EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

Opinion on the results of the Risk Assessment of:

CADMIUM METAL
HUMAN HEALTH

CAS-No.: 7440-43-9
EINECS-n°: 231-152-8

CADMIUM OXIDE
HUMAN HEALTH

CAS-No.: 1306-19-0
EINECS-n°: 215-146-2

Carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1]

Adopted by the CSTEE during the 41st plenary meeting of 8 January 2004

---

[1] Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC)1488/94, which is supported by a technical guidance document.

SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

Opinion on the results of the Risk Assessment of:

**CADMIUM METAL
HUMAN HEALTH**

**CAS-No.: 7440-43-9
EINECS-n°: 231-152-8**

**CADMIUM OXIDE
HUMAN HEALTH**

**CAS-No.: 1306-19-0
EINECS-n°: 215-146-2**

**Adopted by the CSTEE during the 41st plenary meeting
of 8 January 2004**

Terms of Reference

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

1. Does the CSTEE agree with the conclusions of the Risk Assessment Report?

2. If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

According to the Technical Guidance Document on Risk Assessment – European Communities 2003:

- *conclusion i):*   *There is a need for further information and/or testing;*
- *conclusion ii):*   *There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already;*
- *conclusion iii):*   *There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.*

GENERAL COMMENTS

This RAR addresses the question of risks associated with the production of cadmium metal and cadmium oxide, and the use of these substances in the production of stabilisers, pigments, alloys and plated products. A separate targeted RAR addresses specifically the question of risks to the environment from the lifecycle of cadmium batteries. As the latter document does not address issues of human health risks, it is not discussed in this part of the CSTEE Opinion.

This is a very comprehensive document for which the authors are to be complimented. Most of the published literature is cited, however some important omissions have been found by the CSTEE and are pointed out in the text of the present Opinion. Due to the enormous number of pages, the essential information is not easily

extracted. Several chapters lack a summary and conclusion. Therefore, it is not always clear what assumptions the risk characterization is based on and what uncertainties are built into the conclusions.

<u>**Conclusions of RAR:**</u>
Occupational exposure:
The CSTEE agrees with conclusion i) concerning neurotoxic effects of low doses of cadmium.
The CSTEE agrees with conclusion iii) because health risks (respiratory irritation, kidney and bone repeated dose toxicity, carcinogenicity/genotoxicity, effects on fertility and reproductive organs) cannot be excluded upon inhalation exposure.

Consumer exposure:
The CSTEE agrees with conclusion ii) regarding cadmium oxide.
The CSTEE agrees with conclusion iii) for cadmium metal because one cannot exclude the possibility of acute respiratory effects as well as concerning the relevant endpoints associated with carcinogenicity/genotoxicity and possibly reprotoxicity.

Indirect exposure via the environment:
CSTEE agrees with conclusion i) concerning neurotoxic effects of low doses of cadmium.
CSTEE agrees with conclusion iii) because health risks (kidney, bone and lung toxicity, carcinogenicity/genotoxicity) cannot be excluded.

However, CSTEE does not agree with the RAR that conclusion iii) regarding kidney does not apply to adult non-smokers with sufficient iron stores, but, instead, considers that conclusion ii) applies. The reasons for this are 1) that the proposed LOAEL (Cd-U) of 2 µg/g creatinine is uncertain and not sufficiently conservative and 2) estimation of current exposure levels is inadequate. In addition, the CSTEE considers that the group of "adult non-smokers with sufficient iron stores" represents a large and non-uniform part of the population, which is not well defined and includes several susceptible sub-groups.

SPECIFIC COMMENTS
CHAPTER 4: HUMAN HEALTH

This chapter is not well structured in all parts and there are a number of discussions and statements that are not adequate. There are also several repetitions. In particular, certain statements and conclusions differ in different parts of the document. One important example is the statement in several parts of the document that the LOAEL for kidney effects in people exposed occupationally is 5µg/g creatinine, while the conclusion in the risk characterization section is that there is only one LOAEL, 2 µg/g creatinine, independent of the scenario of exposure.

<u>**Exposure**</u>
While the RAR addresses risks associated with the production and specific uses of cadmium metal and cadmium oxide, exposure and risk assessment is carried out using the total risk approach, i.e. based on total exposure to cadmium regardless of its anthropogenic or natural origin.

As noted in a later section of this Opinion, the absence of an assessment of the specific contribution of the above-mentioned activities does not permit the correct conclusions at the risk management level. On the other hand, CSTEE notes that, considering that i) Cd accumulation in kidneys begins at birth and continues throughout a person's life, and ii) Cd is very persistent, the resulting bio-concentration factor in humans can reach up to 40 000. Therefore, from a human health point of view, the total exposure approach is justified.

Occupational exposure occurs mainly via inhalation. On the other hand, for the general population, exposure to cadmium is primarily via the oral route and arises by ingestion of contaminated foods. The diet contributes more than 90% of cadmium exposure in non-smokers. Cigarette smokers suffer additional exposure by inhalation.

The exact chemical form of cadmium in food is not known. However, it is believed that, following exposure to cadmium in any of its chemical forms, the main species which upon absorption circulates in the body is the divalent Cd^{++} ion, mainly bound to proteins (in particular metallothionein).

In the RAR it is estimated that the average dietary Cd intake in European countries is 7-32 µg/d. The CSTEE considers this a fairly good estimate for all of Europe. However, it is noted that the list of dietary intakes of cadmium given in Table 4.1.3.1. includes information published only until 1997 (plus one report from 1999), while there are a number of additional reports published subsequently. Among recently published data one can mention French data (Leblanc *et al.*, 2000) and data from the JECFA assessment of cadmium of June 2003. In addition, the CSTEE is aware that, using data recently collected by a task SCOOP on food contamination with heavy metals (cadmium, mercury and lead), the (former) SCF is updating the dietary intake of Cd by citizens of EU Member States. These new data (not yet made publically available) do not significantly alter the estimates mentioned above, and also confirm that the most contaminated food items are offal (especially kidneys), spinach and seafood.

