TOXICOLOGICAL REVIEW

CADMIUM AND COMPOUNDS

(CAS No. 7440-43-9)

In Support of Summary Information on

Integrated Risk Information System (IRIS)

March 4, 1999

This document is a preliminary draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for internal Agency peer review on its technical accuracy and policy implications.

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington D.C.

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FOREWORD

The purpose of this Support Document is to provide scientific support and rationale for the hazard identification and dose-response assessments for both cancer and noncancer effects (the oral reference dose [RfD] and the inhalation reference concentration ([RfC]), from chronic exposure to cadmium and compounds. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of cadmium and compounds.

Each assessment, both cancer and noncancer, is individually characterized as to the overall confidence in the quantitative as well as the more qualitative aspects of hazard (U.S. EPA, 1995a). Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the individual assessments and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

Contributors-

This composite cancer and noncancer assessment for cadmium and compounds was developed and authored by the Chemical Manager, Gary L. Foureman of the National Center for Risk Assessment in Research Triangle Park, NC 27711, and the scientists at ICF Kaiser, including Harvey Clewell, Bruce Allen and, in particular, Lynne Haber, For further information about this assessment or other questions relating to IRIS the reader is referred to the IRIS information desk at (513) 569-7254.

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The external peer reviewers for this assessment (will be listed by name and association here). The comments of these reviewers, their response to given questions and the actions taken upon their recommendations are in Appendix A.

Subsequent to external review and incorporation of comments, this assessment has undergone an Agency-wide review process whereby the IRIS Program Manager has achieved a consensus approval with Program Offices (Air and Radiation; Planning and Evaluation; Prevention, Pesticides, and Toxic Substances; Research and Development; Solid Waste and Emergency Response; and Water) and the Regional Offices.

1.0 Introduction

The derivation of the noncancer dose-response assessments for oral exposure, the oral reference dose (RfD) and for inhalation exposure, the inhalation reference concentration (RfC), and the cancer hazard and dose-response assessments for cadmium are presented in this Review. The Review is intended to be inclusive of other cadmium compounds that occur commonly and for which there is at least some toxicity data. .

The various cadmium compounds 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.

Cadmium is a ubiquitous substance with an appreciable intake from dietary sources as well as other voluntary sources such as smoking and shellfish eating. Thus background levels are recognized, discussed, and accommodated in this Review and the accompanying assessments

The RfD and RfC are meant to provide information on long-term toxic effects other than carcinogenicity. The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as some carcinogenic responses. It is expressed in units of mg/kg/day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation reference concentration (RfC) is analogous to the oral RfD. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is expressed in units of mg/m3.

The carcinogenicity assessment is meant to provide information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per g/L drinking water or risk per g/m3 air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000.

Development of these hazard identifications and dose-response assessment for cadmium has followed the general guidelines for risk assessments as set forth by the National Research Council (1983). Other EPA guidelines that were used in the development of this assessment include the following: The Risk Assessment Guidelines (U.S. EPA, 1987), the (new) Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991), (proposed) Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity (U.S. EPA, 1994a), (proposed) Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1995b), Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994b), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988) and the Use of the Benchmark Dose Approach in Health Risk Assessment (U.S. EPA, 1995c).

Literature search strategy employed for this compound were based on the CASRN and at least one common name. As a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC, EMICBACK, DART, ETICBACK, TOXLINE, CANCERLINE, MEDLINE AND MEDLINE backfiles. Literature searches were kept current for this assessment up until March of 1999.

2.0 Chemical and Physical Information of Cadmium and Cadmium Compounds Relevant to Assessments

Cadmium is a metallic element found in Group 2B of the periodic table. Cadmium has possible valences of 0, +1, and +2. It forms almost all of its compounds in the +2 oxidation state. Cadmium metal is slowly oxidized in moist air and when heated in air, it rapidly forms cadmium oxide (Carr 1992). Cadmium exists in the environment as both inorganic salts and organocadmium compounds, but the most common form of exposure is to cadmium oxide. Common occupational exposure is to cadmium oxide and cadmium sulfide Physical and chemical properties of elemental cadmium and cadmium compounds for which inhalation or oral toxicity data exist are shown in Table 1.

