____I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

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

___I.A.1 ORAL RfD SUMMARY

Critical Effect	Doses*	UF	MF	RfD**
10% probability of of abnormally high urinary NAG excretion	(Total - dietary background) 8.4E-4 mg/kg-day - 1.4E-4 mg/kg-day	1	1	7E-4 mg/kg-day

** The RfD can vary with different background levels such that the total is never greater than 8.4E-4 mg/kg-day.

Population 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 total (nondietary + dietary) daily oral intake of 0.84 ug/kg/day = 8.4E-4 mg/kg-day. 1.4E-4 mg/kg-day is used as the estimate for daily dietary exposure to cadmium (Toxicological Review, Section 3.5) with the final RfD being the net allowable daily nondietary oral exposure.

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 RfD and RfC are based on the same systemic toxicity, renal dysfunction, and a dose measure related to internal dose (urinary cadmium) was used.

___I.A.2 PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

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 RfD.

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. It is acknowledged that the variables used in this model are for forms of cadmium that are readily soluble and bioavailable such that the outputs would predict maximal levels. This model estimated that urinary excretion of 2.7 ug Cd/day at age 70 corresponds to a daily lifetime intake of 0.84 ug/kg-day, about 59 ug/day for a 70 kg person, if all of the cadmium intake is via the oral route. This amount is inclusive of background dietary levels of cadmium.

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.

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).

RfD. A total daily oral intake of 0.84 ug/kg-day is projected to result in a 10% probability of abnormal urinary protein excretion at age 70. Allowing for typical dietary intake of 0.14 ug/kg-day the net allowable daily nondietary exposure becomes the RfD:

8.4E-4 mg/kg-day - 1.4E-4 mg/kg-day = 7E-4 mg/kg-day

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.

---I.A.3 UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

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 RfD. 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.A.4 ADDITIONAL COMMENTS (ORAL RfD)

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 is 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 supporting the kidney as the most sensitive target of cadmium toxicity as evidenced by increased urinary excretion of several low molecular weight species. These proteins are all readily filtered by the glomerulus and are normally reabsorbed in the proximal tubule of the kidney. Elevated urinary excretion of these proteins is therefore symptomatic of functional proximal tubular damage.

Several studies similar to that of Buchet et al. (1990) have been conducted with large cohorts that have been exposed orally to a wide concentration range of cadmium, from the high levels documented in

the Itai-itai incident (Nogawa and Kido,1993) to the marginally adverse levels in most environmental exposure studies (Nakashima et al., 1997; Hayano et al.,1996) and the principal study. These studies clearly show varying degrees of renal dysfunction related to the extent of cadmium exposure. Occupational studies, where the primary route of exposure is via inhalation, also support the kidney as the primary target of cadmium exposure. As described in the cadmium RfC documentation, numerous occupational studies have shown that effects on kidney function develop after a critical cumulative dose has been reached (Ellis et al. 1985; Kjellstrom et al., 1984; Roels et al., 1983). Studies based on urinary cadmium levels, on cumulative exposure, and on tissue levels of cadmium in the kidney and liver have reported a clear dose-response relationship between cadmium exposure and objective measures of kidney function (Elinder et al., 1985a, 1985b; Ellis et al., 1985; Jarup and Elinder, 1994; Jarup et al., 1988; Kjellstrom et al., 1977; Mason et al., 1988; Thun et al., 1989).

Studies in animals confirm that the oral exposure to cadmium can cause proteinuria and kidney tubular damage, and that kidney damage is related to the concentration of cadmium in the kidney (Friberg, L. et al., 1986; Mangler et al., 1988).

Other effects related to cadmium exposure, such as bone disorders (osteomalacia, osteoporosis, and spontaneous bone fracture) have been observed in human studies following chronic ingestion of high levels of cadmium in food (Kjellstrom, 1992). In a cadmium-contaminated area of Japan, Itai-itai disease, characterized by debilitating osteomalacia, most often affected women with poor nutrition and who had borne several children. In reporting abnormalities in the heel bones of women from a cadmium polluted area, Tsuritani et al. (1996) noted that they correlated with renal tubular damage indicating concurrent adverse renal effects. Tsuritani et al. (1992) also reported a female specific decrease in serum vitamin D that occurred concurrently with increased levels of urinary microglobulins indicating that women may be susceptible to bone damage that occurs with renal damage whereas males are not. Subclinical effects on calcium metabolism, including increased urinary excretion of calcium (Buchet et al. 1990) and increased serum alkaline phosphatase (Staessen and Lauwerys, 1993), have been observed at doses and urinary levels of cadmium excretion concomitant with and slightly below those causing minimal kidney effects. An evaluation of these results is that bone effects from cadmium intake seem to manifest predominately in women and in concert with renal effects. This indicates that effects on bone would be secondary to renal effects and that women rather than men are susceptible to this secondary effect. The Principal Study of Buchet et al. (1990) included women.