In the RAR (4.1.1.3.5) it is also concluded that, based on limited data from UK, the Netherlands, Denmark and Sweden, the upper percentiles (95th or higher) range between 24 and 40 µg/day. The reason for selecting these countries is not clear. From the Table 4.1.3.1, listing published studies, and from the adjacent text, it is obvious that the total range of dietary Cd intake in Europe is much larger. In particular, populations consuming much seafood have considerably higher intakes of cadmium. It is argued in the RAR that a limited number of human studies indicate that Cd from shellfish has a lower availability than Cd from mixed diet. These studies are based on comparisons of Cd in diet and blood. However, reported data from oyster consumers showed blood Cd values of 3.7 µg/L in non-smokers, which, indeed, indicates that considerable amounts of Cd are absorbed (Sharma *et al.*, 1983; McKenzie-Parnell *et al.*, 1988; section 4.1.1.3.5). Also, other studies, designed to study Cd absorption from seafood indicate a similar absorption rate as with mixed diet. In particular, studies in people ingesting crabmeat intrinsically labelled with 115mCd showed whole-body retention of 2.7% (Newton *et al.*, 1984), which is similar to that reported for mixed diets. Thus, in absence of more exact data on the bioavailability of seafood-Cd, the CSTEE considers it appropriate to use the data available.

Unfortunately, there are few dietary intake data giving the 95-percentiles. Studies reported in Table 4.1.3.1 show maximum intake values of 88, 57, 102, 25, 35, 46, 55, and 70 µg/day, but most of the studies are too small for calculation of upper percentiles. In addition, it is reported that oyster consumers had intakes (group averages) of 15-233 µg/day. It should also be noted that duplicate diet studies in general underestimate the true intake by about 10-20% due to decreased food intake during the study. Based on this information, the CSTEE finds it reasonable to assume that the 95-percentile, or upper range, of dietary intake of Cd in Europe is in the range 10-70 µg/day.

There is little discussion in the RAR about children's exposure. Exposure from soil is acknowledged to be an important source of exposure in contaminated areas (4.1.1.3.2), but the Rapporteurs assume that the bioavailability of soil Cd in children is lower than food Cd. This assumption is not very well supported by experimental data presented further on in the same section (Schilderman *et al.* 1997). Gastrointestinal absorption of cadmium is influenced by a number of factors, e.g. age and presence of food in the intestine. Soil intake by children does often take place in between meals, which may facilitate the absorption of soil Cd. Also, young children have a higher gastrointestinal uptake than adults.

Cd has a wide range of uses, e.g. catalyst/stabiliser in polymeric food contact materials, and is also found in textiles (Danish EPA, 2003). The respective intakes (through chewing or sweating) are likely to be low but, given the bioaccumulation properties of Cd, would be worth considering in the context of a total exposure approach.

Effects assessment
1. Toxicokinetics and metabolism
The systemic absorption of ingested cadmium is generally less than 5% (an average of 3% used in the RAR). However, absorption from the GI tract is enhanced in the young, by diets low in iron and zinc and, especially, by low iron status (e.g. in menstruating women), which can result in much higher absorption. An average of 6% for high-absorption individuals is used in the RAR. However as noted by the Rapporteur, absorption rates of 10%

has been reported. Thus the CSTEE considers that, while a 2-fold increased absorption in people with low iron stores may be used as an approximate <u>average</u> absorption, it should be recognised that individuals with higher absorption exist. Therefore, using an absorption rate of 6% cannot be considered a conservative approach.

In the RAR, interconversion between Cd intake and Cd concentrations in urine or tissues is carried out using the Nordberg-Kjellström toxicokinetic model. This is a multicompartment kinetic model describing cadmium metabolism and permits one to relate quantitatively cadmium intake with cadmium accumulation in different tissues as well as cadmium urinary excretion (Cd-U). The output of the model depends critically on the values adopted for certain physiological parameters, such as the absorption rate. Therefore, it is important that the selected values are correct, and derived from adequate validation studies. In the RAR, a value of 3% is used for the average absorption in the general adult population. This value is obtained through "validation" of the toxicokinetic model. The Rapporteurs used two studies (one with 34 individuals only and the second with dietary intake data and Cd-U from different studies) to set values for the absorption of dietary cadmium and for $t_{1/2}$ of cadmium in the body, which could vary 3-10% and 10-40 yrs, respectively. Although it is claimed that the selected "best fit" values result in adequate fit of the data, they still contain significant uncertainty and, as shown later in the Opinion, the Cd-U values calculated as corresponding to the average dietary intake are low compared to empirical data for adults 50 years of age. Obviously, additional studies are needed for the estimation of the physiological parameters for the kinetic model.

As regards the systemic absorption of inhaled cadmium, it varies from typically 25-50% for fumes to 15-30% for particulate forms. The dermal absorption of soluble salts of cadmium is minimal (<1%).

Cadmium in blood (Cd-B) is frequently used biomarker of exposure. However, Cd-B is also influenced by the body burden of Cd. In non-smoking, non-occupationally exposed individuals in Europe, Cd-B levels are generally below 1-2 µg/l, but can reach up to 3 µg/l in people living in contaminated regions, while in smokers median levels range up to 8 µg/l (Table 4.2.1.2.3).

Once absorbed, cadmium is excreted very slowly (half-life ~10-30 years). Consequently, it accumulates over many years, mainly in the renal cortex and, to a smaller extent, in the liver and the lung. The maximum concentrations in kidney cortex are observed at about 50-60 years of age, after which the concentrations decrease. The total cadmium body burden reaches around 30 mg by age 30 years. Some studies of cadmium concentrations in the renal cortex have suggested that there may be a decreasing trend over the past 20 years, perhaps reflecting changes in smoking- or diet-related exposure. However, the overall evidence of a decreasing trend in cadmium exposure in Europe is not conclusive.

In the RAR, the section of transport and distribution (4.1.2.1.3) is difficult to follow. For example, the "summing up", close to the end of the section before the discussion of the inhalation route starts, deals with exposure trends and not kinetics. A general conclusion of this section is missing. Another example is that "critical levels" are discussed in this section (in: inhalation route, studies in human, body burden). In addition, many old studies are described in detail without an appropriate evaluation (Table 4.2.1.3.1 generally contains older studies and should be updated with more recent ones). The analytical accuracy of older studies is never questioned.

