____I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION (RfC)

Substance Name -- Cadmium and Compounds
CASRN – 7440-43-9
Molecular Weight -- 112.41 (cadmium)
Preparation Date -- March 4, 1999

___I.B.1 INHALATION RfC SUMMARY

Critical Effect	Exposures*	UF	MF	RfC**
10% probability of of abnormally high urinary NAG excretion	0.65 ug/m^3 - (Inclusive of a dietary **(Inclusive of 1.4E-4 mg/kg-day. See Tox Review 5.2.4 for consideration of different background oral intakes.)	1	1	7E-4mg/m^3

Epidemiology study

Buchet et al., 1990

*Buchet et al. (1990) calculated that a 10% probability of abnormal excretion of NAG (N-acetyl-beta-D-glucosaminidase) occurred in a population when urinary cadmium levels were 2.7 ug/day. Output from a simple pharmacokinetic model (see Toxicological Review) indicated that a urinary cadmium level of 2.7 ug-day corresponds to a continuous inhalation exposure of 0.65 ug/m^3 that is inclusive of a dietary intake of 1.4E-4 mg/kg-day (Toxicological Review, Section 3.5).

___I.B.2 PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Both the RfD and RfC for cadmium are based on the same study, in which exposure was primarily via ingestion, but also included inhalation exposure. Use of a toxicokinetic model to convert the same urinary cadmium concentration to an oral dose or to an inhalation exposure level is appropriate, because the RfC is based on the same systemic toxicity, renal excretion, as the RfD and there are no portal-of-entry effect, and a dose measure related to internal dose (urinary cadmium) was used.

Buchet, J.P., R. Lauwerys, H. Roels, A. Bernard, P. Bruaux, F. Claeys, G. Ducoffre, P. DePlaen, J. Staessen, A. Amery, P. Lijnen, L. Thijs, D. Rondia, F. Sartor, A. Saint Remy and L. Nick. 1990. Renal effects of cadmium body burden of the general population. Lancet 336: 699-702.

As part of the Cadmium in Belgium (Cadmibel) study, a cross-sectional study was conducted from 1985 to 1989 of a stratified random sample of 2327 men and women from two high exposure areas (one urban and one rural) and two low exposure areas (one urban and one rural). The study design is described in greater detail by Lauwerys et al. (1990). Cadmium intake by this population occurred primarily via ingestion of contaminated water and contaminated food, but also via direct inhalation of cadmium. To

minimize confounding of the study results subjects who were outside the age range of 20-80 years, who had been occupationally exposed to heavy metals, who could provide no reliable information on smoking habits or occupational exposure to heavy metals, or whose 24-hour urine collections were not considered reliable based on established criteria were excluded from the analysis, resulting in a total of 1699 subjects to be studied further. Statistical analyses on the data from this population revealed the following results. Five urinary excretion variables, including calcium and NAG, were significantly and positively associated with urinary cadmium excretion. Cadmium excretion and diabetes were intercorrelated with NAG and one other variable, beta-2microglobulin, suggesting that diabetics are a sensitive subpopulation. Urinary cadmium levels at which >10% of the population would have abnormally high excretion of each of these five variables were calculated, the two most sensitive being calcium at 1.9 ug Cd/24 hr and NAG at 2.7 ug Cd/24 hr. Although abnormal urinary Ca is hypothesized to be associated with bone effects that could occur later in life (Kjellstrom, 1986, 1992) it is not clear that this is an adverse effect. Abnormal urinary protein excretion, such as NAG, is indicative of at least minor and probably irreversible damage to kidney function. Therefore abnormal NAG excretion was designated as the most sensitive urinary marker of an adverse effect and is the basis of the RfC.

