevated chronic exposure in the past

Under the conditions of very high chronic occupational exposure in the past, Cd has caused serious chronic effects, predominantly on lungs, kidney and bones. Several authors reported that long-term inhalation exposure to high levels of Cd led to decreased lung function and emphysema. Chronic obstructive airway disease has been reported leading in severe cases to an increased mortality (Cd RAR, 2004). Chronic rhinitis has been reported in highly-exposed workers (Rydzewski et al., 1998)

The accumulation of Cd in the kidney leads, when a certain level is reached, to "kidney dysfunction". The first clinical sign of this dysfunction is the occurrence of proteins in urine resulting from the impairment of the renal tubule to reabsorb the proteins filtered through the renal glomeruli and normally almost completely reabsorbed by the tubule. This low-molecular weight proteinuria has been observed in workers exposed to Cd, accompanied or not by other signs of tubular dysfunction. In some workers, excretion of high-molecular weight proteins including albumin, transferring, immunoglobulins has also been observed suggesting an effect on the glomerulus (ATSDR, 1999). In most cases, these Cd-effects induced by high levels of exposure are considered to be irreversible. An additional effect on the kidney reported in workers exposed to high levels of Cd is an increased frequency of kidney stone formation (ATSDR, 1999).

Bone disorders (bone decalcification, pseudofractures) in workers appear to have peaked 40 to 50 years ago, when Cd exposure was high and dietary conditions may have been deficient in the countries with the reported cases. A more recent study showed an inverse dose-effect relationship between Cd dose estimates and bone density in Cd exposed workers (Järup et al., 1998).

Finally, heavy occupational exposure to Cd dust has been associated witholfactory impairments, increased frequencies of symptoms such as fatigue, headache and sleep disturbance; disturbances of sensory and motor function, anorexia and anosmia (Murphy 1997, Viaene et al., 1999, 2000)

### *2-1-2 Lung cancer: a Cd risk at the workplace today?*

According to some publications, there is some evidence that long-term occupational exposure to cadmium may contribute to the development of cancer of the lung. Cd and its compounds were classified by the International Agency for Research on Cancer in group 1 as being carcinogenic to humans (lung cancer). The Working Group of the IARC considered that there was *sufficient evidence* in humans and experimental animals for the carcinogenicity of Cd and its compounds. In making the evaluation, the evidence that Cd caused genotoxic effects in a variety of eukaryotic cells, including human cells was, together with other possible non-genotoxic mechanisms, taken into consideration by the IARC Working Group (IARC, 1993).
Indeed, data from experimental systems indicate that some Cd compounds have genotoxic properties. No consensus has been reached yet on the mechanism of action. As suggested by Misra et al. (1998), Cd accumulated in the cells may cause genetic damage either by interacting directly with the chromatin, or by stimulating the production of reactive intermediates that subsequently attack the genetic material, or indirectly by compromising the cell's ability to accurately replicate DNA and/or cope with DNA damage. Results of the human studies are conflicting, some authors reporting chromosomal aberrations or micronuclei in occupationally exposed workers while others did not. Several factors (e.g. sample size, study population, exposure assessment) are likely to have confounded the results but their actual impact cannot be assessed currently with the available information (Verougstraete et al., 2002).

Animal experiments have indicated the carcinogenic properties of Cd compounds in the lung following inhalation, at least in Wistar rats (Takenaka et al. 1983, Glaser et al., 1989). However, the response of other species (hamster, mice) proved negative and even different rat species differ in response (Maximilien and Dero 1992, Schiele 1994). In humans, a statistically significant increase in mortality from lung cancer has been reported in some studies among Cd recovery, nickel-Cd battery and Cd processing workers but not in others. It is unclear whether study results differ because of authentic exposure differences, because of factors unrelated to exposure (confounding factors, biases, etc.) or whether these differences are chance findings. The investigation of the so-called 'Globe cohort' (Cd recovery workers), by Lemen et al. (1976), Thun et al. (1985, 1989), Stayner et al. (1992, 1993) showed a positive relationship between Cd exposure and the risk of lung cancer. A confounding effect of smoking and/or arsenic exposure seemed not to be accountable for the observed excess of mortality (Thun et al., 1985, Stayner et al. 1992).These results apparently played an important role in the overall assessment by the IARC Working Group. However, the US findings have been criticized mainly because of the lack of control for other confounding factors in the studies and the used methodology for reconstruction of exposure (Sorahan 1994, Järup et al., 1998). Since the IARC evaluation, the exposure reconstruction in the Globe cohort and the potential confounding effect of arsenic have been further investigated (Sorahan and Lancashire, 1994). The mortality in the US cohort has been re-analyzed with an updated exposure assessment (Sorahan and Lancashire, 1997). Two other cohorts of Cd-exposed workers have been updated (Sorahan et al., 1995; Järup et al., 1998) and lung cancer mortality rates in a cohort of Ni-Cd workers in the UK became available as well (Sorahan and Esmen, 2004). The recent findings do not convincingly support the fact that Cd *alone* acts as a carcinogen for the lung (Sorahan and Lancashire 1997, Järup et al. 1998, Sorahan and Esmen, 2004).

Overall, the literature shows a small increase in the relative risk of lung cancer in workers exposed to Cd and Cd compounds. Specificity and dose-relationship do not support a role of Cd or Cd compounds as strong carcinogenic agents (SMRs less than 200, with lower limit of CI including or near to 100), an increase that could also be brought about by bias and/or confounding factors (Verougstraete et al., 2003). The relatively low estimated risk regarding the frequency of lung cancer, in spite of the very high exposure incurred by a large majority of workers in the past, was also stressed by Schiele in 1994, who concluded that this was

suggestive of a weak carcinogenic potential (Schiele 1994). Possible causes of underestimation of this risk (exposure misclassifications, incomplete cohorts etc.) should also be kept in mind, but the information available is insufficient to accurately assess their impact. The improvement of exposure reconstruction in the studies published since the IARC Evaluation did not significantly modify the SMR but points to a lower risk in the groups exposed to Cd and Cd compounds in the absence of arsenic. Further attention should be paid to these co-exposures, not only to arsenic but also to other carcinogens such as e.g. silica, asbestos and tobacco smoking (Verougstraete et al., 2003).

The Cd RAR (2004) undertook an extensive review of human carcinogenicity in response to cadmium exposure, with focus upon occupational cohort mortality studies. The document concluded that the possibility that cadmium oxide might cause a risk of lung cancer has neither been excluded nor affirmed by several reviewers and that most of the studies have had to camp with methodological difficulties, or could not totally exclude the effect of confounding factors (smoking, simultaneous exposures to other carcinogens,…). Overall, however, the weight of evidence collected in genotoxicity tests long-term animal experiments and epidemiological studies leads to conclude that cadmium oxide has to be considered at least as a suspected human carcinogen (lung cancer). The conclusions of the Cd RAR, and furthermore, the EU Classification Group have classified CdO and Cd metal (extrapolation done on the basis of the so-called 'ion theory' and as a 'worst case' approach related to the bio-availability of the metal) as "probable" carcinogens (Category 2).

Based on the controversies and observations mentioned above, it was also stated that, from a practical point of view, the current protection of workers against nephropathic risk will lead to exposure levels that offer also protection against the cancer risk, if any (Thun et al., 1991, Bernard and Lauwerys 1992, and OSHA, 1993).

With regard to environmentally exposed populations, a recent study has indicated an increased risk for lung cancer in people living around non-ferrous smelters (Nawrot et al., 2006). For lung cancer, adjusted hazard ratio was 1.73 (1.09-2.72, p=0.019) for a doubling of 24-hr urinary Cd excretion. Interestingly, different exposure variables were used (Cd-U, Cd-soil, residence in the specific area) and it could be observed that, when the specificity of the exposure variable decreases, the variability increases and the association becomes weaker. Confounding effect of co-exposure to arsenic (via air, or drinking water) was considered in the analysis, by using either measured As in urine values, or estimates -generated by statistical methods- for those individuals with missing urinary arsenic data (26% of the study population). As stated by the authors themselves, the study should be interpreted within the context of its possible limitations: an observational study does not prove causality and the number of cancers was fairly small. However, this study was the first to report a significant association between lung cancer and environmental exposure and points to further work to be done, i.e. ensure targeted preventive measures to reduce exposure and further explore the potential confounding effect of simultaneous exposures to other pollutants.