Cd-U is often used as a biomarker of long-term exposure. Under conditions of chronic, low exposure, Cd-U reflects mainly the accumulated body burden. Direct measurements have confirmed that Cd-U reflects the amount of cadmium accumulated in the renal cortex. Kidney damage first leads to increased urinary Cd excretion. When kidney Cd levels decrease, Cd-U also decreases. Typical urinary concentrations in individuals without occupational exposure and not living in heavily polluted regions lie in the range 0.1-2 µg/g creatinine.

<u>Other specific comments:</u>
<u>Studies in humans –other data (p 121).</u> "…estimated that an European or an American adult absorb cadmium orally at an average rate varying between 1.4 and 25 µg/d". This cannot be correct.

2. Acute and repeated dose toxicity

Upon inhalation of high doses, cadmium causes severe pulmonary lesions, while acute oral ingestion results in lesions of the proximal sections of the intestinal tract.

Chronic inhalation exposure has been suggested to lead to decreased lung function and an increase in residual lung volume. However, the most important effects of chronic exposure to cadmium are effects of dietary exposure on the bones and the kidney.

Bone effects

It is clear that chronic exposure to ingested cadmium may result in osteoporosis, osteomalacia, spontaneous bone fractures and loss of bone density, although the exact mechanism of these effects is not known. An inverse relationship between bone mineral density and Cd-U has been found in two recent studies (Staessen *et al.* 1999; Alfvén *et al.* 2002). In one of these studies no quantitative relationships were given, while in the other the effect was observed above 3 µg/g creatinine. Based on this, the RAR proposes a LOAEL of 3 µg/g creatinine. However, LOAEL values of 0.5 and 3 µg/g were also discussed, which reflect the uncertainty of the LOAEL. The CSTEE considers that the relevant database is limited and results in a highly uncertain LOAEL for this toxicity end point, and for this reason it is not possible to conduct a reliable risk assessment for it. On the other hand, the corresponding database for kidney effects, which are discussed below, is more adequate and therefore kidney toxicity is used by CSTEE as the critical effect for Risk Characterisation.

Kidney effects

Chronic exposure to cadmium can cause damage to the proximal tubules of the kidney, detected as increased urinary excretion of low-molecular weight (LMW) proteins (e.g. protein HC or β2-microglobulin) or intracellular enzymes (e.g. N-acetyl-β-D-galactosidase). In more severe cases glomerular dysfunction can occur which can be detected e.g. as increased urinary excretion of albumin. While some of the effects are irreversible and progress to kidney disease even after a reduction of exposure, others (e.g. mild LMW proteinuria) seem reversible after cessation of exposure and not followed by further disease development. For this reason their health significance has been disputed. The CSTEE concludes that, taken together, the biomarkers used for LOAEL estimation represent early signs of renal tubular toxicity, and, thus, constitute suitable biomarkers of adverse effects at the population level. The long half-time of cadmium in the kidney further supports the use of these biomarkers. The CSTEE agrees that it is presently not possible to determine precisely at which Cd body burden a health-relevant alteration of renal function appears, and that a sufficiently conservative assessment should, therefore, be proposed.

Cadmium nephrotoxicity has been studied in workers as well as in a number of large-scale epidemiological studies of general population cohorts living in regions with more or less cadmium pollution. In these studies, urinary LMW protein concentrations are used as markers of nephrotoxic effects which, in combination with corresponding Cd-U values, lead to the evaluation of the critical Cd intakes. Studies in workers have shown clear adverse effects at levels of Cd-U 5 µg/g creatinine or greater. On the other hand, studies in the general population have suggested different levels of Cd-U at which effects were detectible, in the range 0.5-2.6 µg/g creatinine. Following a discussion of the various studies, the Rapporteurs adopt a value of 2 µg/g creatinine as a LOAEL for kidney toxicity, a value defined as an "aggregate" of data of the general population studies by Buchet *et al.* 1990 (2 µg/g creatinine) and Järup *et al.* 2000 (0.5, 1.2 or 2.6 µg/g creatinine, depending on the mode of calculation). The way in which the levels of proteinuria delineating adverse effects from background variation are selected is critical and for this reason this matter is discussed in some detail below:

a) The cut-off values used for defining normal/abnormal values of the effect markers (e.g. LMW proteinuria) in the dose-response evaluations are arbitrarily set at the 90th-95th percentile of the reference population. Thus, if the 95th percentile is used, 5-10% of the reference population by definition lie in the "abnormal" range. However, there is no obvious difference between the upper end of the normal and the lower end of the abnormal intervals for the cadmium-induced tubular kidney effects. Also, as no population is truly unexposed to cadmium, the cut-off value, and the corresponding LOAEL, will be affected by the cadmium exposure of the reference population used for calculation of the cut-off. In this connection it is noted that the reference populations in the above studies were not chosen with regard to low cadmium exposure.

Another reason why the LOAEL will vary depending on the background prevalence in the study population is because, in the RAR, the LOAEL is defined as that exposure which results in an increase of the prevalence of the effect biomarkers above the "background" prevalence by 10%.

It is concluded that the factors mentioned above tend to lead to an overestimation of the LOAEL.

b) The method used for the "aggregation" of the data from the two abovementioned studies, to derive the adopted limit of 2 µg/g creatinine is not stated in the RAR. Concerning the study by Järup *et al.* (2000), the Rapporteurs recalculated the data and arrived at a higher critical concentration than reported in the original publication (2.6 vs 1.0 µg/g creatinine). This critical concentration is defined as the concentration of Cd-U associated with a 10% excess of elevated ("abnormal") values of the effect biomarker (LMW proteinuria), which, in combination with the definition of "abnormal" values described in the previous paragraph, corresponds to a doubling of their prevalence. Furthermore, the study population included occupationally exposed individuals, and an obvious "healthy worker effect" regarding tubular damage was observed. Calculation of LOAEL after exclusion of occupationally exposed individuals (i.e. including only environmentally exposed people) gave a critical value of 0.5 µg/g creatinine. CSTEE notes that estimation of LOAEL for the general population should be based on data from studies on environmentally (and not occupationally) exposed people. Therefore, 0.5 µg/g creatinine (estimated from the Järup *et al.* (2000) study) and 2 µg/g creatinine (estimated from the Buchet *et al.* (1990) study) are the reported LOAEL values most relevant for the risk assessment of exposure via the environment.