In the air, cadmium occurs as or is associated with particulate matter. The size distribution of cadmium particulate material occurring in the occupational setting has been reported by Oberdorster (1989) at MMAD of 1.3 and σ_g of 2.6 and in the rural setting at MMAD of 2.6 and σ_g of 3.6) as described by Dorn et al. (1976).

The widely varying solubilities of the various cadmium compounds is relevant to all considerations of biokinetics with these compounds. Quantitative analyses in this assessment are made on the basis of freely soluble cadmium in which the metal ion would be maximally available for any given dose.

3.0 Toxicokinetics/Toxicodynamics Relevant to Assessments

The pharmacokinetics of cadmium depend on the form of cadmium inhaled or ingested 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 for any cadmium compound, soluble or not. Absorption via the lung is much higher than for the gut. Different cadmium compounds have different solubilities that may greatly influence bioavailability although data are currently deficient to quantitate most of these differences. Cadmium distributes mostly to the kidney and liver. Absorbed cadmium is excreted in the urine and feces.

3.1 Inhaled cadmium

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). That systemic distribution is much higher following cadmium oxide exposure than cadmium sulfide exposure was confirmed by Glaser et al. (1986) who 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.

Oberdorster and Cox (1989) exposed rats to cadmium chloride aerosol via nose-only inhalation and administered cadmium oxide fume or dust, or cadmium sulfide dust, to rats via intratracheal instillation. Monkeys were exposed to all three compounds (excluding cadmium oxide fume) via intratracheal instillation. The pulmonary retention half-time for all three compounds was shorter in rats (months) than for monkeys (years). Pulmonary retention of cadmium oxide dust in the rats was biphasic, with retention half-times of 9 days and ~7 months. Shorter retention half-times were observed for cadmium oxide fume than cadmium oxide dust, consistent with faster solubilization of smaller particles. Cadmium sulfide had a faster biphasic half-time of 11 and 76 days, and the half-times for cadmium chloride were similar. In monkeys, the order of long-term retention half-times was cadmium oxide (~431 days) < cadmium chloride (~850 days) < cadmium sulfide (~1070 days). Rhoads and Sanders (1985) observed much faster lung clearance of cadmium oxide administered intratracheally to rats, although it was also biphasic. They found that 67% of the material had a clearance half-time of 4 hours, and 33% had a half-time of 13 days. For whole-body clearance, they

Table 1. Physical and Chemical Properties of Cadmium Metal and Cadmium Compounds[a]

Property	Cadmium	Cadmium oxide	Cadmium chloride	Cadmium sulfide
Chemical formula	Cd	CdO	$CdCl_2$	CdS
Valence	0	+2	+2	+2
CAS Number	7440-43-9	1306-19-0	10108-64-2	1306-23-6
Molecular weight	112.41	128.41	183.32	144.47
Physical state (25°C)	Blue-white metal	Dark-brown powder or crystals[b]	Colorless crystals	Light-yellow or orange crystals[b]
Melting point	320.9°C	>1500°C	568°C	1750°C at 100 atm
Boiling point	765°C	Decomposes 900-1000°C	960°C	Sublimes in N_2 at 980°C
Solubility in water	Insoluble	Insoluble	140 g/100 mL at 20°C	$1.3x10^{-4}$ g/100 mL at 18°C
Vapor Pressure	1 mmHg at 394°C	1 mmHg at 1000°C	10 mmHg at 656°C	No data

[a]Data from Weast 1989 unless otherwise noted
[b]Budavari 1989

found that 6% had a half-time of 2 days, and 94% had a half-time of about 220 days. The reason for this difference in half-times is unclear, although it is possible that the cadmium oxide particle size was more "fume-like" than "dust-like." Klimisch (1993) exposed rats to cadmium chloride or cadmium sulfide aerosols for 6 hours/day for 10 days, and found clearance half-times of 1 and 87 days for cadmium chloride, and 1.4 and 42 days for 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; Jarup 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.