Based on the controversies and observations mentioned above, it has been stated that, from a practical point of view, the current protection of workers against nephropathic risk will lead to exposure levels that offer also protection against the cancer risk in occupational settings (Thun et al., 1991, Bernard and Lauwerys 1992, and OSHA, 1993). However, recent results in environmentally exposed populations living around smelters indicate that lung cancer constitutes a relevant endpoint deserving further attention.

### *2-1-3 Cd-related health risks under present-day workplace conditions*

**Effects to the kidney**

Under the present-day conditions of chronic occupational exposure to Cd, and according to current knowledge, the kidney is the most sensitive target organ. The earliest effect of Cd on the kidney is usually characterized by an increased urinary excretion of low molecular weight proteins (i.e. molecular weight <40 kDa) such as beta-2-microglobulin (B2MG), Retinol Binding Protein(RBP), which reflects a tubular effect induced by the accumulation of Cd in proximal tubular cells, and may be accompanied by other signs such as enzyme leakage (e.g.N-acectyl-beta-D-glucosaminidase (NAG)) and depressed resorption of aminoacids, glucose, calcium, copper, uric acid, and inorganic phosphate (Roels et al., 1989; Bernard and Lauwerys 1990, Bernard et al. 1990, ATSDR, 1999). Because in health subjects the tubular reabsorption of these low-molecular weight proteins is almost complete (more than 99.9%), a small decrement in the tubular reabsorption capacity produces a marked increase of the urinary excretion of microproteins which in most advanced cases of Cd nephropathy can reach levels more than 1000 times above normal (Bernard et al., 2004). Less commonly, an increased urinary excretion of proteins of higher molecular weight (e.g. albumin, immunoglobulins, transferrin) can occur, suggesting an effect on the glomerulus an effect at the glomerular level has also been observed, leading to (Bernard et al. 1979 ;Bernard et al.1990). At current actual levels of Cd exposure at the workplace, the early effects are the most important risk to control.

**Or, as WHO stated : "from the viewpoint of preventive medicine, the detection of early effects on the kidneys is of particular importance in order to prevent more serious renal effects and those on lungs and bones" (IPCS 1992).**

**Most occupational settings operate by monitoring both the level of exposure (cadmium in urine and blood) and bio-indicators of effects (low molecular proteins such as RBP or β2MG)**

Above a specific threshold level (see below), the increase in urinary cadmium is correlated with the increase of microproteinuria. In the absence of renal lesions, urinary Cd (Cd-U) is a good indicator of the Cd body burden and especially of the amount of Cd, accumulated in the kidney cortex. Consequently, Cd-U is a useful parameter to assess the life-time integrated Cd-exposure of Cd-workers.

In this respect, WHO defined a guidance value of 5 µg Cd/g creatinine for Cd-U (IPCS, 1992). This has recently been confirmed by the conclusions of the Cd RAR based on a great number of studies conducted in the 1980's and 90's. These studies establish a critical concentration in the renal cortex associated with LMW proteinuria at 200-300 ppm, corresponding to 5-10 µg/g creatinine cadmium in urine. Based on these studies, the Cd RAR makes reference to a LOAEL of 5 µg/g creatinine. The Cd RAR further concludes that at levels >10 µg/g creatinine, the microproteinuria appears irreversible.

However, the Cd RAR also refers to epidemiological studies on the general population that have assessed the critical exposure levels of cadmium on renal effects. Estimated LOAELs of 2-2,6 µg Cd/g creatinine (Buchet et al, 1990, Jarüp et al., 2000) were reported. It should be noted that the early renal changes observed in these populations environmentally exposed to Cd via the oral route have been appreciated and interpreted by experts with some contrasted opinions. For some scientists, these early renal effects -associated with low levels of environmental exposure (Cd-U <5 µg/g creatinine)- most likely reflect benign, non-adverse responses. For others, elevated concentrations of LMW in urine are an indicator of kidney damage. Even if they do not necessarily progress to severe or clinically relevant renal disease, the early dysfunctions of the renal tubular cells are to be considered as an adverse effect because it should be aimed at

detecting the earliest effects of Cd, at a stage where it is possible to prevent health effects. While it might be possible that some of the lesions are reversible, they early renal changes in exposed populations should also be considered as adverse because the half-life of Cd in the kidney is very long.
The Cd RAR further describes *"it appears prudent to recommend that workers should be offered the same degree of health protection than people from the general population, in which renal and/or bone effects were already detected at lower exposure levels and to adopt a LOAEL of 2 µg Cd/g creatinine".*

On the other hand, the possible mitigating effect of the "healthy workers" concept was not considered. This so-called healthy worker effect could contribute to different estimates for a given dose-response parameter (e.g. ED10) derived from occupational studies, compared to general population studies because variability in the threshold within populations is expected due to interindividual variability in toxicokinetics and toxicodynamics of cadmium. This does not mean that cadmium workers and general population have different thresholds, but rather, that these occupational and general population studies yield different estimates of a common threshold distribution for humans (Diamond, 2005). Basically, the so-called healthy workers effect may alter the strength of the response. To this end the effect, renal dysfunction, is a progressive effect that functions by yet to be defined inter-individual differences. The occupational LOAEL defines a level at which there is an increased probability for the development of microproteinuria. Whether or not microproteinuria occurs varies among individuals. This is why modern medical surveillance practice monitors not only the individual's exposure to cadmium, but also the renal function of the individual in the workplace, and it is designed to permit intervention (medical removal) in the event that responses to cadmium begin to manifest in the individual worker. Early intervention with the onset of incipient microproteinuria permits exposure reduction measures at a point where renal alterations remain modest and reversible. Of great importance in relation to establishing the safety margins to apply in the medical follow-up of workers is the avoidance of exceeding the critical concentration of Cd in kidney at which irreversible progression of renal dysfunction occurs.

In this respect, a number of studies have consistently reported the level of 10µg/g creatinine. A European collaborative research project on the development and validation of markers for nephrotoxicity established the threshold of 10 µg Cd/g creatinine for Cd-U for the tubular parameters B2MG and RBP (Roels et al 1993). At a Cd kidney burden not exceeding the critical level, the filtration reserve capacity of the kidney is not compromised (Roels et al 1993).

The irreversibility of Cd (micro)proteinuria has been demonstrated in workers heavily exposed to Cd, even after cessation of exposure. Moreover, persistent microproteinuria has been found predictive of an exacerbation of the age-related decline of the glomerular filtration rate. The urinary β2MG levels reported in the related studies varied between 100 and 100 000 µg/g creatinine (Roels et al 1982, Roels et al 1989, Järup et al 1993). From studies in Japan, however, it is suggested that the persistence of (micro)proteinuria depends on the intensity of Cd-exposure and the severity of the renal dysfunctions observed at the end of exposure. The authors suggested that recovery of "limited" (see further) microproteinuria may be possible (Tsuchiya 1992; Nomiyama & Nomiyama 1992).

This phenomena has been confirmed by more recent papers by Bernard et al. (Bernard et al., 1997; Bernard 2004), who recommend the following guidelines for interpreting β2MG and RBP measurements in workers exposed to cadmium :

- <300 µg/g creatinine : normal values
  300 – 1000 µg/g creatinine: incipient cadmium tubulopathy (possibility of some reversibility after removal from exposure if urinary Cd is not too high i.e. below 20 µg/g creat) .

- 1000 – 10,000 µg/g creatinine : irreversible tubular proteinuria that may accelerate decline of the GFR (glomerular filtration rate) with age. At this stage, the GFR is normal or slightly impaired
- >10,000 µg/g creatinine : overt cadmium nephropathy usually associated with a decreased GFR.