For the reasons given above, the CSTEE considers that the adoption of a LOAEL of 2 µg/g creatinine alone for risk characterisation, as done in the RAR, is not based on strong scientific evidence and does not imply a conservative assessment. For the sake of comparison, CSTEE has used the whole range of possible LOAEL values in the estimation of MOS values (see below).

Irritation, corrosivity and sensitisation
There are no studies, or the results of the available studies are unclear, regarding the irritant, corrosive or sensitising properties of cadmium. However, the RAR concludes that, in view of the risk reduction measures which need to be taken as a result of the carcinogenicity of cadmium and its compounds, there is no justification for recommending studies for these toxicity endpoints. The CSTEE agrees with this conclusion.

Immunotoxicity.
Cd has been often shown to act on the immune system (Dogra *et al.*, 2002) and on biological mechanisms involved in local inflammatory reactions (Pearson *et al.*, 2003). Following exposure to Cd, activation of the corticosteroid-associated regulatory circuit (Lall and Dan, 1999), thymus atrophy and regulation by metallothionein (Liu *et al.*, 1999) have been reported. Apoptosis of B cells (involving the MAP kinase pathway), and T cell reactivity to metallothionein and heat shock proteins induced by Cd exposure, are among the suspected mechanisms of action.

The reported effects are auto-immunity through action on auto-reactive T-cells (Leffel *et al.*, 2003; Jelocvan *et al.*, 2003) but mostly immunosuppression which can result in increased susceptibility to virus infection (Seth *et al.*, 2003). By increasing individual susceptibility to neoplastic diseases, such immunosuppression can play a role in carcinogenesis by Cd and its compounds (see Section on carcinogenicity).

Neurotoxicity
There is evidence from animal studies, and limited evidence from studies in occupationally exposed humans, that cadmium may cause damage to the central and peripheral nervous systems. Such evidence exists both for adults and for the developing organism. However, the strength of this evidence, especially in humans, is relatively weak because of the limited data available. Taking into account the well known neurotoxicity of other heavy metals, the RAR concludes the neurotoxic potential of cadmium should be further investigated. The CSTEE agrees with this conclusion.

3. Genotoxicity

Studies on the genotoxicity of soluble salts of cadmium have given conflicting results. While some *in vitro* studies are negative, especially in bacterial systems, other studies, including studies in mammalian cells, have yielded positive results for the induction of DNA strand breaks, protein-DNA crosslinks, chromosome aberrations and other markers of genotoxicity. Cadmium can induce genotoxicity by interacting directly with DNA, causing oxidative stress, and inhibiting DNA repair. Recently published information suggests that the latter mechanism may be particularly important, since it has been shown that, even at environmentally relevant concentrations, cadmium can effectively inhibit mismatch repair (a mechanism critical for the maintenance of genome stability) and cause substantial mutagenesis in yeast (Jin *et al.* 2003).

Results on the *in vivo* genotoxicity of cadmium compounds are also conflicting. For example, cadmium chloride has been found to cause micronuclei and chromosome aberrations in mice, while cadmium oxide is negative in similar tests, a result that may reflect the bioavailability of cadmium in each case.

The RAR concludes that, taking into account all the available experimental evidence, cadmium has a genotoxic potential. The CSTEE agrees with this assessment.

As regards human studies, again mixed results have been reported from studies of populations exposed orally to high levels of cadmium. While a number of studies found no increase in biomarkers of genotoxicity, other studies have reported increased levels of chromosome aberrations and sister-chromatid exchanges in individuals who developed Itai-Itai disease following exposure to high concentrations of cadmium in their food. Increased levels of biomarkers of genotoxicity have also been found in populations with high environmental cadmium exposure in China and the Czech Republic. In some studies a correlation between Cd-U and the levels of chromosome aberrations have been found, supporting a genotoxic role of cadmium. The RAR concludes that it is not possible to exclude the possibility that human oral exposure to cadmium, at the levels found in the environment, results in genotoxicity. The CSTEE agrees with this assessment.

Although workplace inhalation exposure to cadmium can be relatively high, corresponding studies on the induction of genotoxicity have given mixed results, probably because of limitations regarding the assessment of exposure. After discussing the results of the various studies, the RAR comes to the conclusion that it is not possible to exclude the possibility that inhaled cadmium also gives rise to genotoxicity in humans, a conclusion with which the CSTEE agrees.

4. Carcinogenicity

Cadmium and its compounds have been evaluated as a group by IARC and classified in category I (carcinogenic to humans) (IARC, 1993).

Animal studies have clearly shown that cadmium compounds (cadmium oxide and cadmium chloride) can cause lung cancer in rats and mice after inhalation or intratracheal exposure. Furthermore, oral treatment of rats with cadmium chloride has resulted in the induction of leukemia, interstital cell tumours of the testis and proliferative lesions of the prostate.

Epidemiological studies in cadmium-exposed workers have provided evidence of increased risks of prostate and lung cancer. Such studies often suffer from problems related to their size, assessment of exposure to cadmium, and confounding exposures to other carcinogens (mainly to arsenic and, in some cases, nickel, as well as tobacco smoke). Based on an assessment of these studies, especially of the results of the most comprehensive analysis of the results of a series of studies on cadmium recovery workers in the US (Sorahan & Lancashire, 1997), the RAR concludes that the observed increased in lung cancer is unlikely to be accounted for by confounding exposures to arsenic or tobacco smoke, and that a causal role for cadmium is likely. On the other hand, taking into account all the reports on the relation between inhalation exposure to cadmium and risk of prostate cancer, the RAR concludes that the evidence for an association between the two is not convincing. The CSTEE agrees with these conclusions.