3.2 GI absorption

Gastrointestinal absorption of Cd is reported to be quite low: 1-2% in rats and mice, 0.5-3% in monkeys, and 3-8% in humans (Ragan and Mast, 1990; Jarup et al., 1998). The apparently lower absorption by laboratory animals may be more related to differences in the standard rodent and typical human diets than to differences in physiological factors (Andersen et al., 1992). Absorption of ingested cadmium by humans is influenced by the chemical form of cadmium and the organism's physiological status, with absorption increased by low intake of calcium, iron, zinc, and copper (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. There is thus no basis for designating between oral water and oral food intake as was done in the previous IRIS cadmium oral RfD assessment.

A study of cadmium absorption in juvenile rats indicate the possibility of increased absorption in neonatal animals although no corroborative evidence exists for humans. Sasser and Jarboe (1977) reported absorption of 12% at 2 hours, 5% at 24 hours and 0.5% at 6 weeks after birth.

3.3 Biochemistry of Cadmium

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.

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 appears to be the most reliable marker of renal cadmium burden, and thus, cumulative exposure to cadmium. Normal urinary cadmium excretion is about 1 µg/day (Nordberg et al., 1985). Blood cadmium is thought to reflect current exposure more closely than body burden, which is the focus of this assessment.

Cadmium has a very-long biological half-life in humans. 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 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). Urinary cadmium excretion plateaus at human exposures above 0.5 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). Such a prolonged half-life in combination with continuous exposure dictate that steady state levels would be attained only after several half-lives, i.e. near the end of humans 70-odd year life span. The quantitative procedures in this assessment for evaluation of urinary cadmium excretion use a half-life in human as 20 years - intermediate between the 10-30 year range.

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).

3.4 Toxicokinetic Models

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, as shown in Figure 1. As shown, Oberdorster 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. As described in Sections 5.1 and 5.2, and in Appendix B in greater detail, an adaptation of the Oberdorster model and its estimates of internal cadmium distribution was used in this assessment to estimate the cadmium exposure levels corresponding to specified urinary cadmium levels for the development of the oral RfD and the inhalation RfC. Half-lives of 20 and 10 years were used to determine the sensitivity of the model to different values. It is also anticipated that the model could be made cadmium-compound specific such that liver and kidney concentrations and urinary cadmium levels could be calculated for different cadmium compounds given that the fractional absorptions and partition coefficients are available or could be determined.

It should be noted, however, that these none of these models have the capacity to incorporate such factors that may influence cadmium toxicity during long term exposures such as metallothionein induction or zinc status. Variability is also a major issue that available models do not currently address. Too, only limited human data exist on which the models may be tested.

3.5 Environmental and Background Exposures to Cadmium - including smokers and shellfish eaters

Cadmium is not only ubiquitous but also, in some sources of exposure, may be present at concentrations near those derived in the assessments in this Review. For example, the FDA considers the tolerable daily intake of cadmium at 55 ug/person /day and gives estimates of the dietary intake of cadmium (exclusive of shellfish) at approximately 20% of this value, 10 ug/person/day (FDA, 1993). The FDA also cites epidemiological data indicating that adverse effects (renal dysfunction) will occur in 5% of the nonoccupationally exposed population after 50 years averaging only 108 ug/day. By comparison, the levels recommended in this assessment in

reference to kidney damage (the RfD and RfC) when based on a 70 kg person are approximately 59 ug/person-day. Considering that these values do not incorporate variability, this margin of safety is quite small. As any cadmium intake is additive to the cumulative kidney effects documented below, such high and varied background levels as a consequence of diet obligates any assessment to integrate this contribution into the levels finally recommended.

Subpopulations such as smokers and shellfish eaters have background levels higher still, increasing their risk dramatically for experiencing cadmium-induced adverse effects by the end of their lives. FDA (1993) states that smoking one pack of cigarettes per day might result in the exposure to approximately 10 ug and absorption of 1 to 3 ug cadmium, an amount approximately equal to the amount absorbed from the diet. This prediction has received confirmation as direct measurement in body tissues of smokers are roughly doubles cadmium body burden as seen in individuals not smoking (ADSDR/TP-88/08, 1989). FDA (1993) also estimated that for individuals who consume an average of 15 g/day of molluscan bivalves with mean cadmium levels of 0.6 ppm, cadmium intake will average 9 ug/person/day; for consuming an average of 17 g/day of crustacean shellfish that contain mean cadmium levels of 0.2 ppm, cadmium intake will average 3 ug/person/day. Based on these consumption levels, which are average for those who regularly eat shellfish, these levels also come close to equaling the normal dietary intake.