These results demonstrate that the possible development of tubular dysfunction upon Cd exposure is a gradual process that can be avoided by preventing the accumulation of too high concentrations of Cd in the kidney; if the critical kidney burden is exceeded, and eventually tubular dysfunction develops, this effect appears to be reversible when the worker is removed from exposure at a stage when the tubular dysfunction is still limited. The effect only proves progressive at prolonged high exposure.

**Effects to the bone**

The Cd RAR discusses the experimental data and reviews available on effects of cadmium exposure to bone tissue. There are a few reviews that refer to the bone tissue as the target organ for populations exposed to Cd by the oral and by the inhalation routes.

The hazard is relatively well identified both in experimental and epidemiological studies but the mechanism is not completely elucidated:

Two mechanistic pathways have been proposed:

(a) *indirect:* bone lesions are a secondary response to the kidney damage and the indirect mechanism is mainly connected with disorders in the metabolism of calcium and vitamin D,

(b) *direct*: Cd acts directly on the bone cells enhancing bone resorption and decreasing the bone formation

In workers, the occurrence of bone disorders appears to have peaked 40 to 50 years ago when Cd exposure at the workplace was high and the dietary conditions may have been deficient in the countries with reported cases (e.g. Adams et al. 1969, 1980; Blainey et al., 1980; Bonnell, 1955, Nicaud et al., 1942, etc. cited in Friberg et al., 1986). The cases were characterised by bone decalcification and pseudofractures on X-ray examination and required very large doses of vitamin D for treatment (Kjellström, 1992). More recently, a cross-sectional study carried out in workers exposed to cadmium provided results compatible with a role of Cd in the genesis of osteoporosis, as an inverse dose-effect relationship was demonstrated between Cd dose estimates (Cd-B) and forearm bone density. The occurrence of fractures or height loss was not examined (Järup et al., 1998).

Overall, the available studies performed did not allow deriving a precise critical Cd dose at which these effects occurs (LOAEL or NOAEL). Therefore, in the EU Cd RAR, by default, the value extracted from studies performed in environmentally exposed populations (3 nmol Cd/mmol creatinine) has been taken forward in the Risk Characterisation section.

The current monitoring programs in the workplace do not include the monitoring of eventual effects of cadmium on bone.

In this respect, further research is needed, firstly, on the methods to monitor the direct mechanistic action of cadmium on bone, and secondly, to establish a proper LOAEL for bone effects from occupational exposure to cadmium.

Details on a proposed study are provided in Appendix A of this report.

## 2.2. Present-day Cd exposure and monitoring at the workplace

Under the present conditions of Cd-related industrial processes, the Cd-concentration in the workplace air is generally well controlled at levels in the order of tens of µg/m³ and below. This is achieved by technical improvements such as automatisation and containment of dust-generating processes, strict control and treatment of Cd-fumes and Cd-dust, and a continuous improvement of, and attention to, general hygienic conditions at the workplace.

Since inhalation is the major Cd-exposure pathway at the workplace, the worker's exposure to Cd is generally assessed by measurement of the total Cd-concentration in workplace air or by personal air sampling.

In practice, however, when exposed to pulverulent materials (dusts and fumes) containing cadmium compounds, the cadmium concentration in air can rarely be related to internal impregnation levels, for at least two reasons :

1) According to the nature of the work and individual behavior, the ratio between exposure through inhalation and exposure through ingestion varies on a very large scale. For this reason, checking the cadmium contents in the air of the work premises cannot be a sufficient preventive measure.

2) According to the chemical nature and the physical characteristics (particularly the size) of the inhaled or ingested particles, the assimilation rates can be considerably different.

In a study of workplaces with high total air Cd-concentrations, it was noticed that generally less than 25% of the total Cd in air was in the respirable range and that this value decreased as the total value increased (Lauwerys et al, 1974).

Cd-containing dust particles that are too large to get into the lungs can enter the gastrointestinal tract by mucociliary transfer. Different Cd-related processes result in exposure to different chemical forms of Cd : in thermal processes Cd-fumes, quickly transformed into CdO, are predominant; in other industrial processes, CdS, $CdSO_4$, etc. are involved. These various Cd-species have quite different solubilities that will strongly influence their uptake and absorption by the human body. These factors are not taken into account in usual workplace air sampling.

Moreover, if in the high Cd-air concentrations in the past a correlation did actually exist between exposure through inhalation and Cd air content, industrial experience shows that this relationship is no longer evident at the present, much lower Cd levels in air at the workplace. Under present-day conditions, other Cd transfer pathways can be relevant for the workers' exposure, depending very much on workers' individual hygiene and habits.

### 2.3. A risk management scheme for the full protection of workers, chronically exposed to Cd at the workplace

Regardless of the Cd-transfer route leading to exposure and the physical and/or chemical form of Cd involved, it is the resulting amount of Cd absorbed by the body and ultimately accumulating in the kidney cortex that is relevant for workers' health under present-day conditions of chronic occupational exposure. For this reason, estimation of kidney cortex Cd-level, through the determination of Cd in urine, followed by the biomonitoring of bioindicators of effects, are the preferred parameters to integrate workers' true exposure and an individual’s susceptibility to develop effects over a longer period of time. Blood-cadmium level, on the other hand, reflects present-day Cd exposure on a short time basis (1-3 months).

Considering that :

i) the kidney is the target organ under conditions of chronic Cd-exposure, and that protection of workers against earliest effects of Cd-induced tubular dysfunction also implies protection against other potential adverse Cd-effects that could be encountered at higher exposures;

ii) the urinary levels of Cd and tubular microprotein markers associated with the earliest tubular dysfunction are well established,

iii) the first sign of Cd-induced nephropathy (tubular dysfunction) is well known, can be determined properly and appears to be reversible;

iv) further work is underway to establish at what levels effects are seen in bone, and to determine bioindicators to be used to monitor these effects in workers.

industry has developed a stepwise management scheme for the protection of all Cd-exposed workers, based on the medical biomonitoring of parameters for Cd-exposure and renal function, and aimed at the prevention of the earliest effects of Cd-induced tubular dysfunction.

Following the example of the Lead Directive, the risk management scheme involves a decisional scale based at the same time on urinary Cd-levels and bioindicators of effects for individuals at the workplace. Management actions evolve in accordance with the decisional areas outlined in the scheme. This risk management scheme, together with an extensive guidance for industrial hygiene, is presented in the next chapter.

# PART II – Management of the Cadmium risk in chronic occupational exposure

## Introduction

The current working conditions in the Cadmium industry (metal production or processing and use of different compounds) do not present such exposure levels that there are risks for health through exposure during a short period. The risks only become significant after long-lasting exposure : for instance 5 years, and more probably 10 years or more.

However, in cases of exceptional work, it has to be ensured that there is no possibility of strong absorption by inhalation (for instance concentrations in the air exceeding 1 $mg/m^3$), which can cause serious effects (particularly chemical pneumonitis).

Regarding such a risk, it is essential for the worker to wear respiratory protection with constant flow positive pressure supplied with clean air; it may, moreover, be useful, during the following days, to check the Cd content in the blood (see 4-1 and 4-2).

The following recommendations apply to the management of long-lasting exposure to relatively low ambient air concentrations (at or above levels of 5 $\mu g/m^3$) at the workplace.

## The Management of the Cadmium Risk on the work premises

The management of the cadmium risk on the work premises is based on 4 types of action :

1 Establishment and maintenance of a clean working environment
2 Individual protection
3 Information - training of the exposed workers and their staff and line managers.
4 Medical supervision adapted to the Cd risk.

Categories (1), (2) and (3) are direct preventive measures aimed at limiting absorption of the workers, either through inhalation or ingestion, to a level without risk of toxic effect.

In practice, however, when exposed to dusts and fumes in materials containing cadmium compounds, the external exposure levels can rarely be related to assimilation levels, for at least two reasons :

- According to the nature of the work and individual behavior, the ratio between exposure through inhalation and exposure through ingestion varies on a very large scale. For this reason, checking the cadmium contents in the air of the work premises cannot be a sufficient preventive measure.

