Gezondheidsraad
Health Council of the Netherlands

To the Minister of Social Affairs and Employment

Subject	: Advisory letter *Cadmium and inorganic cadmium compounds*	
Your reference	: DGV/BMO-U-932542	
Our reference	: U 7800/BvdV/fs-459-R68	Publication no. 2013/14E
Annexes	: 3	
Date	: July 5, 2013	

Dear Minister,

The Health Council received a request from your ministry to advise on the consequences of occupational exposure to cadmium and inorganic cadmium compounds (see Annex A). These substances were evaluated by the European Union's Scientific Committee on Occupational Exposure Limits (SCOEL) in 2010.[1] The Dutch Expert Committee on Occupational Safety (DECOS) (see Annex B) examined the SCOEL advisory report alongside studies published since 2010. In this advisory letter, I inform you of the Committee's findings regarding the health-based recommended occupational exposure limits for cadmium (Cd) and inorganic cadmium compounds.

SCOEL evaluation[1]

Occupational exposure to cadmium and inorganic cadmium compounds is primarily via inhalation. Additionally, oral exposure to cadmium occurs due to consumption of contaminated food and/or smoking. Cadmium accumulates in the body and has a very long half-life (10-20 years). Therefore, the accumulated cadmium body burden, rather than the cadmium concentration in the air, determines systemic effects, particularly on kidneys and bones. Cadmium in the urine (Cd-U) is the best measure for the body burden and the most suitable parameter for risk assessment. On the other hand, the concentration of cadmium in ambient air may be used as a measure for the effects on the lungs, which are exposed directly to the air. The dose-effect/response relationships between body burden and systemic effects are well-documented in a large number of epidemiological studies, which were used by the SCOEL for quantitative risk assessment, i.e. derivation of biological limit values (BLV). The SCOEL considers the kidney to be the most susceptible target organ for systemic cadmium toxicity. A BLV of 2 µg Cd/g creatinine in the urine was recommended by the SCOEL in 2010 for protecting employees against systemic cadmium toxicity, particularly against effects on kidneys and bones.

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Long-term inhalation of cadmium-containing dust and vapours may also lead to local lung effects, such as lung emphysema and – potentially – lung cancer. The SCOEL is of the opinion that the BLV provides insufficient protection against this risk and that an additional limit value, based on cadmium in the ambient air, is necessary to protect employees from these local effects. Existing epidemiological studies examining the relationship between cadmium and lung cancer were found to be insufficient for derivation of such values. The data from these studies do not allow the carcinogenicity of cadmium alone to be examined, as there is always co-exposure to other substances. However, there is one epidemiological study that may be used for quantitative risk assessment which examined non-carcinogenic respiratory effects (lung function). Based on this study, the SCOEL derived an OEL (occupational exposure limit) of 4 µg Cd/m^3.

Committee evaluation

Derivation of a biological limit value based on toxic effects on the kidneys

Like the SCOEL, the Committee considers the kidney to be the organ most susceptible to systemic cadmium toxicity following workplace exposure. The Committee shares the SCOEL's opinion that urinary cadmium (Cd-U), as a measure of cadmium body burden, is more suitable for risk estimation of renal damage than measurements of cadmium in the ambient air. Furthermore, the Committee shares the SCOEL's opinion that long-term inhalatory exposure to cadmium may result in local lung effects, such as lung emphysema and – potentially – lung cancer.

The SCOEL (2010)[1] reports that damage to kidney tubules is the first sign of renal toxicity in individuals with occupational exposure to cadmium; concentrations of U-ß2M, U-NAG and U-ALB are sensitive parameters for this.[a] Disruption of tubular reabsorption is usually seen (U-ß2M, U-NAG). A number of studies has shown that a body burden of cadmium corresponding to an excretion of 5-10 µg Cd/g creatinine is a limit at or above which this renal tubular damage is observed (lowest observed adverse effect level, LOAEL). A higher LOAEL than currently defined could have been obtained from a number of these studies. This is due to the presence of older employees in the studies; these employees used to be exposed to much higher cadmium concentrations, but have likely already lost a large part of their cadmium burden at the time of the

[a] U-ß2M = ß2-microglobuline in urine, U-NAG = N-acetyl glucosaminidase in urine, U-ALB = albumin in urine.