3.5.1 Cd in the Diet

Data from the FDA total diet study (cited in FDA, 1993) suggest that the mean lifetime exposure to total cadmium from all food to be 10 ug/person /day (0.14 ug/kg-day). Green leafy vegetables, potatoes, liver, and milk are listed as the major sources. These are average male and female values and do not include shellfish. Ellen et al. (1990) also found an average daily cadmium intake of 10 ug/person/day in a total diet study of 110 individuals. This value is close to the value of 13.8 ug/person/day obtained from examining dietary cadmium intake of 24 individuals in five Canadian cities (Dabbeka et al.,1987). .

3.5.2. Cd in the Environment (air, dust, water)

Cadmium levels in drinking water are typically negligible. Konz and Walker (1979) reported levels not exceeding 1 ug/L and Meranger et al. (1981) an average of 0.5 ug/L. Exposure from consumption of 0.5 ug Cd/L drinking water would be 1 ug/person/day with the majority of this intake accounted for in the FDA total diet study.

Cadmium levels in urban air are reported to be in the range of 5 to 40 ng/m^3 with rural areas considerably lower at 1 to 5 ng/m^3 (Elinder, 1985). FDA used the middle of the urban range, 25 ng/m^3, to estimate a background cadmium exposure around 0.5 ug/day. Based on the

speciation of the cadmium (and therefore the fractional uptake) this amount could appreciably add to the daily uptake. The form of environmental cadmium is, however, unknown.

Carey (1978) reports that a typical soil level for cadmium is 260 ppb (0.26 ppm). Uptake of soil cadmium by plants would be accounted for in the diet levels discussed above. This source of cadmium may be underestimated in regards for the exposure of children as they ingest much more soil than do adults and may possibly have an increased intestinal absorption for cadmium. increased ingestion of soil and the possibility of increased absorption of metals in children.

3.5.3. Summary

Diet is the main source of background exposure to cadmium in the normal population. In view of the available information, the mean lifetime exposure to total cadmium from all food is considered to be 10 ug/person /day (0.14 ug/kg-day). These value applies to average adult male and females and does not consider additional levels from smoking or shellfish eating. This dietary background exposure is considered and incorporated into the oral RfD and inhalation RfC assessments.

Typical environmental contributions (i.e., not near metal smelting operations) contributions to the dietary intake of cadmium are considered negligible.

4.0 Hazard Identification

4.1 Studies in humans -epidemiology, case reports, clinical controls

Cancer (Inhalation)

General

Overall, these studies that follow show a relationship between occupational exposure to cadmium and lung cancer that is related to cumulative exposure, but that may also be related to known confounding factors. Early reports of an association between cadmium exposure and prostate cancer have not been supported by more recent follow-ups with the same cohorts. However, any relationship between cadmium and prostate cancer may be partially obscured by the relatively high incidence of prostate cancer in the general population, and the low numbers of prostate cancer deaths in the cohorts studied. In particular, studies based on mortality may not be sufficiently sensitive, since increased screening for prostate cancer in exposed populations could lead to increased survival.

A number of epidemiology studies have been conducted to evaluate the carcinogenic potential of occupational exposure to cadmium, with some cohorts followed for extended periods

in multiple studies. A series of studies conducted on a cohort at an American smelter in Colorado that had been used for both arsenic and cadmium reported an increase in lung cancer deaths related to cumulative cadmium exposure (Lemen et al., 1976; Thun et al., 1985; Stayner et al., 1992, 1993; Lamm et al., 1992; Sorahan and Lancashire, 1997). To date, however, none have been able to eliminate the possibility of confounding from either or both arsenic or smoking both of which are strongly associated with lung cancer mortality. Significant excesses in the number of lung cancer deaths were also observed in cadmium workers in the United Kingdom (Kazantzis et al., 1992) although arsenic is cited here also as a potential confounding factor. Significantly increased mortality from respiratory cancer was observed in a study of nickel cadmium battery workers, but no relationship to exposure duration was observed (Sorahan, 1987). An excess of lung cancer deaths that did not reach statistical significance was also reported in a nickel-cadmium manufacturing plant in Sweden (Elinder et al., 1985c). A link between occupational exposure to cadmium and prostate cancer has been suggested (Kipling and Waterhouse, 1967; Lemen et al., 1976; Potts, 1965), but this finding has not been supported by more recent follow-up (Sorahan and Waterhouse, 1985; Thun et al., 1985). Detection of a cadmium-related increase in prostate cancer mortality is complicated by the relatively high prevalence in the general population and by recent improvements in prostate cancer screening.