- According to the chemical nature and the physical characteristics (particularly the size and solubility) of the inhaled or ingested particles, the assimilation rates can be considerably different.

In order to ensure the protection of workers subjected to an exposure risk, it is thus essential to supplement the measures according to (1), (2) or (3) with medical supervision enabling the Cd-body burden and early biological effect levels to be estimated; by such means the necessary measures can be taken in time to prevent toxic effects.

This approach is possible because there is a wide range of effective and sufficiently timely biological indicators (hereinafter referred to as BI) relative to the risk of nephropathy. This approach is illustrated and justified by the industrial experiences described in Part I.

## 1. Establishment and Maintenance of a clean working environment

This comprises a set of collective measures guaranteeing sufficiently limited exposure on the work premises. This approach has to be implemented as a priority; the individual protection measures (see section 2) are only complementary.

These collective measures can be classified in six main categories.

### *1-1 Ventilation - Suction*

In order to be effective, fairly precise rules of commonsense and technological conception must be respected.

* Work with metallurgic circuits should use intervention openings which are as small as possible.

* To optimize the geometry of the suction hoods.

* Fine tuning of the suction networks (network = many extraction points ending up in a ventilation system plus filtration or purification); above all do not modify a network and do not add extra equipment without checking the requirement of rebalancing the whole system.

* As the particles which have to be captured mostly have a very varied size distribution and density (in view of the nature of metalliferrous compounds), it is necessary to calculate the networks so that the suction speed at the suction orifice is never less than 0,5 m/s. It is better to aim for 1 m/s; sometimes it is useful to go up to 1,5 m/s.

According to the quality of these adjustments, for a given installation capacity (suction + purification), and thus for a given operating cost, the decontamination efficiency may vary considerably.

It is often necessary to provide special decontamination installations for maintenance workshops to which devices or movable pieces are forwarded.

### *1-2 Processing and storing in circuits which are as closed as possible*

Such measures vis-à-vis fine dusty materials may seem obvious; they require, in fact, a thorough and detailed conception and methodical and meticulous implementation afterwards, particularly :

- closed intermediate packaging and storing of materials which have to be treated again; this is all the more necessary the finer the products are.

- application of well-defined emergency procedures in case of malfunctioning.

### *1-3 Cleaning of the floors, surfaces, superstructures and equipments*

The cleaning of the floors, surfaces, superstructures and equipments in a normal working situation is important in order to minimize the presence of particles to a sufficient low degree (e.g. respect of an OEL -Occupational Exposure Limit - in the air of the work premises).

This cleaning may never be done by sweeping. Mostly, one can choose between the two following techniques :

- Spraying (sometimes high pressure spraying, particularly for superstructures) with water collection and purification.

*Note :This may mean that the electrical circuits in the workshops have to be made watertight.*

- Dry suction by means of movable devices (with a high or medium capacity according to the layout of the premises), or by means of a fixed network with suction vents allowing flexible devices to be connected.

### *1-4 Specific cleaning during intervention for preventive maintenance or in case of damage.*

This has to be done according to carefully established protocols for each type of installation or material : preliminary cleaning, during dismantling and reassembling, at the end of the intervention, concerted intervention plans between persons responsible for production and maintenance, etc.

### *1-5 Working positions or stations with excessive exposure levels should be automatised as much as possible.*

### *1-6 Control of products resulting from the purification systems and the waste*

It is necessary to control the products resulting from the purification systems and the waste with respect to the risks for the employees on the work premises as well as for the environment.

Recycling is carried out as far as possible.

The efficiency of the measures referred to above should be checked by measurements of the air quality (Cd content in the air at the workplace = Cd-A), and should be confirmed by the biological exposure indicators (see section 4).

The first approach consists of sampling the aerosol particles in the air at selected points to estimate either the efficiency of a suction system (and possibly to improve it), or the situation at a particular site in the working area. This is achieved by samplers placed at fixed positions.

A second approach consists of measurements by means of sampler worn in operator breathing zone.

These two approaches are complementary. The cadmium sampling and measuring systems should be chosen according to the existing European or national regulations or standards.

The sampling duration may vary from a few minutes up to 8 hours, according to its purpose (task orientated, check compliance with exposure limits,...).

## 2 Individual protection

Whatever the collective decontamination quality may be, and even if the measurements of the air inhaled give correct results, there is still a risk of excessive absorption via other routes; this risk has to be controlled extremely well by means of precautions taken individually.

In most Cd industries, the technical and economical constraints of the processes and installations make it impossible to totally eliminate contact with dusts on working clothes, the face, hands, nails, hair, eyebrows, etc... which may lead to ingestion.

The risk level increases significantly for :

- smokers : cigarette smoke inhibits clearance of dust from the respiratory tract by the mucociliary pathway. Cigarettes at the workplace may be contaminated on their surface with subsequent generation of fume and inhalation of this. Tobacco naturally has a high cadmium content and non cadmium-exposed smokers have higher Cd body burden that non-smokers;

- men with beards or moustaches : dust particles are deposited on facial hair with increased risk of ingestion. Facial hair impairs the seal of respiratory protection devices with considerable reduction of their efficiency;

- people who bite their nails.

It is essential to define and to apply simple, but strict, rules aimed at limiting the absorption risks through ingestion at a very low level (see 2-2 and 2-3). Prior to this, however, the role of respiratory protection has to be specified (2-1).

### *2-1 Respiratory protection*

In some cases it is technically impossible to maintain exposure at all times below the occupational exposure limit (OEL) which is recognized as sufficient to ensure full protection against the inhalation risk. Such situations may be :

a. either in a normal working situation in certain installations or at certain working posts (operations with a limited length of time),
b. or during intervention or particular maintenance work (e.g. : dismantling or cleaning inside a device, demolition of furnace brickwork, intervention inside a bag filter).

It may thus be necessary for certain persons to wear respiratory protection devices; but only for a period of less than 50% of a normal day's work (or post) (this restriction in the use of respiratory protection is mentioned in many regulations).

A. For a dust level slightly higher than an OEL, a half-mask fitted with a filter cartridge with a P2 or P3 efficiency level is generally enough (For P2 and P3 performances, see European standards = CEN).

It is essential, however, to check that the model used has a good facial fit for the individual. There are possibilities, in collaboration with specialized organizations, to test the total efficiency rate of these half-masks, with efficiency essentially depending on the "leak at the face".

It should be noted that these rates, which in standardized laboratory tests (CEN standards) often range between 95 and 99,5%, in industrial situations often drop to between 70 and 95%.

B. For increased efficiency - all the more so since the particles are finer (metallurgic fumes for instance) - it is necessary to use models which are far more expensive, and less easily tolerated by the persons wearing them (or for shorter periods). Those devices, panoramic masks or half-masks, are supplied with clean air from outside the air on the work premises and ensure a permanent over-pressure of this clean air inside the mask.

This category is recommended particularly for works with heating : soldering, grinding, blowlamp cutting, etc... or for exposure to very fine fumes.

C. A third category is being tested in some industries; it comprises assisted ventilation helmets supplied with filtrated ambient air (level P2 or P3 according to the models). These are also very expensive and opinion is divided as to their efficiency.

Proper use of these devices, once the model has been chosen for a definite use, depends on two factors :

- cleanliness; the protection is only real if the device is clean and particularly if no particles are accumulated inside before it is placed on the face (or on the head for visor helmets). This precaution is not easy to comply with, as the device has to be stored in a dust-tight covering and it has to be placed with clean hands on a clean face and clean hair, etc...

- keep in a good general condition : mechanical, electrical, etc...

For instance :
- on the edges of a facial piece which has to seal against the face;
- check the valves;
- check the screwing system or the placing of filtrating cartridges;
- check the batteries, the fans, the valves;
- change every defective piece.