TOXICOKINETIC MODELING: Basic knowledge on absorption, disposition and urinary excretion of cadmium were used to estimate the level of daily cadmium intake that would result in the urinary excretion of 2.7 ug Cd/24 hr at age 70, the cadmium excretion rate associated with a 10% probability of abnormal NAG excretion. This basic knowledge was integrated into a simple one compartment model that is described and demonstrated in the Toxicological Review. Is it acknowledged that the variables used in this model are for forms of cadmium that are readily soluble and bioavailable such that the outputs would most likely predict maximal levels of cadmium per external dose. The model considers airborne cadmium exposures to be in particulate form with size characteristics as reported by Dorn et al. (1976) for rural and urban settings. The U.S. EPA particle deposition model (U.S. EPA, 1994) was then used to estimate the average pulmonary deposition used in this model. This model estimated that urinary excretion of 2.7 ug Cd/day at age 70 corresponds to a continuous lifetime exposure of 0.65 ug/m^3.

ALLOWANCE FOR BACKGROUND CONTRIBUTION: The diet is considered to be the principal source of background cadmium exposure with other environmental sources (air, water, and soil) considered negligible unless otherwise shown. Dietary levels of cadmium are estimated from several sources at 10 ug/person-day (Toxicological Review, Section 3.5) or 1.4 E-4 mg/kg-day. This oral input was considered simultaneously with the inhalation input in arriving at the continuous life time exposure of 0.65 ug/m^3.

The background component may be allowed to vary to accommodate different values for the dietary component (such as with eaters of cadmium rich food sources). Changes in the background dietary contribution (such as may occur with high cadmium diets) would necessitate alterations in the RfC to accommodate this additional accumulation in the kidney. The Toxicological Review (Appendix B) lists ancillary RfC values generated for various ranges of dietary inputs.

RfC: A continuous lifetime exposure of 0.65 ug/m^3 (7E-4) mg/m^3 is the RfC. Inhalation of this concentration over a lifetime is projected to result in a 10% probability of abnormal urinary protein excretion at age 70. This concentration is inclusive of a simultaneous dietary intake of 0.14 ug/kg-day (10 ug/person-day). For dietary intakes higher than this, refer to the ancillary RfC listings in Section 5.2.4 of the Toxicological Review.

This assessment acknowledges that smoking adds significantly to the body burden of cadmium. Smokers have been shown to have 2-3 times higher cadmium concentration in their kidneys than similar-aged nonsmokers (Chung et al.1986; Järup, 1998). Smoking-related intake of cadmium is not considered in this assessment. Additional intake of cadmium by smoking would lessen the period of time in which the critical urinary excretion rate would be attained to less than 70 years.

Using 2 ug Cd/24 hour as a marker for adverse levels, and assuming oral absorption of 5%, daily excretion of 0.005% (5E-5/day) of body burden, and 1/3 of the body burden in the kidneys, the authors calculated that 2 ug/24 hr corresponds to ~50 ppm cadmium in the renal cortex, or 50 years of oral intake of about 1 ug/kg/day. This value is much lower than the 200 ppm critical cadmium concentration in the renal cortex estimated from occupational studies. It is unclear if the difference is due to different definitions of abnormal urinary protein levels, different estimates of toxicokinetic parameters, or different sensitivities of the general and worker populations.

---I.B.3 UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF = 1. This assessment is based on a sensitive endpoint (renal dysfunction) and chronic lifetime exposures in a population that includes sensitive populations, women, diabetics and (most likely) exposures during childhood. No uncertainty factors are proposed. The value of 2.7 ug Cd/ 24 hr presented by Buchet et al. (1990) is the maximum likelihood rather than a lower bounds estimate of a 10% probability of response. Lower bounds estimates (i.e., the 95% confidence limit) are often chosen in risk assessment practices due to their lower values and therefore conservative nature. However, the biological significance of a statistical lower bounds estimate on a population that includes known and potential sensitive populations is unclear. Therefore, the maximum likelihood estimate is chosen as the basis for the RfC. Until such time that further guidance or response information becomes available, the 10% probability of response for this endpoint in the human population is treated as a NOAEL.

MF = 1

---I.B.4 ADDITIONAL COMMENTS (INHALATION RfC)

Cadmium compounds are meant to include the common forms cadmium sulfide, cadmium chloride, and cadmium oxide. These and other forms cadmium vary widely in their solubility and availability, from freely soluble salts such as cadmium chloride to nearly insoluble complexes such as cadmium sulfide. Considerable information exists on cadmium oxide, a freely soluble form that has been documented to occur in occupational settings but that has also been implicated in airborne environmental exposure scenarios. Adverse effects of cadmium are nearly always associated most closely with the metal ion, not in the other part of salts or complexes. In consideration that this assessment is intended to protect public health, quantitative analyses are made on the basis of freely soluble cadmium in which the metal ion would be maximally available for any given dose.