In the initial study, Lemen et al. (1976) studied 292 men from the cohort, with follow-up through 1973. Workers who had been employed for 2 or more years between January 1, 1940, and December 31, 1969 were included in the study; no attempt was made to exclude workers exposed while the plant was an arsenic smelter (prior to 1926). Life table analysis comparing mortality with the U.S. white male population found a statistically significant excess of deaths from respiratory cancer (12 Obs, SMR=2.34, $p<0.05$). A nonsignificant excess of prostate cancer deaths was observed for the total cohort (Obs=4, SMR=347, $p>0.05$) which became statistically significant when the analysis was restricted to workers with 20 or more years of exposure (4 Obs, SMR=452, $p<0.05$).

Thun et al. (1985) conducted a study extending the cohort, with additional follow-up time. The study population consisted of 602 white men who worked in a production area at the smelter for at least 6 months between 1940 and 1969, with follow up through 1978. Separate analyses were conducted for the pre- and post-1926 cohorts in an attempt to reduce the confounding effects of arsenic. Cumulative exposure was calculated on an individual basis by multiplying days worked in a given general work category by average inhalation exposure for that category. Exposure ranged from 20 to 1500 $\mu g/m^3$ prior to 1950, and decreased to 7 to 150 $\mu g/m^3$ by 1965-1976. For each time period, exposure estimates were based on area monitoring data by department, collected by Smith et al. (1980). Exposure estimates were adjusted for respirator usage and type of sampling method. The study authors divided the post-1926 cohort (576 men) by cumulative exposure: <584, 585-2920, and >2921 mg/m^3-days. A modified life-table analysis was conducted, in comparison with expected rates for the U.S. white male population, adjusted for age and calendar period, and standardized mortality ratios (SMRs) were calculated. A statistically significant exposure-response relationship was observed between lung cancer deaths and

cumulative exposure to cadmium. All lung cancer deaths were observed in workers employed for at least 2 years (SMR=229, 95% CI=131-371). The study authors also reported total deaths from respiratory cancer, including cancers of the lung, trachea, and bronchus, but 16/20 respiratory cancers were lung cancers and no exposure-response analysis was conducted for total respiratory cancers. They also noted that, because national lung cancer death rates overestimated regional rates by 10-25%, the measured excess of lung cancer deaths was probably an underestimate. There was no significant increase in mortality from prostate cancer, nonmalignant respiratory disease, nonmalignant renal disease, or hypertension. The study authors noted that no new deaths from prostate cancer were observed since the original Lemen et al. (1976) study. One of the deaths in the initial study was excluded from the Thun et al. (1985) study, because the subject had not worked for 6 months in a production area, and one dead worker with prostate cancer was not included in the analysis, because prostate cancer was not listed as the underlying cause of death, although it was listed as a contributing cause.

Confounders were dealt with in Thun et al.(1985) as follows. The authors noted that intermittent arsenic processing in this plant continued into the 1930's, and the workers in certain departments were also exposed to arsenic due to contamination of the feed material. Levels of arsenic in the areas of highest exposure were reported to be as high as 300 to 700 $\mu g/m^3$ in the 1950's, but worker exposure was much lower, due to respirator use and decreasing air levels in later years. The expected number of lung cancer deaths in the cohort that could be attributed to arsenic exposure was estimated, assuming an average arsenic concentration in air of 500 $\mu g/m^3$ in high-arsenic areas, a 75% respirator protection factor, and an estimated 20% of person-years in high-arsenic areas. Based on these assumptions, the average arsenic exposure was estimated at 25 $\mu g/m^3$. The study authors estimated that this exposure should have resulted in no more than 0.77 lung cancers due to arsenic; this value was updated to 0.52-0.97 by OSHA (1992). The study authors also noted that urinary arsenic levels of workers in high arsenic areas from 1960 to 1980 are consistent with exposure to 14 $\mu g/m^3$, suggesting that the assumptions resulted in an over-estimate. Based on interviews of 70% of survivors or next-of-kin, the authors also found that the percent of smoking in the workers was comparable to that in the general population.