This maintenance is far more complex and expensive for the devices of the B and C categories mentioned above, than for half-masks of the A category.

The periodic washing of half-masks can be carried out either by the person wearing the device, or by the Hygiene and Safety Service : washing with soap and running water or in

an ultrasonic vat containing a detergent solution, or according to the manufacturer's instruction.

For other models, it is preferable for washing and maintenance to be centralized by the Hygiene and Safety Service.

The filter cartridges have to be changed, either when mechanically damaged, or when obviously loaded with particles, or when the user experiences difficulty in breathing. There are no general rules for changing frequency; this has to be estimated in each particular case.

### *2-2 Individual hygiene at the workplace*

- Regulations specify that it is forbidden to drink, eat, smoke or to use chewing gum in the areas of the work premises which are exposed to certain metals and their compounds, and that the employer is responsible for the application of this measure. This measure has to be applied in the cadmium industry.

- Further to the point above, a no smoking policy is recommended on the whole working premises since cigarettes may be contaminated on their surface with subsequent generation of fume and inhalation of this. Furthermore, tobacco naturally contains a high cadmium content.

- Nail biting is a habit which can be very dangerous because of the ingestion risk, and which can even lead to unfitness, according to biological tests. There is a similar risk with persons with the habit of licking their lips, or wiping their faces with the hands or forearm (often the person does it without being aware of it). A talk with everyone who has one of those habits is essential.

- Men with facial hair should be advised about the increased risk of dust accumulation and of reduction of seal efficiency of the respiratory protection devices.

- A careful and complete shower (hair included) is necessary at the end of each post or day's work, as well as after each particularly dirty task.

- The lay-out of the changing-rooms must provide clean and dirty areas to enable working clothes to be kept separate from town clothes (shoes included).

- Working clothes have to be washed as frequently as the kind of work dictates, in a specialized installation without cadmium dust being scattered around.

- Food and drink must be stored <u>outside</u> any place where contamination can occur.

### *2-3 Protected premises (clean)*

Premises where it is possible to drink, eat must :

* be kept in positive pressure with clean air;

* comprise an entrance airlock with the possibility of washing the hands and face (it is recommended that the nails be brushed before eating, that the mouth be rinsed out before drinking, etc)

It may be useful for this airlock to include a system for cleaning boots or shoe soles, as well as a device for sucking dust off the working clothes.

Provision may be made for removal of working clothes before entering the canteens or provision may be made for disposal overalls;

* be cleaned : floor, walls, ceiling, tables, chairs, bathroom,.. as frequently as necessary.

A smoking room is not necessarily required, as smoking is recommended to be completely banned on the site. If it is provided, then facilities for washing hands and face must be available.

*Note : Certain precautions listed in paragraphs 2-2 and 2-3 may seem of secondary importance to some readers. According to the discussions carried through for some years now between manufacturers from various continents, they have been recognized as important and efficient. If not respected, they can render the efforts made under1 and 2-1 totally useless.*

## 3 Information - Training

Protection according to chapter 1 and 2 can only be efficient if constant and thorough efforts are made, through persuasion and dialogue with all the exposed persons as well as with the various levels of the hierarchy.

This is necessary in order to ensure :
- the good operation of the installations,
- the good application of the procedures,
- efficient cleaning of the premises,
- efficient personal hygiene,
- proper acceptance of medical supervision (see section 4).

According to the experience acquired over the past 3 to 10 years by many manufacturers, the aim is to combine various means, including :

* Brochures, leaflets, videos.

* Information and discussion sessions, with transparencies.

* Many more posters, notices, pictograms,...

* Dialogue between the participants in a "progress group" spirit.

* Video recording in the industrial workshop, followed by viewing and discussion between the parties involved : assessments, proposals, projects,...

* Need for well-supported and long-term action, mobilizing all levels of the hierarchy.

The typical animation structure comprises mostly the company head (or production head), representatives of the intermediate hierarchy and of the exposed workers, members of the

Hygiene and Safety Committee, the occupational doctor and the industrial hygienist (or person in charge of safety).

The information - training actions must be aimed at the maintenance personnel as well as to the production personnel and also have to be directed at temporary personnel (temporary employees, trainees, intervening companies) as well as permanent personnel.

## 4 Specific medical supervision

### *4-1 Presentation of biological indicators (BI) related to the Cd risk*

These main BI are summed up in Table 1, which presents the abbreviations, the units of measurement and approximate information regarding the biological effects.

The choice of those BI is the result of :
- the industrial experience ,
- literature references (Lauwerys & Malcom 1985; Bernard & Lauwerys 1992, Bernard et al., 1997)

Parameters of **exposure** to cadmium

**Cd-Blood** Reflects recent exposure and absorption, particularly in the first stage of occupational exposure. From the beginning of relatively steady exposure, Cd-B rises over a limited period (6 months to 2-3 years depending on exposure conditions), and tends to stabilize afterwards on a given level according to the ongoing exposure. At that time, mobilization of Cd bound to metalothionein makes an increasing contribution to Cd-B, which then reflects not only actual exposure, but also cumulative exposure and hence body burden.

Short time elevations of Cd-B may be caused by episodes of excessive exposure. If exposure ends, a fairly rapid decrease of Cd-B is observed during a first stage; in a second stage, the decrease levels off, depending on accumulated body burden.

**Cd-Urine** As long as the functional state of the kidneys is normal, the Cd-U content is well correlated with the total Cd body burden. Therefore Cd-U is the main indicator to be considered in the management of long-term risks.

Total Cd body burden is reflected by the Cd content in the renal cortex; the value 10 µg/g creatinine for Cd-U corresponds approximately to the value 200 µg Cd/g wet kidney tissue (wet load) in the renal cortex.

In the professional environment, these two values are usually considered by toxicologists as limits below which pathological changes in the kidney generally do not occur.

When an important and irreversible tubular-type renal affection occurs (increase in microproteinuria - see B2MG-U and RBP-U), Cd-U tends to increase and the Cd-content in the renal cortex to decrease.

In conclusion, both Cd-B and Cd-U are parameters to assess occupational exposure to cadmium.

Taking into account the good correlation between Cd-U and life time accumulated Cd body (kidney) burden, Cd-U is considered as the preferred parameter to assess long-term occupational exposure (several years), and is used as such in the risk management system presented in Table 2. Cd-B is particularly useful to assess exposure during the first stage of occupational life. Afterwards, it becomes more complex to interpret, reflecting both present-day exposure and body burden. It remains however a useful parameter to assess short-term exposure excursions at any time of occupational exposure, including removal from the workplace.

Parameters of **Effect** of cadmium

**B2MG-Urine** Beta-2-microglobulin (B2MG) is a protein with a low molecular weight (LMWP) (< 40.000) which is part of the metabolites stemming from the human body's activity. The kidney has to filter this protein towards the urine when purifying the blood.

The increase of this content in the urine is a functional indicator of an alteration of the tubular re-absorption.. The test is sensitive and can be applied using commercially available methods. Its only drawback is that B2MG is unstable in acidic urine (pH<5.6) (Bernard, 2004) When taking a urine sample it is thus necessary to measure its pH. If this is below pH 5, the sample should be discarded.

It is then possible to take another sample later on, or to have the subject ingest 1 g of sodium bicarbonate and to take a sample 2 hours later. Unless the patient has been given bicarbonate before urine collection, a loss of the B2MG is unavoidable in 10 to 30% of the urine samples (Bernard 2004)

*Note :Not all clinicians agree on this second procedure. Some of them consider that it provokes a renal extra load. It must not be used for any subject suffering from renal insufficiency due to other causes than cadmium.*

or to measure RBP-U instead of B2MG-U (equally representative of a tubular affection).

This third solution is the best one.

**RBP-Urine** Retinol Binding Protein (RBP) is a microprotein (molecular weight < 40.000) equivalent to B2MG-U as an indicator of the possible tubular effect of cadmium. It is stable in urine at pH levels higher than 4,5.