Evidence of possible prostate carcinogenesis has been observed mainly in populations living in cadmium-polluted regions who, as a result, had a high dietary intake of cadmium. For example, studies in different regions in Canada and Japan showed that the rate of prostate cancer varied in parallel with the local environmental concentrations of cadmium (Bako *et al.* 1982; Shigematsu, 1982). The latter study also reported increased rates of leukemia and cancer of the bladder and kidney among males and cancer of the kidney, lung and breast among females. As in other cases, many of these studies suffer from weaknesses in the assessment of exposure and adequate control of confounding factors. Some studies have also reported higher levels of cadmium in the tissues (mainly prostate) from patients with corresponding cancers than in matched controls, although this result has not been confirmed by other studies. The RAR concludes that the overall evidence does not support a carcinogenic action of cadmium on the prostate after oral exposure. While agreeing with this conclusion, the CSTEE considers that the RAR has not sufficiently considered the possible carcinogenic effect of cadmium on the kidney. Recent case-control studies on renal-cell cancer and cadmium by Pesch *et al.* (2000), Mandel *et al.* (1995), and Hu *et al.* (2002) indicate a significant association. Earlier epidemiologic studies regarding kidney tumours in humans, which have not been considered in the RAR, are cited in the publication by Mandel *et al.* (1995). It is noted also that other publications, like those by Rhomberg *et al.* (1995), Müller *et al.* (1994), West *et al.* (1991) and Hadfield *et al.* (1998), at least considering a possible contribution of cadmium to human carcinomas at additional sites, have not been discussed. More recently Wesseling *et al.* (2002) have described increased risks for brain-nervous system tumours in a cohort of 413,877 Finnish women with blue collar occupations in 1970 associated with exposure to cadmium and other proven or suspected carcinogens.

Based on all the evidence discussed, the RAR's conclusion is that cadmium must be considered as a suspected lung carcinogen by inhalation. However, because the CMR WG has recently recommended classification of cadmium as category 2 (risk phrase: R45; may cause cancer), indicating a carcinogenic potential irrespective of the exposure route, the RAR's conclusions include conclusion iii) for carcinogenicity and genotoxicity for all scenarios where exposure occurs.

The CSTEE notes that the conclusion "suspected lung carcinogen by inhalation", proposed in the RAR, is in contrast to that of IARC (1993), which has classified cadmium and cadmium compounds as carcinogenic to humans (Cat. 1) regardless of route of exposure. This discrepancy is not addressed in the RAR.

5. Reproductive and developmental toxicity
The RAR reviews the animal and epidemiological evidence. Its conclusions are that there is evidence from animal studies of reproductive and developmental toxicity, with effects on the male and female reproductive organs and the induction of reduced fetal weight, and structural as well as neurobehavioural abnormalities. Corresponding epidemiological evidence in humans does not exist for reproductive effects and is limited or inconclusive for developmental effects (reduced birth weight, neurobehavioural abnormalities). It concludes that cadmium has a potential for induction of reproductive toxicity, while the limited evidence of developmental toxicity in humans needs to be further addressed urgently.

After the finalization of the RAR document, a study showing estrogenic effects of low doses of cadmium has been published (Johnson *et al.*, 2003). According to this report, cadmium given as a single intraperitoneal dose (5 μg per kg body weight) to ovariectomized rats, increased uterine wet weight, promoted growth and development of the mammary glands and induced hormone-regulated genes. In the uterus, the increase in wet weight was accompanied by proliferation of the endometrium and induction of progesterone receptor (PgR) and complement component C3. In the mammary gland, cadmium promoted an increase in the formation of side branches and alveolar buds and the induction of casein, whey acidic protein, PgR and C3. *In utero* exposure to cadmium also mimicked the effects of estrogens. Female offspring experienced an earlier onset of puberty and an increase in the epithelial area and the number of terminal end buds in the mammary gland. Additional studies exist describing effects indicating a potential hormonal activity of cadmium (e.g. Stoica *et al.* 2000; Martin *et al.* 2002; Martin *et al.* 2003). The CSTEE notes that these results have implications for the reproductive and developmental toxicity potential of cadmium, and that, if the findings of *in vivo* hormonal effects after intraperitoneal administration are confirmed by further studies using the oral route, the risk assessment of cadmium may need to be updated in a near future.

Conclusions of RAR:
Occupational exposure:
CSTEE agrees with conclusion i) concerning neurotoxic effects of low doses of cadmium.
CSTEE agrees with conclusion iii) because health risks (respiratory irritation, kidney and bone repeated dose toxicity, carcinogenicity/genotoxicity, effects on fertility and reproductive organs) cannot be excluded upon inhalation exposure.

Consumer exposure:
CSTEE agrees with conclusion ii) regarding cadmium oxide.
CSTEE agrees with conclusion iii) for cadmium metal because one cannot exclude the possibility of acute respiratory effects as well as concerning the relevant endpoints associated with carcinogenicity/genotoxicity and possibly reprotoxicity.

Indirect exposure via the environment:
CSTEE agrees with conclusion i) concerning neurotoxic effects of low doses of cadmium.
CSTEE agrees with conclusion iii) because health risks (kidney, bone and lung toxicity, carcinogenicity/genotoxicity) cannot be excluded. However, CSTEE does not agree with the RAR that conclusion iii) regarding kidney effects does not apply to adult non-smokers with sufficient iron stores. [CSTEE notes, in connection with this conclusion, that in the overall conclusions (0.3.1) this conclusion is said to apply to "all scenarios except adult non-smokers"]. The reasons for this are 1) that the proposed LOAEL (Cd-U) of 2 μg/g creatinine is uncertain and not sufficiently conservative and 2) estimation of current exposure levels is inadequate. In addition, CSTEE considers that the group of "adult non-smokers with sufficient iron stores" represents a large and non-uniform part of the population, which is not well defined and includes several susceptible sub-groups.

Comments on Risk Characterisation
In the RAR it is stated that, because the available database does not allow an exact determination of the kidney Cd concentration at which renal function starts to change, a sufficiently conservative assessment should be applied and the importance of expressing uncertainties, rather than being too exact about a LOAEL, is noted (4.1.2.6.3). CSTEE agrees with this approach, but cannot see that it has been implemented:

Estimation of LOAEL
The RAR uses a value of 2 μg/g creatinine Cd-U as LOAEL for kidney toxicity to estimate the MOS values in the context of Risk Characterisation. For reasons already discussed in detail (pp. 4-5), the CSTEE considers that this value contains significant uncertainty and does not imply a conservative assessment, as claimed in the RAR. CSTEE considers that it would be more appropriate to consider the whole range of possible LOAEL values suggested by the scientific literature, and has used such an approach to derive its own estimates of MOS values (discussed in a later paragraph).