Absorbed cadmium is transported to the liver, where it stimulates the synthesis of metallothionein, a low-molecular-weight protein with a high binding capacity for cadmium and other metals. Metallothionein is inducible in most tissues by exposure to cadmium, zinc, and other metals. The cadmium-metallothionein complex is then released back into the blood, and transported to the kidney, where it filtered by the glomerulus and reabsorbed by the proximal tubule cells (Foulkes, 1978). Proteolysis of the metallothionein then occurs in kidney lysosomes, releasing free cadmium, which stimulates new metallothionein synthesis (NTP, 1995; Squibb and Fowler, 1984). Renal damage is believed to result if free cadmium does not become bound to metallothionein, due to either the localization of cadmium or an excessive concentration of cadmium. The binding capacity of kidney metallothionein is lower than that of liver metallothionein, resulting in unbound kidney cadmium at administered doses where all liver cadmium is bound to metallothionein (Goyer et al., 1989; Kotsonis and Klaasen, 1978). These authors suggested that this tissue-specific difference in binding capacity accounts for the high cadmium sensitivity of the kidney.

There is abundant human evidence from occupational studies in which the primary route of exposure was via inhalation, to support the kidney as the primary target of cadmium exposure via this route. Analyses of these various studies and estimation of corresponding NOAEL(HEC)s or BMC(HEC)s provide a basis for comparison to the toxicokinetic model output value of 0.65 ug/m^3, the RfC. Ellis et al. (1985) evaluated renal function in a 82 male workers with cumulative exposures up to 10,000 ug/m^3 x years; a NOAEL(HEC) of 0.036 ug/m^3 and a BMC(HEC) at a 10% response rate of 0.57 ug/m^3 were estimated. Mason et al. (1988) reported proteinuria in a cohort of 75 workers who had been exposed for up to 39 years to cadmium; a NOAEL(HEC) of 3.7 ug/m^3 and a BMC(HEC) based on a 5% response of 0.93 ug/m^3 was estimated from these data. From information of Elinder et al. (1985a,b) who evaluated renal function in 60 workers exposed to cadmium for 4-24 years, an estimate of a BMC(HEC), 5% response was made at 1.5 ug/m^3. Järup et al. (1988) analyzed proteinuria among a cohort of 185 cadmium workers and reported a NOAEL at 691 ug/m^3 x years and a BMC(10% response) of 1030 ug/m^3 x years; estimates were made of these data for a NOAEL(HEC) at 0.69 ug/m^3 and for a BMC(HEC) at 5.2 ug/m^3 . A BMC(HEC) 5% response of 3.3 - 10 ug/m^3 was estimated from the data presented by Thun et al. (1989) on renal dysfunction of 45 cadmium workers. All save 2 of these various estimates are well within the range of the RfC of 0.65 ug/m^3 (7E-4 mg/m^3).

A key issue regarding the RfC for cadmium was whether the kidney or lung is more sensitive. Respiratory effects from cadmium exposure have been noted so far only in the occupational setting (Davison et al., 1988; Smith et al.,1976) presumably due to the direct irritative effects of the cadmium particles. In animals, respiratory tract lesions were observed by NTP (1995) and by Prigge (1978a) in subchronic studies in rats and mice. Glaser et al. (1986) also reported increased BAL findings in rats continuously exposed for 30 days. The identification of the kidney as more sensitive than the lung is supported by the finding that the kidney effects are irreversible or only slowly reversible (Elinder et al., 1985b; Mason et al., 1988; Thun et al., 1989), while reversal of lung effects has been observed upon cessation of exposure (Chan et al., 1988).