For several years certain toxicologists have tended to prefer this BI to B2MG-U. At present, however, only a small number of laboratories are capable of measuring this indicator with a good precision.

**Albumin-U** Albumin is a protein with a high molecular weight (> 40.000). Isolated cases of an increase (associated to a low MW proteinuria) of its content in urine indicates a functional impairment of the glomerular filtration.

The five BI above are considered as direct indicators of cadmium exposure (Cd-B, Cd-U) and effects (B2MG-U, RBP-U, Albumin-U)[4] and are representative of the risk linked to this metal and its compounds.

The biomonitoring of the effects parameters is used in complement with the monitoring of the exposure parameters in order to account for the inter-individual variability of responses to cadmium exposure.

### *4-2 Sampling procedures*

**Urine**

There are 2 methods of taking urine samples :

* To collect all urine during 24 hours.

This method presents serious disadvantages and uncertainties. The person involved has to be given a bottle that he takes home. The clinician cannot always be sure that the urine is meticulously collected (forgetting, bringing someone else's urine,...);

* "Spot" collection of urine on the work premises, with correction of the rough result of cadmium content either by measuring the creatinine, or by measuring the urinary density (or the refraction index - conversion factors exist) and correction with respect to the density 1,020.

The second method ("spot" urine) is mostly used; it is advisable to collect the urine samples in the morning on the person's arrival at work to minimize contamination and provide standard conditions for collection.

In all cases, extreme care must be taken to avoid contamination of the urine sample during micturition.

The only procedure offering a good guarantee is to have a shower before micturition.

*Note : To be valid the urine sample must not be too diluted, for instance :*

- Creatinine-U > 0,5 g/L,
- or urinary density > 1,010.

**Blood**

Strict precautions must be taken to avoid contamination of skin in the collection of blood samples. The time is not important, but the sample has to be taken with an empty stomach for serum creatinine.

### *4-3 Precision of the analyses*

1. It essential to mention that the analyses are generally not too precise (precision = combination of "accuracy" and "fidelity"), due to the low levels to assess and to the difficulty of carrying out the analysis itself.

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[4] **Alpha-1MG** alpha-1 microglobulin is also very stable in urine but according to some studies might be less sensitive as marker of tubular dysfunction and possibly also less specific because of its larger molecular weight (26 kDa) (Bernard, 1996)

Two examples from international inter-laboratory circuits, between well-trained laboratories :

- for a Cd-B result of 8 µg/L, the confidence interval with a 95% probability is between 5,5 and 10,5[5];

- for a Cd-U result of 12,5 µg/L it ranges from 9 to 16 !

It is thus very important for those analyses to be carried out by reliable laboratories, with a very good technical level and regularly using quality control procedures.

2. The quality control procedures must comprise well-defined standardizations, periodic anti-drift tests, the use of reference materials[6] to check accuracy and regular involvement in inter-laboratory circuits (this is only organized in a few countries, but there are good international circuits).

3. Besides reliability and accuracy problems regarding the measuring method itself, the contamination risks of the sample must also be considered. These are relatively low for Cd-B but more important for Cd-U. For instance, if in a series of results ranging from 2 to 5 there is a value higher than 8, contamination has to be suspected.

4. A laboratory being considered for use should agree to provide its customers with the detailed results of its quality control procedures and involvement in circuits.

5. Every person requesting analyses must inquire about the quality of the laboratory to which he is applying. A technical audit should be made and duplicate samples may be submitted (periodically) blind for intra- and inter-laboratory comparison (tests for repeatability and drift risk).

For the good relationship between the laboratory and the customer to continue, the latter must transmit all control results to the laboratory even when they are good.

6. Because of all these variabilities, detailed and efficient biological supervision requires sampling to be spaced out over time and one BI to be interpreted on the basis of several successive results.

For the same reasons, it is useful to observe 2 BI or more for one type of biological effect (for instance, tubular affection risk) instead of only one BI.

### *4-4 General approach in biological monitoring*

Each time that monitoring can be based on a wide and diversified range of BI, it would be wrong to base a decision (technical measure to improve a workshop, specific training actions for exposed workers, unfitness decision,...) on the observation of one parameter (either Cd-A, or a BI), which exceeds a limit for this single parameter.

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5 This means that, if the circuit average is marred by a very low lack of accuracy with respect to the real value, the 5,5 to 10,5 width interval has a 95% chance of containing an individual result given by one of these "well trained" circuit laboratories.

6 There are official EEC reference materials for cadmium (and lead) contents in the blood which are guaranteed and sent out by BCR, 200, rue de la Loi, B-1049 Brussels (Belgium).

Excess must always be confirmed by one or two other measurements for the same BI.

The evaluation is always better if it is based on the set of various available BI and it is up to the occupational doctor to define his diagnosis and to take his decisions considering the whole of the picture; in some cases he can consult the occupational hygienist, particularly for conclusions and collective objectives regarding a workshop, a group of workers, etc.

*Consequently, the outline of the biological monitoring proposed in section 4-5 and 4-8 below must be considered as indicative only. It is up to each occupational doctor to choose, in the context of a given factory, the natures and the frequencies of the studied parameters, as well as how to interpret the results and to elicit decisions from it.*

In health surveillance, the emphasis must be placed on measures of primary prevention in order to maintain the levels of Cd as low as possible. The efficacy of these measures can be controlled by measuring the metal in urine or blood, and usually a periodic screening for renal dysfunction is implemented only when excessive levels of Cd are found in urine and blood. For these reasons and also to achieve the best cost-benefit ratio, screening tests for tubular proteinuria are always used in combination with a biomonitoring programme measuring Cd in urine and blood. This combination is also important for the interpretation of the results since a persistent increase in the urinary excretion of B2MG or RBP, after exclusion of other causes, can be ascribed to Cd only when it is associated with an increased Cd body burden. A screening for tubular proteinuria is normally recommended in all subjects who persistently show an urinary Cd above 5 µg/g creatinine (Bernard, 2004).

### *4-5 Action areas*

Given the variability between individuals, the many different exposure scenarios, the differing hygiene habits of workers, as well as other socio-economic factors such as the number of years left at work, it is imperative that a comprehensive surveillance programme be based on several threshold levels, each threshold corresponding to an heightened level of risk prevention.

a) Below certain exposure and effect BI thresholds, Cd exposure is very unlikely to cause any harm to workers, and the surveillance programme should be focused on keeping risk awareness high, teaching proper work and hygiene habits, and on identifying early on deviations in work content, work habit and personal hygiene parameters susceptible to cause a change in these low exposure, low effect BI levels (Table 1, Box 1).

b) If exposure and effect BI levels exceed low thresholds, Cd exposure may create in the long run a deviation from acceptable exposure and effect BI levels, and depending on the personal characteristics of the worker, such levels may potentially evolve into above-acceptable, and possibly irreversible (low and/or high) molecular weight protein excretion (Table 1, Box 2 and/or 4).

In this area, the levels are above these low thresholds, the surveillance programme should focus on the identification of causes of exceedance. The source of such exceedance may lie in a combination of changes to work content, work habit and/or personal hygiene.

Of course, once identified, the cause for exceedance should be addressed in a proper and swift way. In this configuration, freedom should be given to the occupational doctor to assess whether removal from exposure is necessary.

c) If exposure and effect BI levels exceed high thresholds, then the emphasis of the surveillance programme should be the removal of the worker from Cd exposure until the worker's BI return to nominal levels. Little or no flexibility should be given to the occupational doctor regarding the decision of displacing the worker (Table 1, Box 3 and/or 5).

### *4-6 Pre-employment examination*

This examination may comprise the following elements, attention in particular should be given to

- Clinical examination :

* Past medical history (particularly those concerning the kidneys and the respiratory tract; but also diabetes; for women, pregnancy and associated pathologies).

* Previous occupational history, exposure to dangerous substances including certain metals and their compounds.

* Behavioral data : hygiene, smoking, hygienic habits (nail-biting), do-it-yourself activities outside the work premises,...

* Clinical examination, including blood pressure, respiratory tests and an estimation of the suitability to wear respiratory protection devices.