Estimation of current exposure
a) In spite of the rather large database for measured Cd-U in Europe (section 4.1.2.1.4), in the RAR risk characterization the exposure data (Cd-U values) to be compared with the LOAEL values are calculated from estimated intake values (Table 4.1.3.2, p. 94 and Table 4.3.3.1). The dietary intakes (7-32 μg/d) used for these calculations represent average exposure in European countries. Thus the wide variation in dietary intake of Cd, e.g. via high intake of rice, vegetables or seafood, is not considered.

b) The chosen average daily dietary Cd intakes are converted into to Cd-U using the toxicokinetic model described by Kjellström and Nordberg (1978; 1985). In these calculations a number of assumptions concerning absorption, tissue distribution, retention ($t_{1/2}$) and urinary excretion of Cd are made (discussed above, p. 2-3), in which the values of the corresponding physiological parameters represent the average situation, e.g. average absorption and excretion rates. The CSTEE finds that use of these values leads to

unrealistically low modelled Cd-U (0.16-0.56 µg/g creatinine as compared to observed mean values in non-smokers of 0.3-2 µg/g creatinine as indicated in Table 4.2.1.3.1). Conversely, use of the model as in the Report to calculate daily intakes of cadmium equivalent to a LOAEL of 0.5-2 µg/g creatinine (assuming that 0.5 µg/g creatinine corresponds to a long-term daily <u>uptake</u> of 1 µg/day), leads to estimated intakes in the range 33-132 µg/day and 17-66 µg/day for 3% or 6% gastrointestinal absorption, respectively. These modeled values are much higher than the empirically observed mean intakes of 7-32 µg/day.

The RAR rapporteurs claim that their application of the toxicokinetic model works well, even conservatively, to convert uptake into Cd-U. The CSTEE does not share this view. It notes that the calculated Cd-U values are validated by comparison with data in Table 4.3.3.3. However, the modeled critical values 0.16-0.56 µg/g cannot be validated in a correct way as the reported empirical values (studies from Belgium, Sweden etc.) are not stratified according to age, smoking, and occupational exposure. Thus, it is not possible to state that the modeled values represent a conservative estimate. Furthermore, CSTEE does not agree with the RAR conclusion (p. 28, para. 1) that the critical values (0.16-0.56) overestimate the values from Germany (median 0.18, which is exceptionally low) and the Netherlands (geometric mean/median 0.44/0.34). If anything, they fit with these data and underestimate data from Belgium (geom. mean 0.84, 0.6, 0.9) and Sweden (median 0.82, 0.66). Also, there is no reason for choosing these particular studies, as many more studies are available that could be listed and compared with the calculated Cd-U (and LOAEL).

Finally, the relationship between kidney Cd (10 and 40 mg/kg, corresponding to a LOAEL Cd-U of 0.5 and 2 µg/g creatinine, respectively) and dietary intakes suggested by the use of the RAR model (33-132 and 17-66 µg/d) differs greatly from those reported by Buchet *et al.* (1990) and Järup *et al.* (1998), as well as from relationship observed between empirical data (see p. 13, Table 1).

Based on the discrepancies discussed above, which have not been discussed in the RAR, the CSTEE concludes that the calculations of Cd-U based on intake data, carried out in the RAR, are not scientifically justified.

c) In a second approach to risk characterisation employed in the RAR, MOS values are calculated by comparing the LOAEL of 2 µg/g creatinine with empirically measured Cd-U data in five European and one US study (Table 4.3.3.4). The RAR conclusion in this case is that the MOS are substantially greater than those estimated as above, but still below 3 (the MOS value considered in the RAR as the minimum acceptable) for a significant fraction of the population. The CSTEE again notes that a comparison not of a single LOAEL value but of a range of possible LOAEL values (0.5-2.6 µg/g creatinine) with the empirical 90-percentiles would lead to MOS values well below 3 for all but one of the studies. [It is also noted that the MOS corresponding to the 90-percentile for females in the study by Järup *et al.* (2000) is erroneously set in Table 4.3.3.4 at 4.0, whereas it should be 1.5]. Furthermore, most of the empirical Cd-U values listed in Table 4.3.3.4 represent people with ages ranging from well below to above 50 years (in most cases about 20-80 years), while the LOAEL used is the critical concentration estimated for about 50 years of exposure. As Cd-U increases with age until 50-70 years of age and then deceases, this means that the estimated "MOS" values in Table 4.3.3.4 are likely to be overestimated.

In conclusion, the CSTEE considers that the RAR uses inadequate current exposure data in the MOS calculations (average exposure, unreliable conversion of Cd-U from dietary intake data, and empirical exposure data representing a wide age range).

MOS values
The exception of adult non-smokers from conclusion iii) in the RAR is based on a calculated MOS of 12.2-3.58, which is compared with a "minimum MOS" of 3 (corresponding to extrapolation from LOAEL to NOAEL). As already discussed, the CSTEE considers that these MOS values contain a large degree of uncertainty and also are likely to be overestimated. Because of this uncertainty, CSTEE has used a range of possible LOAEL values suggested by the available studies, including values of 0.5 and 2.0 µg/g creatinine which are the most relevant for the general population exposed through the environment, to obtain a range of estimates of MOS values. The outcome is shown in Table 1 below.

In Table 1 three kinds of critical values are used to obtain MOS estimates (Cd-U, kidney Cd and Cd intake). Starting with Cd-U, three possible LOAELs (0.5, 2.0 and 2.6 µg/g creatinine), suggested by different studies, are considered and compared with the empirically observed range of Cd-U concentrations. The MOS values thus calculated are in the range 0.1-2.6, when the 95th percentiles of exposure are used, or 0.25-9 when the mean exposure values are used.

As an alternative biomarker, the critical kidney Cd values corresponding to the Cd-U LOAELs are also estimated in Table 1 by assuming, as is done in the RAR, that a Cd-U of 2.5 µg/g creatinine corresponds to about 50 mg/kg in kidney cortex, and compared with the corresponding empirical data. Again, calculated MOS values are in the range 0.1-2, and 0.5-9, based on 95th percentile and average values, respectively.