Two human occupational data sets where pulmonary and renal effects were reported in the same cohort afford an opportunity to directly address the issue of kidney vs lung sensitivity. Comparison of benchmark concentrations were calculated based on urinary protein excretion (Mason et al., 1988) and pulmonary function tests in the same cohort. Pulmonary effects at a BMC(HEC) based on a 5%

differential in carbon monoxide) transfer coefficient were estimated at 11 ug/m^3 (Davison et al., 1988). The BMC(HEC) based on renal tubular proteinuria (urinary RBP greater than 95th percentile of referent population) in this same cohort was estimated at only 0.93 ug/m^3. Edling et al. (1986) found no effect on lung function in a group of 57 male workers exposed to 50-500 ug/m^3 cadmium from cadmium-containing solders, compared to a group of 31 unexposed male controls from a nearby company. Measured endpoints included single breath washouts (closing volume) and a variety of spirometric endpoints, including FVC, FEV at 1 second (FEV1), and maximum mid-expiratory flow (MMF). Cumulative exposure was estimated at 340-9900 ug/m^3 x years (median 1700 ug/m^3 x years) with an estimated NOAEL(HEC) of 8 ug/m^3. In studying a subset of subjects of this same cohort, Elinder et al. (1985b) found that levels of β2m and albumin in urine correlated with urinary cadmium levels, and the glomerular filtration rate was significantly ($p<0.05$) below the age-predicted value. The incidence of tubular proteinuria was 25% in the group with 2-≤5 µg Cd/g creatinine, compared to 7% in the group with ≤2 µg Cd/g creatinine. A BMC(HEC) estimated from the designated kidney dysfunction (abnormal ß-2m, > 300 ug/g creatinine) at 1.5 ug/m^3 was considerably less than this value. These data suggest that the kidney is by far more sensitive than lung to the effects of even inhaled cadmium. It should be kept in mind, however, that measures of renal toxicity are also much more sensitive than those currently available for respiratory effects.

Another possible reason for the observation of lung effects in only some occupational studies, even at high exposures, is that lung injury caused by high-level cadmium exposure may be partially reversible, so that several years after exposures have been significantly reduced, lung function may be close to normal. Chan et al. (1988) re-examined the lung function of 44 cadmium workers from a cadmium-nickel battery factory, 3 years after an initial study. Of the 44 originally cadmium-exposed workers, 17 were still exposed (4-11 year exposure), and 27 were no longer exposed (from under 1 year to 10 years). Cadmium concentrations in air ranged from 30 to 90 ug/m^3, depending on the job task, and the average urinary cadmium concentration was 17 ug/g creatinine, reduced from the initial levels. Results of pulmonary function tests, particularly total lung capacity, were improved in all workers, with greater improvements in those who were no longer exposed to cadmium. Prevalence of respiratory symptoms were also decreased in the workers as a whole. This study shows that the restrictive effects of cadmium oxide dust may be reversible if workers are removed from exposure, or exposure levels are reduced early.

Effects of cadmium exposure are not limited to the lung and the kidney. Although neurotoxicity is not generally associated with inhalation exposure to cadmium, some studies have specifically assessed neurological effects (Hart et al., 1989; Viaene et al., 1999) although with small sample sizes of individuals that had been extensively exposed.

Suggestions that cadmium exposure increases the risk of elevated blood pressure have not been supported by epidemiological studies (Mason et al., 1988; Schuhmacher et al., 1994; Smith et al., 1980; Staessen et al. 1991; Staessen and Lauwerys, 1993; Thun et al., 1985, 1989). However, Roels et al. (1990) observed effects on the blood pressure regulatory protein kallikrein, without a corresponding effect on blood pressure. This effect may be secondary to effects on the kidney.

In a study of the reproductive effects of occupational exposure to cadmium, Gennart et al. (1992) compared a group of 83 married male cadmium workers and 138 married male controls who worked in other factories and may have been exposed intermittently to solvents. There was no effect on birthrate among the wives of the cadmium workers, although this is a crude measure of fertility and the use of

contraception was not evaluated. Mason (1990) found no significant effect of occupational cadmium exposure on the pituitary-testicular endocrine axis, as measured by serum testosterone, luteinizing hormone (LH), and follicular-stimulating hormone (FSH). A separate analysis of the subgroup of workers with renal tubular dysfunction also found no significant effect on levels of these hormones. There was, however, a slight increase compared to controls in the percent of exposed workers with FSH levels below the 95th confidence limit (7/66 versus 4/83; no statistical test conducted). The exposed population consisted of most of the men still alive (77/103) who had worked at a U.K. copper-cadmium alloy plant for at least 1 year (mean cumulative exposure 808 ug/m^3 x years; estimated continuous exposure of about 4 ug/m^3), and the reference population consisted of age-matched unexposed workers from the same plant.