- Biological examination :

This should comprise the observation of several BI, for instance, as outlined in the following example, and mainly based on an increasing scale of the Cd-U values (see units in Figure 1) as well as a baseline (low and/or high) molecular weight protein excretion measurement.

**Cd-U < 2** and :
- clinical examination normal
- complementary BI : Cd-B ≤ 3[3]

⇒ consider FIT

**2 < Cd-U ≤ 5**
- Determine with the subject if the causes for increased Cd body burden are either non-occupational or due to previous occupational exposure(s).
- Complementary BI for exposure :
  a) Cd-B ≤ 5[4]
  b) Moreover, assessment of complementary BI that allow the detection of possible nephropathy is needed
  e.g. : β2MG ≤ 300 or RBP ≤ 300 and albumin ≤ 15

⇒ if the above levels for additional BI are respected : consider FIT

⇒ if any of the above parameters exceed the value given : consider UNFIT

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(3) Cd-B is increased in smokers from a level of ≤ 1 µg/l up to 3 µg/l.

(4) Cd-B > 3 indicate previous cadmium exposure. Results should be interpreted with Cd-U to assess body burden.

**Cd-U > 5** (confirmed)
⇒ consider UNFIT

### *4-7 Program of periodic examinations for supervision of chronic moderate exposure*

Periodic examinations for the supervision of chronic moderate exposure to cadmium begin when the worker's Cd-U >2 µg/g creatinine or Cd-B >2 µg/L.

#### *4-7-1 The outline of the risk management*

The outline of the risk management is based on the following combination of observations (see Table 1) :
- Cd-A with the National OEL in air

- Cd-U as main BI for overall chronic exposure, but systematically associated with other BI of effects as soon as Cd-U exceeds 2 µg/g creatinine

- Cd-B as main BI for recent exposure and as main driver for an ongoing surveillance programme

- LMWP and/or HMWP as BI of effects (RBP and/or B2MG and/or Albumin) as soon as Cd-U exceeds 2 µg/g creatinine

<u>Note</u> : *Under no circumstances should the risk management be limited to the adoption of an OEL in the air because of the great variability, according to the subjects, of the percentage of absorption having other origins than inhalation.*

By means of these parameters, Table 1 defines 5 areas in which the actions to be taken are specified relative to the nature and the frequency of the observation.

This outline is an indicative guide that each occupational doctor can adapt according to the framework and his own approach.
Main BI :

| | |
|---|---|
| Cd-Blood | ≤ 8 |
| Cd-U | ≤ 5 |
| B2MG-U | ≤ 300 |
| RBP-U | ≤ 300 |
| Albumin-U | ≤ 15 |

Creatinine clearance on an empty stomach ≥110 ml/min[(5)]

The numerical values mentioned above are considered as "guidance values" which are acceptable for adult workers as long as periodic biological monitoring with suitable frequency is carried out.

It is useful to recall that :

Cd-A : a "specific Cd supervision threshold" of 5 µg/$Nm^3$ should trigger mandatory participation in the surveillance programme for workers. Workers exposed below this

(5) or > = 80 ml/min. if definition according to Cockcroft.

threshold would be subject to BI measurement requirements during the normal course of the general occupational health surveillance programme.

Cd-U : as principal BI of chronic overall exposure, but systematically associated with other BI of effects as soon as Cd-U exceeds 2 µg/g creatinine:

- as long as Cd-U ≤2 µg/g creatinine and Cd-B ≤5 µg/L, no further action should be required but regular monitoring, training and keeping awareness high (Table 1, box 1)

- as Cd-U > 5 µg/g creatinine, then the emphasis of the surveillance programme should be the removal of the worker from Cd exposure until the worker's BI return to nominal levels. Little or no flexibility should be given to the occupational doctor regarding the decision of displacing the worker (Table 1, box 5).

Cd-B : as principal BI of recent exposure is used as a main driver for the ongoing surveillance of the worker:

- as Cd-B >5 µg/L, irrespective of whether Cd-U is ≤2 µg/g creatinine or between 2 and 5 µg/g creatinine, the surveillance programme should be geared at identifying causes for exceedance. The source of such exceedance may lie in a combination of changes to work content, work habit and/or personal hygiene. Such causes should be properly and swiftly addressed and corrected (Table 1, Box 2 and/or 4).

- as Cd-B > 8 µg/L, then the emphasis of the surveillance programme should be the removal of the worker from Cd exposure until the worker's BI return to nominal levels. Little or no flexibility should be given to the occupational doctor regarding the decision of displacing the worker (Table 1, Box 3).

- The Cd-U and Cd-B are indicators of the worker's exposure to cadmium, whereas the RBP-U and β2MG-U are bio-markers of renal function of the worker. Both need to be monitored to properly protect the worker against effects to cadmium.

- as long as Cd-U ≤5 and/or Cd-B <8 and as long as the proteinuria indicators are checked, the renal affection risk is extremely small;

- when Cd-U is >5 and /or Cd-B >8, and if β2MG-U and/or RBP-U is below 300 and/or Albumin is below 15, there is no short-term risk and it is reasonable to wait for these levels to be confirmed by two or three successive BI measurements before possibly determining unfitness;

Generally, a limited microproteinuria is observed within the range of 300 to 500, but when the worker has subsequently been removed from exposure, reversibility towards normal urinary excretion levels of this microproteinuria is observed.

It is as a precaution that unfitness is pronounced when Cd-U is confirmed >5 (2 or 3 measurements at 6 month intervals), while no notable deterioration of the renal parameters is observed ; since this level indicates a high Cd body burden.

It is as a precaution that unfitness is pronounced when RBP-U and/or β2MG is confirmed >300 or Albumin >15 since although initially limited and reversible, microproteinuria may start to be observed.

When a worker has ceased exposure on medical advice, continued medical supervision should be maintained for 5 years, if possible, to determine if renal dysfunction has reversed (at least once a year). This continuation of supervision can also be useful after retirement.

*Important note :*
*More than the overstepping of the guidance values mentioned in 4-7-1 for β2MG-U, RBP-U and Albumin-U, the removal criterion is linked to a progressive rise of these parameters observed during many successive examinations. This is matter of estimation by the occupational doctor.*

#### *4-7-2 Return to an exposed work post, after removal.*

This return can only be considered if the removal has been caused by increases of either Cd-U, or Cd-B, without important proteinuria and if after comparison with values similar to first fitness criteria, it is :

- Cd-B <5
- Cd-U < 5
- β2MG-U < 300 or RBP <300
- and Albumin < 15

*Note : On the medical doctor's own initiative, one or another BI (e.g. Cd-B) can be measured more frequently (Table 1).*

### *4-8 Monitoring in the case of occasional (not regular) exposure or exposure of a fairly short duration (one to several months)*

Depending on the duration, intensity and more or less repetitive nature of the exposure, it is up to the occupational doctor to decide what biological indicators to use and to define the intervals of biological examinations.

In particular during the first months (e.g. up to six months) it can be considered to use Cd-B as a primary indicator for exposure.
In any case where exposure lasts for more than a year, however, the general scheme is advised, even when exposure to Cd is only occasionally.

### *4-9 Interim outline of risk management for workers whose exposure started prior to 2000*

Individuals employed in the cadmium refiners manufacturing and user plants who have been exposed for many years may not be able to meet the lower limits set as precautionary measures for exposure as set in section 4-7-1 (Table 1). This is due firstly, to the accumulation of cadmium and its long half-life and secondly, because of the fact that these individuals were employed in environments where plants were operating under higher limit levels by which plants have been legally operating. Because of this, it is suggested that, for an interim period of time, decisions rely mainly on LMWP proteins for employees of several years standing (employed before 1 January 2000) and a higher limit for Cd-U at 10 micrograms Cd/g creatinine and Cd-B at 10 µg/L. The justification is that monitoring data from several years is available for these individuals and that although these are showing higher chronic exposures, these are showing no

signs of effect (i.e. microproteinuria), that is, provided that the RBP, β2MG and/or Albumin remain < 300, and/or <15 – considered fit) using the same parameters as other employees.
There is no discrimination on the effects, and only on the cumulative exposure parameters (Cd-U). This is seen as an interim strategy in order to avoid the termination of contracts of long-term employees who still prove fit to work.