Stayner et al. (1992) published a follow-up through 1984 of the Thun cohort, including 162 deaths. A modified life table analysis was conducted comparing mortality to that of the U.S. white males. Person-years were categorized in four ways: cumulative exposure, latency (elapsed years since first exposure), year of observation, and age. As in Thun et al. (1985), individual employment histories were grouped into one of seven broad general work categories. Separate analyses were conducted on Hispanics and non-Hispanics, to account for the fact that Hispanics smoke less and have a lower lung cancer death rate than non-Hispanic whites. Respiratory cancer mortality (including cancer of the lung, trachea, and bronchus, henceforth termed "lung cancer" for this cohort) was significantly increased in the non-Hispanic population (SMR = 211, 95% CI = 131-323), while a reduction was seen in the Hispanic population. An exposure-response relationship between respiratory cancer mortality and cumulative cadmium exposure was observed for the top three cumulative exposure groups among non-Hispanics (585-1460 mg/m^3-days and

up), and among all workers in the highest exposure group ($\geq$2921 mg/m^3-days). When person-years were stratified by latency, a significant response was observed only for a latency $\geq$20 years, consistent with findings for other chemical-induced lung cancers. These data serve as the dose-response data for the cancer analysis in this assessment (Section 5.3.2).

In an assessment that was characterized as indirect, Stayner et al. (1992) conducted an evaluation on these data using year-of-hire as a measure of arsenic exposure. Arsenic was used heavily between 1928 and 1940 and decreased, but still produced, after that year. First, workers first employed prior to 1926, when the plant was an arsenic smelter, were excluded from analysis. Dose response models were then analyzed with and without a dichotomous variable to account for hire before 1940 and with or without another variable for arsenic work exposure subsequent to 1940. The year-of-hire variable (or, indirectly, arsenic exposure) was not a significant predictor of lung cancer mortality in the analyses. Although this analysis failed to provide evidence that the effect of cadmium on lung cancer was significantly modified by year-of-hire (again, an indirect indication of arsenic exposure), it is acknowledged that year-of-hire is a crude surrogate for arsenic exposure. The authors state that detailed information on individual worker exposure and plant usage of arsenic stock would be necessary to more definitively evaluate potential confounding by arsenic.

Lamm et al. (1992) conducted a nested case-control study of the 25 cases of lung cancer in the same cohort through 1982, using three controls per case, matched by date of hire and age at hire. Unlike the Stayner study, cohort members with dates of hire prior to 1926 (from 1902) were included for both cases and controls. The study was designed with the predicted expectation of finding the ratios of cadmium exposure for cases and controls to differ for each hire period, in a manner parallel to the SMRs. They found that both cumulative cadmium exposure mean exposure to cadmium were practically the same for cases and controls (ratio of means, 0.99), both overall and also after stratification by period of hire. Lung cancer risk was, however, closely related to period of hire (prior to 1926, SMR=492; 1926-39, SMR=283; 1940-69, SMR=88), which was considered a likely surrogate for arsenic exposure. Although insufficient data was presented to definitively judge the influence of smoking (only 72% of the cases and 57% of the controls had available smoking histories) the odds ratio for these members was estimated at 8.2 and is consistent with the accepted range of lung cancer associated with smoking. It was concluded that exposure to arsenic (from the feedstock) and cigarette particulates, rather than cadmium exposure, may have caused the observed increase in lung cancer.