The respiratory tract is the primary target of subchronic exposure of animals to cadmium compounds, and kidney toxicity has been reported in only one inhalation study. No chronic inhalation studies have evaluated kidney function, and the lack of kidney effects in the subchronic studies is attributed to insufficient cumulative exposure (NTP, 1995).

Both inhalation and oral studies show that cadmium is a developmental toxin. Studies in animals indicate that the most sensitive endpoint appears to be neurodevelopmental effects (Baranski ,1984; Baranski, 1985; Baranski et al., 1983; Popieluch et al., 1995; Dési et al., 1998) with effects extending into neurotransmitter levels (Antonio et al.,1998) . Decreased fetal weight and occurs at somewhat higher doses, with teratogenic effects occurring at still higher levels than those eliciting renal effects under chronic exposure conditions. Developmental effects observed in inhalation studies of cadmium include decreased pup weight and increased incidence of decreased ossification of the sternebrae at maternally toxic levels (NTP, 1995), and decreased motor activity and other behavioral measures (Baranski, 1984). Overall, these studies indicate that cadmium can cause neurodevelopmental effects at doses close to 0.1 mg/kg-day. However, these doses are still much higher than the RfD identified for effects on the kidney in humans at 0.00084 mg/kg-day.

TOXICOKINETICS

The toxicokinetics of cadmium depend on the form of cadmium inhaled and the physiological and dietary status of the exposed organism. Inhaled cadmium is absorbed from the lungs, or from the gut after clearance from the lungs; absorption from the gastrointestinal tract is low. Cadmium distributes mostly to the kidney and liver. Absorbed cadmium is excreted in the urine and feces.

As for all inhaled particles, lung deposition of cadmium compounds depends on the particle size, with higher deposition for smaller particles and fumes. Once deposited in the lung, both cadmium chloride and cadmium oxide are solubilized and distributed systemically, even though cadmium oxide is poorly soluble in water. By contrast, clearance of cadmium sulfide occurs primarily via mechanical transport by alveolar macrophages, rather than via solubilization (Glaser et al., 1986; Oberdorster and Cox, 1989; Oberdorster, 1992). Cadmium particles are also transported to the gastrointestinal tract via mucociliary clearance. Absorption of deposited cadmium oxide has been estimated at as high as 90%, while only about 10% of deposited cadmium sulfide is absorbed following inhalation exposure (Oberdorster and Cox, 1989; Oberdorster, 1990). Thus, systemic distribution is much higher following cadmium oxide exposure than cadmium sulfide exposure. Glaser et al. (1986) found that comparable body burdens (liver plus kidney

levels) were obtained in rats exposed almost continuously to 0.1 mg Cd/m^3 as cadmium oxide or a 10-fold higher concentration of cadmium as cadmium sulfide.

No direct data are available on cadmium deposition, retention, or absorption in the human lung. However, the numerous studies showing increased kidney, liver, and urinary cadmium in occupationally-exposed populations (Ellis et al. 1985; Elinder et al. 1985a, b; Järup et al. 1988; Kawada et al. 1990; Roels et al. 1983; Smith et al. 1980; Thun et al. 1989) indicate that inhaled cadmium is absorbed.

The concentration of cadmium in liver of occupationally-exposed workers generally increases in proportion to intensity and duration of exposure (Davison et al. 1988; Ellis et al. 1985). After the onset of renal damage, kidney concentrations of cadmium begin to decline (Braithwaite et al., 1991; Roels et al. 1981).