## 5 Recordkeeping requirements

The OSHA (2004) guidelines recommend that recordkeeping requirements for an employer operating a facility with the potential for occupational exposure to cadmium consist of 3 types; air monitoring, medical surveillance, and training records.

### *5.1 Air Monitoring records*

It is recommended that records of air monitoring include the following:
- The date, duration, and results of air monitoring tests, in terms of an 8-hour time-weighted average (TWA) for each sample.
- The name and job classification of all employees for which the monitoring is intended to represent.
- A description of the sampling and analytical methods used and evidence of their accuracy.
- The type, if any, of respiratory protection worn by the monitored employee(s).
- A note of any conditions that may affect the outcome of the monitoring results.
- The employer must maintain these records for at least 30 years.

### *5.2 Medical Surveillance records*

The employer must maintain records for every employee subject to medical surveillance, and it is recommended to include the following information:

- The name of the employee
- A description of the employee's duties
- A copy of the physician's written opinions and an explanation sheet for biological monitoring results.
- A copy of the medical history and results of the clinical examination and all test results.
- A description of any employee symptoms that might be related to cadmium exposure
- A copy of the information provided to the physician.
- These records must be maintained for the duration of the employer's employment with the company plus 30 years.

Furthermore, the European Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work outlines the requirements for health and exposure records. These and their availability shall be in accordance with national laws and/or practice.

### *5.3 Training records*

It is recommended that the employer place in the employee file a record showing the training sessions attended as well as the date and the content of these training sessions. This record should also include the signatures of the employee and of the trainer.

Table 1

**Indicative diagram of CADMIUM risk management in chronic moderate occupational exposure**

Cd-U : must be done at least every 24 months, during the overall periodic medical review.

Cd-B : must be done at least every 12 months, during the Cd biological exposure control visit. Doctor may require higher frequency if Cd-A of worker is well above 5 (but below legal OEL).

Low and/or high molecular weight protein excretion : must be part of the annual biological exposure control visit.

Cd-A : (8hr TWA). Must be measured every year as part of overall plant compliance programme. Should be spot checked if worker moves from area (1) to (2) or above.

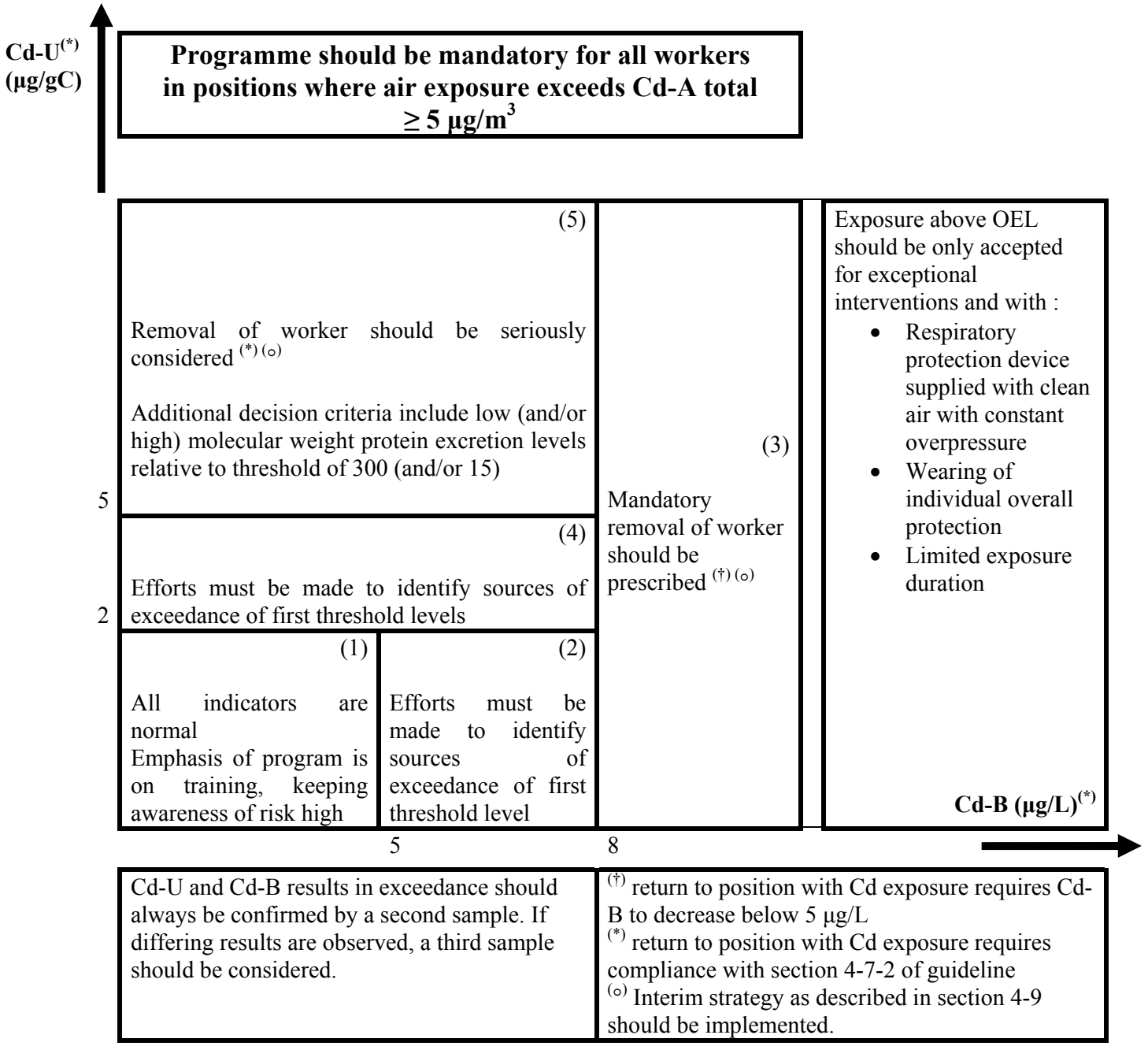

Figure 1

# Abbreviations and meanings

| Cd-A : Cd content in the air (µg/Nm³) | - U : in the urine<br>- B : in the blood<br>- Se : in the serum<br>- C : creatinine | | **Biological Indicator (BI)** (***) | | | |
|---|---|---|---|---|---|---|
| **Symbol** | **Meaning** | **Standard Unit** | **Tubular effect** | **Glomerular effect** | **High body burden** | **Recent impregnation** |
| Cd-B | Cd content in the blood (cadmiemia) | µg/L | | | (X) | X |
| Cd-U | Cd content in the urine (cadmiuria) | µg/gC | X | (X) | X | (X) |
| β2MG-U | Beta-2 microglobuline (*) in the urine | µg/gC | X | | (X) | |
| β2MG-B | Beta-2 microglobuline (*) in the blood | µg/L | | X | (X) | |
| RBP-U | "Retinol Binding Protein" (*) in the urine | µg/gC | X | | (X) | |
| Alb-U | Albumin (**) in the urine | mg/gC | | X | (X) | |
| | | | | | (X) | |
| | | | | | (X) | |
| | | | | | | |
| GFR | "Glomerular Filtration Rate"<br>Its measurement can be carried out through inuline or creatinine clearance | ml/min (brought back to a body surface of 1,73 $m^2$) | | X | | |

(***) In comparison with X, (X) indicates a less marked, or less specific, relationship between effect and biological indicator.
(**) Protein with a high molecular weight (HMW). There are other proteins which may be used as BI related to cadmium.
(*) Protein with a low molecular weight (LMW). There are other proteins which may be used as BI related to cadmium.

DIURESIS : increased urine flow, in ml/min (or its composition).

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