Finally, the Cd-U LOAELs are converted into the corresponding intakes, assuming that 2.5 µg/g creatinine corresponds to a long-term daily intake of 50 µg/day (Buchet *et al.*, 1990, Järup *et al.*, 1998) and used to calculate MOS values by comparison with empirically determined intakes. The resulting values in this case lie in the range 0.14-4.7 and 0.34-7.4, based on 95th percentile and average values, respectively.

Summarising, as can be seen in Table 1, in contrast to the MOS values of 12.2-3.58 which are estimated in the RAR for adult non-smokers, values in the range 0.1-4.7 are obtained when using upper exposure levels, and 0.2-9 when using mean exposure levels. In view of these estimates CSTEE does not consider that conclusion iii) is justified but that conclusion ii) is derived.

Table 1: CSTEE calculations of MOS values

	Critical values								
	Cd-U (µg/g creatinine), 50 y			kidney Cd (mg/kg), 50 y [b]			Cd intake (µg/day)[c]		
LOAEL	0.5	2	2.6	10	40	52	10	40	52
MOS calculations based on upper 95th percentiles									
Exposures, 95th percentiles[a]; non-smokers/ smokers	1-4			26-50/46-80			11-70		
MOS	0.1-0.5	0.5-2	0.6-2.6	0.1-0.4	0.5-1.5	0.6-2	0.1-0.9	0.6-4.0	0.7-4.7
MOS calculations based on means									
Exposures, mean values[a], non-smokers	0.3-2			6-20			7-32		
MOS	0.2-1.7	1-7	1.3-9	0.5-1.7	2-7	2.6-9	0.3-1.4	0.6-3.6	0.7-7.4

a. Data from tables 4.1.3.1, 4.2.1.2.4, 4.2.1.3.1, 4.3.3.3
b. Assuming, as done in the Report, that Cd-U of 2.5 µg/g creatinine corresponds to about 50 mg/kg in kidney cortex.
c. Assuming that 2.5 µg/g creatinine corresponds to a long-term daily intake of 50 µg/day (Buchet et al, 1990, Järup et al, 1998)

In expressing its scepticism over the significance of Cd-U values below 2 µg/g creatinine, the RAR states that certain scientists consider that clear adverse renal effects, with demonstrated clinical relevance (in occupationally exposed people), occur at an Cd-U of 5 µg/g creatinine. The CSTEE notes that even this level of Cd-U, divided by current exposure levels (95th percentiles, 1-4 µg/g creatinine), would result in MOS 1.25-5.

In conclusion, taking into account the fact that all MOS calculations in the RAR are based on LOAELs rather than NOAELs, and having in mind the uncertainties in the assessment of exposure and LOAELs already discussed, the CSTEE considers that the resulting MOS values do not provide sufficient protection. The genotoxic and carcinogenic properties of cadmium further add to this concern.

As already noted, it may be argued that the critical effect used for estimation of LOAEL is an early sign of renal tubular toxicity which might be reversible and therefore might not require a high minimum MOS value. The

CSTEE considers that, in assessing the significance of the estimated MOS values, it is important to take into account the following considerations:

a) Although the earliest signs of kidney malfunction observed may be reversible, it should be remembered that, for most people, it is difficult to decrease the exposure, as most of the Cd exposure is via basic foods such as cereals and vegetables, and that the half-time of cadmium in soil is very long. Also, large segments of the population show these early signs at an age of 50 years, and their kidneys are supposed to function for several more decades.

b) Epidemiological studies described in the RAR have shown that cadmium explains as much as 10% of the variance in the kidney markers in the general population, implying that cadmium has a considerable effect already at the current exposure levels,

c) There is increasing evidence for interactions between cadmium and common diseases like diabetes, possibly also high blood pressure, in the induction of kidney damage. Furthermore, there is a considerable body of data indicating variation in sensitivity to cadmium, e.g. increased gastrointestinal absorption due to nutritional factors other than iron (mainly low zinc intake), multiple pregnancies, exposure to other nephrotoxic agents (e.g. solvents and lead, the latter often associated with Cd exposure), kidney diseases, etc.

The preceding discussion illustrates the difficulties which arise from the attempt to use specific critical values of biomarkers of exposure and effect. CSTEE notes that all exposure and effect biomarkers evaluated are originally continuous variables and that a probabilistic approach could have been employed, e.g. by calculating a benchmark dose (e.g. 10% effect level) and applying an assessment factor on that before comparing with the current exposure levels.

As regards the RAR MOS calculations in connection with bone effects, the CSTEE does not agree with the selection of a critical dose of 3 µg/g creatinine in Table 4.3.3.5, since it considers that the available data do not permit the adoption of a critical dose using sound science.

4.1.3.3.3. RISK CHARACTERIZATION FOR FUTURE CONDITIONS: MODELLING

As mentioned above, it is the opinion of CSTEE that conclusion iii) for environmental exposure should apply also for scenario 1a (non-smoking adults with sufficient iron stores). Therefore, there is no use for section 4.1.3.3.3, the aim of which is to assess whether conclusion iii) would apply in the future. Even if that would be the case, CSTEE does not agree with the statement "that a conclusion ii) can be proposed for the average soil compartment in the environmental risk assessment taking risks to the non-smoking population into account". In particular, a conclusion cannot be based on the average soil.

In addition, CSTEE does not agree with the calculation of critical dietary Cd intake (Table 4.3.3.7) because it does not take into account inter-individual variation. The weak scientific basis for using an absorption rate of 3% for the whole population is discussed above.

References

Alfven T, Jarup L, Elinder CG. (2002) Cadmium and lead in blood in relation to low bone mineral density and tubular proteinuria. Environ Health Perspect. 110, 699-702.

Bako G, Smith ES, Hanson J, Dewar R (1982) The geographical distribution of high cadmium concentrations in the environment and prostate cancer in Alberta. Can J Public Health, 73, 92-4

Buchet JP, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F, Ducoffre G, de Plaen P, Staessen J, Amery A, *et al.* (1990) Renal effects of cadmium body burden of the general population. Lancet, 336 (8717), 699-702.