As reduced iron stores have been shown to lead to increased gastrointestinal absorption of cadmium both in humans and experimental animals, women may be considered as a potential susceptible population (Berglund et al.,1994).

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.

Animal studies are somewhat equivocal in indicating the nature of the effect cadmium may have on newborn and young animals as compared to adult. Cadmium apears to be better absorbed in the neonate (Sasser and Jarboe, 1977) although other data indicate that neonates are more resistant possibly due to higher content of metallothionein (Goering and Klaassen, 1984; Klaassen and Wong, 1982. Nuerodevelopmental effects are reported as discussed above (various studies of Baranski, Popieluch et al., 1995; Dési et al., 1998; Wong and Klaassen, 1982) whereas Nagymajtényi et al. (1997) report that neurotoxicological effects were seen in rats treated by gavage from 8-12 weeks of age but not in rats that were exposed via milk during lactation.

Gennart et al (1992) showed no effect on birthrate among the wives of the cadmium workers. There are no studies investigating reproductive or developmental effects of ingested cadmium in humans.

The pharmacokinetics of cadmium depend on the physiological and dietary status of the exposed organism as well the form of cadmium ingested. The amount of cadmium absorbed and available to the body from the soluble cadmium chloride or acetate is far greater than with forms of cadmium that are essentially insoluble such as cadmium sulfide. As noted above this assessment is based on forms of cadmium that would yield the highest levels of cadmium in the body and is therefore conservative from the perspective of public health protection.

Absorption of cadmium from the gastrointestinal tract is low. Cadmium distributes mostly to the kidney and liver, and is excreted in the urine and feces (Jarup, 1998; Ragan and Mast, 1990; Nordberg et al., 1985). In a comparison of the rates of accumulation of cadmium ingested in food and water, Ruoff et al. (1994) found that the bioavailability of cadmium in food is not significantly different from the bioavailability of cadmium in drinking water when food and water are provided ad libitum and the cadmium dose is less than 4 mg/kg/day. They noted that bioavailability may be more influenced by the contents of the gastrointestinal tract than by the exposure medium and, as pointed out above, on internal iron stores. Therefore this assessment does not discriminate between water and food as being different with regards to intake as did the previous RfD.

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. Mettallothionein 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 Klaassen, 1978).

Although urinary cadmium is most frequently measured, most ingested cadmium 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 the urine of occupationally exposed workers increases proportionally with body burden of cadmium (Roels et al. 1981). Also, the concentration of cadmium in the liver of occupationally-exposed workers generally increases in proportion to the 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). 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 total cadmium body burden, and thus, cumulative exposure to cadmium. Normal urinary cadmium excretion is about 1 ug/day (Nordberg et al., 1985). 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). 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 using a whole-body half-life of cadmium of 10 years, intestinal cadmium absorption estimated at 5%, inhaled cadmium estimated at 90%, and 50% estimated to eventually arrive in the kidneys. A modification of the Oberdorster (1990) model is used in this assessment and is presented in the Toxicological Review. As discussed above, conservative parameters are used in this model, e.g., the 90% figure for cadmium oxide is used to estimated cadmium solubilized from the lung to the body compartment.

_I.A.5 CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: High
RfD: High

There is high confidence in the principal study and medium to high confidence in the database, resulting in medium to high confidence in the RfD. The principal study was reasonably well-conducted, used as large a cohort of the general population as feasible, excluded people with confounding exposures and included potential susceptible subgroups (women, diabetics). The critical effect from the principal study, renal dysfunction, is supported by a number of other epidemiological studies of oral intake of

cadlium. The kidney has ben shown to be the target organ even in long-term occupational studies (see the RfC documentation) where cadmium exposure is via the inhalation route. Developmental toxicity data are available only in the rat, and there is no multigeneration reproduction study although dominant lethal studies (which show no effects) are available. The developmental toxicity data are among the most sensitive animal studies, showing neurodevelopmental effects at doses as low as about 0.1 mg/kg-day although this dose is almost three orders of magnitude higher than the dose calculated to result in kidney effects in humans at 0.84 ug/kg-day. Although cadmium accumulates in the body, the placenta appears to act as a barrier to fetal exposure. Therefore, it is unlikely that a multigeneration study would observe neurodevelopmental effects in rats at doses comparable to those that cause kidney effects in humans. The toxicokinetic model developed in this assessment is judged to adequately predict the limited human data available and is parameterized in a parsimonious manner in comparison respect to other models.

The levels of cadmium intake based on this RfD, 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.A.6 EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Toxicological Review for Cadmium and Compounds. IRIS.

I.A.7 EPA CONTACTS (ORAL RfD)

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