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study, while the kidney damage caused by the higher burden had already been caused. The final SCOEL recommended BLV is 2 µg Cd/g creatinine.

In addition to the information from the SCOEL, the Committee evaluated a number of more recently published epidemiological studies not listed in the SCOEL report. These are studies in which a BMD (benchmark dose) analysis was performed in order to determine critical concentrations for the development of renal effects.[2-8] The BMDL-10[a] for U-ß2M in the individual studies studies varied from 3.37 to 9.9 µg Cd/g creatinine. The BMDL-10 for U-NAG ranged from 2.13 to 2.72 µg Cd/g creatinine. For U-ALB (disruption of glomerular filtration), the BMDL-10 varied between 4.23 and 4.85 µg Cd/g creatinine. The Committee concludes that a body burden of cadmium corresponding with 2 µg Cd/g creatinine may be considered a NOAEL (no observed adverse effect level) for renal effects.

Based in part on the outcomes of the BMD analyses, the Committee feels the SCOEL recommended biological limit value of 2 µg Cd/g creatinine is acceptable.

Derivation of a health-based recommended occupational exposure limit based on non-carcinogenic effects on the lung

Long-term inhalatory exposure to cadmium may, in addition to systemic effects, result in local effects in the lung, such as lung emphysema and – potentially – lung cancer.

The Committee shares the SCOEL (2010)[1] opinion that limiting the cadmium body burden using a biological limit value (BLV) is not sufficient for protecting employees from these local effects. The Committee agrees with the SCOEL reasoning that, considering the local effects of cadmium on the lung, a health-based recommended occupational exposure limit (HBR-OEL) based on these effects is required to protect employees. Chronic inhalation of cadmium-containing dust and vapour has been associated with the development of both non-carcinogenic and carcinogenic effects. The Committee shares the SCOEL's opinion that the existing epidemiological studies of the relationship between cadmium and lung cancer are not suitable for quantitative risk assessment. These studies always include co-exposure to other substances (see next paragraph). However, there is one epidemiological study examining non-carcinogenic respiratory effects (lung function) that can be used for a quantitative risk assessment.[9] Therefore, the Committee has a preference for using the non-carcinogenic respiratory effects of cadmium for determining a health- based recommended occupational exposure limit.

[a] BMDL = lower confidence interval limit for a BMD.

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The SCOEL selected the study by Cortona et al. (1992)[9] for risk assessment. The results of the study by Cortona et al. (1992)[9] show that cumulative exposure to cadmium oxide vapours (CdO) of 500 µg Cd/m^3 x year lead to changes in the residual lung volume[a] (RV, increase of about 7%). This cumulative value of 500 µg Cd/m^3 x year is equivalent to exposure to 12.5 µg Cd/m^3 (LOAEL) for 40 years. Using an uncertainty factor of 3, this results in an occupational exposure limit (OEL) of 4 µg Cd/m^3. The Committee realises that the study by Cortona et al. (1992)[9] had a number of limitations, but is also aware that there are no other suitable studies, and therefore feels the choice of this study is justified. The Committee considers and recommends this value of 4 µg Cd/m^3, based on non-carcinogenic effects, to be a health-based recommended occupational exposure limit (HBR-OEL).

Does this health-based recommended occupational exposure limit also protect against lung cancer ?

The Committee subsequently evaluates to what extent the health-based recommended occupational exposure limit (HBR-OEL) of 4 µg Cd/m^3 derived by the SCOEL also protects against possible carcinogenic effects of cadmium and cadmium compounds on the lung in humans. The Committee used the report and recommendations of the DECOS Subcommittee on the Classification of Carcinogenic Substances (see Annex C). In its report, the Subcommittee concludes that it cannot be ruled out that cadmium causes lung cancer, but that available human data do not allow a distinction to be made between the effect of cadmium alone and the effect of other factors (such as arsenic). In rats, but not in other species, lung tumours were found following inhalatory exposure to cadmium oxide, chloride, sulphate and sulphide. These studies show that exposure to low cadmium concentrations in rats can cause lung tumours, but that these tumours were induced under unrealistic exposure conditions (23 hours/day, 7 days per week for 18 months). The Subcommittee therefore classifies cadmium into category 1B ('the substance is presumed to be carcinogenic to man').[10] Additionally, the Subcommittee is of the opinion that cadmium is genotoxic. However, this genotoxicity is not caused by a direct interaction between cadmium and DNA, but via another mechanism, such as the formation of reactive oxygen, the induction of cell proliferation or inhibition of DNA repair mechanisms. These are non-stochastic genotoxic mechanisms. This means that for a quantitative risk assessment based on carcinogenic effects a threshold model approach would be preferred.