Although urinary cadmium is most frequently measured, most cadmium that is inhaled or ingested is excreted in the feces. This excreted cadmium represents mostly material that was swallowed, but not absorbed from the gastrointestinal tract, although biliary excretion does occur (Nordberg et al., 1985). Cadmium excretion in urine of occupationally exposed workers increases proportionally with body burden of cadmium (Roels et al. 1981). Unless renal damage is present, the amount of cadmium excreted represents only a small fraction of the total body burden, reflecting the long retention time of cadmium in the body, although urinary cadmium excretion increases markedly in the event of renal damage. In the absence of such marked renal damage, urinary cadmium is a marker of kidney cadmium burden, and thus, cumulative exposure to cadmium. Normal urinary cadmium excretion is about 1 ug/day (Nordberg et al., 1985).

Cadmium has a very-long biological half-life. The biological half-life of cadmium is reported as 10-30 years in kidney, and 4.7-9.7 years in liver (Ellis et al. 1985). Urinary cadmium excretion plateaus at human exposures above 0.500 mg/m^3 x yr, possibly because of renal saturation at this level and the inability of the kidney to further increase excretion (Smith et al. 1980). The human variability in the biological half time of cadmium in the kidney was estimated to range from a few years to at least 100 years (Sugita and Tsuchiya, 1995).

The placenta may act as a partial barrier to fetal exposure to cadmium. Cadmium concentration has been found to be approximately half as high in cord blood as in maternal blood (Lauwerys et al. 1978). Accumulation of cadmium in the placenta at levels about 6 to 7 times higher than maternal or fetal cord blood cadmium concentrations has also been reported (Kuhnert et al. 1982).

Toxicokinetic models of cadmium have been published (Kjellstrom and Nordberg 1978; Oberdorster 1990). The Kjellstrom and Nordberg (1978) model is an 8-compartment model that incorporates some physiological aspects. However, the lung and intestine "compartments" in this model are not true physiological compartments. Rather, they are input functions controlling the amount and rate of cadmium delivery to other compartments. Oberdorster (1990) developed a toxicokinetic model of cadmium for a route-to-route comparison of cadmium toxicity in the kidneys and lungs. He estimated that 90% of deposited cadmium oxide is solubilized from the lung to the body compartment, and 10% is mechanically cleared to the gastrointestinal tract. Of the cadmium distributed to the body compartment, 50% is

estimated to eventually arrive in the kidneys. Oberdorster estimated a whole-body half-life of cadmium of 10 years. Intestinal cadmium absorption was estimated at 5%, with the rest being excreted in the feces.

_I.B.5 CONFIDENCE IN THE INHALATION RfC

Study: High
Data Base: Medium
RfC: Medium

There is high confidence in the principal study and medium to high confidence in the database, resulting in medium to high confidence in the RfC. This inhalation RfC is based on toxicokinetic modeling of urinary excretion of cadmium, and not measured air levels of cadmium. This approach is considered valid as urinary cadmium levels reflects the internal cadmium body burden. Also, this model-predicted RfC is consistent with estimates of exposures from occupational studies that were related with mild renal proteinuria. The principal study was reasonably well-conducted, used a large sample of the general population, excluded people with confounding exposures, and included various potential sensitive subgroups such as women and diabetics. Extensive epidemiology data are available documenting kidney effects in workers exposed to cadmium via the inhalation route. Analysis of several of these studies indicate that kidney effects occur before lung function deficits although indicators of kidney damage are more sensitive than those for lung function. Developmental toxicity data are available in the rat and mouse, but there is no multi-generation reproduction study. The developmental toxicity data, specifically neurobehavioral effects, are among the most sensitive animal studies, but the exposure levels at which effects were seen are several orders of magnitude higher than the exposure level calculated to result in kidney effects in humans. Although cadmium accumulates in the body, the placenta appears to act as a barrier to fetal exposure. Therefore, it is unlikely that a multi-generation study would observe neurodevelopmental effects in rats at concentrations comparable to those that cause kidney effects in humans.

The levels of daily cadmium intake based on this RfC (in oral equivalents), is about 59 ug/person-day inclusive of a dietary background level of 10 ug/person-day, is close to levels recommended by WHO/FAO (1989) at about 60 ug/person/day for a 60 kg person and suggested by FDA (1993) at 55 ug/person/day

___I.B.6 EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Toxicological Review for Cadmium and Compounds

I.B.7 EPA CONTACTS (INHALATION RfC)

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