Danish EPA (2003) Survey of chemicals in consumer products, 23.

Dogra, S., Waseem, M., Khanna, AK; and Kaw, JL. (2002) Immunotoxicity of soluble and insoluble salts of cadmium instilled intra-tracheally. Indian J. Exp. Biol. 40, 262-267.

Hadfield MG, Adera T, Smith B, Fortner-Burton CA, Gibb RD, Mumaw V. (1998) Human brain tumors and exposure to metal and non-metal elements: a case-control study. J Environ Pathol Toxicol Oncol., 17, 1-9.

Hu J, Mao Y, White K. (2002) Renal cell carcinoma and occupational exposure to chemicals in Canada. Occup Med, 52,157-64.

Järup L, Hellstrom L, Alfven T, Carlsson MD, Grubb A, Persson B, Pettersson C, Spang G, Schutz A, Elinder CG (2000) Low level exposure to cadmium and early kidney damage: the OSCAR study. Occup Environ Med. 57, 668-72.
Jelovcan S, Gutschi A, Kleinhappl B, Sedlmayr P, Barth S, Marth E. (2003) Effects of low concentrations of cadmium on immunoglobulin E production by human B lymphocytes in vitro. Toxicology 188, 35-48.

Jin YH, Clark AB, Slebos RJ, Al-Refai H, Taylor JA, Kunkel TA, Resnick MA, Gordenin DA. (2003) Cadmium is a mutagen that acts by inhibiting mismatch repair; Nature Genetics, 34, 326-9

Johnson MD, Kenney N, Stoica A, Hilakivi-Clarke L, Singh B, Chepko G, Clarke R, Sholler PF, Lirio AA, Foss C, Reiter R, Trock B, Paik S, Martin MB. (2003) Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. Nature Medicine, 9, 1081-4

International Agency for Research on Cancer monographs on the evaluation of the carcinogenic risk of chemicals to man (1993) Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry, vol. 58.

Lall, SB, and Dan, G. (1999) Role of corticosteroids in Cadmium induced immunotoxicity. Drug and Chemical Toxicology, 22, 401-9.

Leblanc JC, Malmauret L, Guerin T, Bordet F, Boursier B, Verger P. (2000) Estimation of the dietary intake of pesticide residues, lead, cadmium, arsenic and radionuclides in France. Food Addit Contam. 17, 925-32.

Leffel EK, Wolf C, Poklis A, White KL Jr. (2003) Drinking water exposure to cadmium, an environmental contaminant, results in the exacerbation of autoimmune disease in the murine model. Toxicology 188, 233-50.

Liu, J., Liu, Y; Habeebu, SS, and Klassen, CD (1999) Metallothionein-null mice are highly susceptible to the hematotoxic and immunotoxic effects of chronic CdCl2 exposure. Tox. Appl. Pharmacol., 159, 98-108.

Mandel JS, McLaughlin JK, Schlehofer B, Mellemgaard A, Helmert U, Lindblad P, McCredie M, Adami HO (1995) International renal-cell cancer study. IV. Occupation. Int J Cancer. 61, 601-5.

Martin MB, Voeller HJ, Gelmann EP, Lu J, Stoica EG, Hebert EJ, Reiter R, Singh B, Danielsen M, Pentecost E, Stoica A. (2002) Role of cadmium in the regulation of AR gene expression and activity. Endocrinology, 143, 263-75.

Martin MB, Reiter R, Pham T, Avellanet YR, Camara J, Lahm M, Pentecost E, Pratap K, Gilmore BA, Divekar S, Dagata RS, Bull JL, Stoica A. (2003) Estrogen-like activity of metals in MCF-7 breast cells. Endocrinol., 144, 2425-36.

Muller I, Helmers E, Barchet R, Schweinsberg F. (1994) Cadmium concentration in the renal cortex of kidney tumor patients and controls. J Trace Elem Electrolytes Health Dis., 8, 173-6.

Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlagel B, Schill W (2000) Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter urothelial and renal cancer study. Int J Epidemiol., 29, 1014-24.

Pearson CA, Lamar PC, Prozialeck WC. (2003) Effects of cadmium on E-cadherin and VE-cadherin in mouse lung. Life Sci. 72, 1303-20.

Rhomberg W, Schmoll HJ, Schneider B. (1995) High frequency of metalworkers among patients with seminomatous tumors of the testis: a case-control study. Am J Ind Med., 28, 79-87.

Schilderman PA, Moonen EJ, Kempkers P, Kleinjans JC. (1997) Bioavailability of soil-adsorbed cadmium in orally exposed male rats. Environ Health Perspect. 105, 234-8.

Seth P, Husain MM, Gupta P, Schoneboom A, Grieder BF, Mani H, Maheshwari RK. (2003)
Early onset of virus infection and up-regulation of cytokines in mice treated with cadmium and manganese. Biometals. 16, 359-68.

Shigematsu I, Kitamaru S, Takeuchi J, Minowa M, Nagai M, Usui T and Fukushima M: A retrospective mortality study on cadmium-exposed populations in Japan. In: Wilson, D. & Volpe, R.A., eds, Edited Proceedings of the Third International Cadmium Conference, Miami, FL, 3-5 February 1981, London/New York, Cadmium Association/Cadmium Council, 115-118, 1982.

Sorahan T, Lancashire RJ (1997) Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: an analysis with detailed job histories. Occup Environ Med., 54, 194-201.

Staessen JA, Roels HA, Emelianov D, Kuznetsova T, Thijs L, Vangronsveld J, Fagard R. (1999) Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group. Lancet. 353 (9159), 1140-4.

Stoica A, Katzenellenbogen BS, Martin MB. (2000) Activation of estrogen receptor-alpha by the heavy metal cadmium. Mol. Endocrinol.. 14, 545-53.

West DW, Slattery ML, Robison LM, French TK, Mahoney AW. (1991) Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. Cancer Causes Control, 2, 85-94.

Wesseling C, Pukkala E, Neuvonen K, Kauppinen T, Boffetta P, Partanen T. (2002) Cancer of the brain and nervous system and occupational exposures in Finnish women. J Occup Environ Med., 44, 663-8.