[a] Volume remaining in the lungs after maximal expiration.

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The Committee agrees with the Subcommittee recommendations and used them for the further assessment of the arguments formulated in the SCOEL report[1] (on pages 16 and 17) regarding validation of the HBR-OEL:

- The SCOEL notes that co-exposure to substances other than cadmium (mostly arsenic) always play a role in epidemiological studies. Therefore, the SCOEL is of the opinion that human data are inadequate for a quantitative risk assessment of cadmium alone. The Committee agrees with this position. Furthermore, the Committee notes that the epidemiological study by Nawrot et al. (2006)[11], which is mentioned in the SCOEL report but not discussed in detail, does correct for co-exposure to arsenic, but that this study is not representative for individuals under occupational circumstances due to oral exposure and mixed composition of the study population. This study can therefore also not be used for quantitative risk assessment in employees.
- The SCOEL is of the opinion that the mechanism for carcinogenicity is not fully understood, but that indirect genotoxic mechanisms are involved, for which a threshold value could be identified (Bolt & Huici-Montagud, 2008[12]). The Committee agrees with this opinion, which is also the conclusion of the Subcommittee report (see Annex C).
- The SCOEL draws attention to the fact that a threshold limit value for genotoxic effects of 1,000 µg/m³ x year (or 25 µg/m³ for 40 years) can be derived from the epidemiological study by Forni et al. 1992.[13] The Committee supports this. This study examined the genotoxic effects of 40 employees in the cadmium industry after inhalatory exposure to cadmium vapour and dust. Only in the subgroup with the highest cumulative exposure (>1,000 µg/m³ x year) was an increase in the number of chromosomal aberrations observed.
- The SCOEL also draws attention to the limited epidemiological evidence showing that exposure to cadmium does not result in additional cancer cases in concentrations high enough to cause renal and respiratory toxicity (Sorahan & Esmen, 2004[14]). The Committee confirms this.
- Finally, the SCOEL draws attention to the fact that animal data (rat) show that the lowest concentration that leads to primary lung carcinoma is 12.5 µg Cd/m^3 [15,16], while no lung tumours were found in rats after exposure to 10 µg Cd/m^3.[17] The Committee agrees, and furthermore notes that these tumours were induced under unrealistic exposure conditions (23 hours/day, 7 days per week, for 18 months).

The SCOEL is of the opinion that the above-mentioned data make it sufficiently plausible that the HBR-OEL of 4 µg Cd/m^3 protects against genotoxic and – potential – carcinogenic effects in

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humans. The Committee agrees with this, and notes that the human data in particular support this conclusion. Additionally, the Committee notes that, as found in human studies, the kidneys are more sensitive to cadmium than the lungs. This implies that measures that sufficiently protect the kidney will at the same time protect the lungs. Therefore, the Committee expects that the combination of a BLV and a HBR-OEL provides sufficient protection against the non-carcinogenic and – potential – carcinogenic effects of cadmium and inorganic cadmium compounds.

Conclusion and recommendations

Based on the considerations outlined above, the Dutch Expert Committee on Occupational Safety agrees with the reasoning and values derived by the SCOEL. The Committee concludes that the limits recommended by the SCOEL provide sufficient protection against the non-carcinogenic and – potential – carcinogenic effects of occupational exposure to cadmium and inorganic cadmium compounds.

The Committee recommends the following for cadmium and inorganic cadmium compounds:

- a biological limit value of 2 µg Cd/g creatinine in urine and
- a health-based recommended occupational exposure limit of 4 µg Cd/m^3.

I endorse the conclusions and recommendations of the Committee, and hope this advisory letter answers your questions.

Yours sincerely,
(signed)
Professor W.A. van Gool,
President

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Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for

advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in Annex B.

Annex **B**

The Committee

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The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Evaluation of the Subcommittee on Classification of carcinogenic substances

Carcinogenicity of cadmium and cadmium compounds

Cadmium was classified previously as a human carcinogen (Group 1) by the International Agency for Research on Cancer (IARC).[1,2] The subcommittee does not agree with IARC's conclusion on the human data. Although both lung and prostate cancer are reported in employees following occupational exposure to cadmium, the available epidemiological studies in the past and to date are deficient or of dubious quality. The subcommittee indicates that cadmium and its compounds cannot be ruled out as a cause of cancer in humans, but that the data do not allow to discriminate unambiguously between a true carcinogenic effect of cadmium per se, and an effect of other occupational carcinogens (such as arsenic) or non-occupational factors.[3-8]

Regarding the animal data, the subcommittee evaluates the studies summarized below. Oldiges et al. (1984) exposed rats to various concentrations of cadmium chloride aerosol. Histopathological examination after 13 months revealed primary lung carcinomas.[9]

Takenaka et al. (1990) and Glaser et al. (1990) exposed rats to cadmium chloride aerosols, cadmium sulphate, cadmium sulphide and cadmium oxide as dust and fume.[10,11] Primary lung carcinomas were observed after 6-18 month exposure to all cadmium compounds.

Heinrich et al. (1989) exposed hamsters and mice to different concentrations of aerosols of cadmium sulphide, cadmium sulphate, cadmium oxide dust and cadmium oxide fume.[12] The incidence of lung tumours in mice was significantly increased after 6-12 months exposure to cadmium oxide fumes, while the other compounds were not found to induce tumours. In hamsters, no carcinogenic effect could be demonstrated for any of the compounds.

The subcommittee decides not to rely on the epidemiologic data and to include the animal data for the classification process. The subcommittee concludes that positive findings, i.e. the development of lung cancer after long term exposure to cadmium compounds, are available in two animal species; the rat and the mouse. Therefore, the subcommittee is of the opinion that cadmium is 'presumed to have carcinogenic potential for humans' (category 1B) according to the new classification system of the Health Council.

Mechanism of genotoxicity

Several in vitro and in vivo studies have been published on the genotoxic potential of cadmium and its compounds. The subcommittee notes that in vitro studies have often been performed with cadmium concentrations with no relevance for humans and that no clear and coherent mechanism of genotoxicity has been established as yet. However various genotoxic mechanisms are hypothesized at lower concentrations that contribute to carcinogenic activity. For instance;

1 Cadmium compounds have been shown to impair almost all major DNA repair pathways including nucleotide excision repair, base excision repair and mismatch repair.[3,4,13,14]
2 Cadmium compounds have been shown to give rise to increased formation of reactive oxygen species (ROS) which are involved in the induction of DNA strand breaks and chromosomal aberrations both in vitro and in vivo.[3,4,13,14]
3 Cadmium compounds induce cell proliferation, inactivate tumour suppressor protein p53, and provoke resistance toward apoptosis.[3,4,13,14]

All three abovementioned processes indicate multiple non-stochastic genotoxic mechanisms for cadmium and its compounds. Although cadmium is able to produce point mutations and chromosomal effects such as aberrations and sister chromatid exchange in many in vitro and in vivo systems, no overt proof of direct genotoxic activity of cadmium has been found to date.[15] Cadmium does not covalently bind to DNA.

Therefore, the overall mechanistic evidence supports the view that genotoxicity is not caused by a direct attack of cadmium on the DNA, but via other processes which are triggered by cadmium. The subcomittee concludes therefore that the genotoxic mechanism(s) of cadmium should be considered as non-stochastic.

As cadmium and its compounds have non-stochastic genotoxic mechanisms an exposure limit should be derived using a threshold model. The subcommittee realizes that the epidemiological studies on cadmium and lung cancer do not present exposure-effect relations that allow derivation of such a threshold. The animal material is limited as well, only for rats a threshold is reported (Glaser et al. 1990).[11]

Therefore, the subcommittee recommends that, unless a threshold value can be derived, the procedure of linear extrapolation may be considered to establish a health based reference value.

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Meeting date: 17 September 2010.