The reason for differences between the results of Lamm et al. (1992) and Stayner et al. (1992) with the same cohort is not clear. Part of the reason may be because the cohorts were not identical, with four of the cases in the Lamm study excluded by Stayner because they were hired before 1926 and three of the cases of Stayner et al. excluded by Lamm because they were diagnosed between 1982 and 1984. Overmatching by date of hire may also have contributed to the negative result in the Lamm study, in light of the strong correlation between exposure and date of hire (Doll (1992). To evaluate these differences, Stayner et al. (1993) conducted a nested case-

control study, using approximately 50 controls per case, and matching based on survival to the same age as the case. Statistically significantly increased odds ratios, with a statistically significant dose-response trend, were observed for both the overall cohort and for the subgroup hired after 1940, when arsenic levels were low. In an evaluation of these studies Doll (1992) noted that for the reasons given above as well as insufficient knowledge of actual worker exposure, neither Lamm et al (1992) nor Stayner et al (1992) eliminated the possibility that arsenic was a confounder for the observed lung cancers.

Sorahan and Lancashire (1997) conducted an exhaustive re-analysis of individual exposures of the Colorado cohort using individual time/pay sheets over the period of 1926 to 1969. This re-analysis allowed assignment of individual worker exposure based on over 600 job titles and 22 departments compared to the 7 broad categories used by Stayner (1992) and Thun (1985). A total of 105 433 man-half-months were documented such that individuals exposure were known for 91% of all hours worked. Additional information on arsenic exposure was also given in this report indicating that arsenic was present in feedstocks until 1958, with the annual mean percentage being 1% to 4% between 1940 and 1958. The expansion of the listing of job titles also permitted a more accurate assignment of job titles to potential arsenic exposure as well as whether the predominant form of cadmium was to either cadmium oxide, cadmium sulfide, or cadmium sulfate. For example, airborne concentrations of arsenic trioxide near the roasting and calcining furnaces ranged from 700 ug/m^3 in 1950 to about 100 ug/m^3 in 1979 as compared to levels of 0.3 and 1.4 ug/m^3 in the casting and retort departments. These newly derived data allowed for formulation of seven variables whose influence on the observed lung cancers may be evaluated: 1 - age attained, 2 - year of starting employment, 3 - estimated cumulative exposure to cadmium, 4 - estimated exposure to cadmium in the presence of exposure to arsenic trioxide, 5- estimated exposure to cadmium in the absence of exposure to arsenic trioxide, 6 - ever being employed in the arsenic department, and 7- Hispanic ethnicity. Regression analyses on these variables was conducted to establish whether the lung mortality experienced by the different cumulative exposure groups could be described in terms of these variables or whether the inclusion variable 3 (cumulative exposure to cadmium) made a significant contribution to the ability of the overall model to describe the data. The significance of this contribution was assessed by the likelihood ratio test comparing deviance and degrees of freedom with and without inclusion of the variable cumulative exposure to cadmium. Four groups of cumulative exposure to cadmium (< 400, 400-99, 1000-1999, >2000 mg.m^3 days) were established. Modeling results demonstrated there to be a significant positive trend between cumulative exposure to cadmium and risks of mortality from lung cancer. The relative the risks for the cumulative groups were 2.3 (95% CI, 0.72-7.36), 2.83 (95% CI, 0.75-10.72), and 3.88 (95% CI, 1.04-14.46), respectively. These trends were more pronounced when employment histories were lagged by either 10 or 20 years. A separate analysis examined the independent effects of exposure to cadmium in the presence of high exposures to arsenic trioxide (variable 4) and exposure to cadmium received in the absence of arsenic trioxide (variable 5); a significant trend for a risk of lung cancer was found only for variable 4, in the presence of arsenic. Several hypotheses are consistent with these results and include; cadmium (oxide) in the presence of arsenic trioxide is a human lung carcinogen; cadmium (oxide) and arsenic trioxide are human

lung carcinogens and cadmium sulphate and cadmium sulfide are not; arsenic trioxide is a human lung carcinogen and cadmium (as oxide, sulphate or sulfide) is not. The limited number of deaths from lung cancer in this cohort to date (twenty one) are insufficient to determine further which of these hypotheses, if any, is correct. Complete smoking histories are lacking for this cohort. These results indicate that the confounding influences of both smoking and arsenic exposure on the lung cancer mortality seen in this cohort are yet to be totally resolved.

Several studies that have been conducted of a British cohort of nickel cadmium battery workers, who were exposed to cadmium oxide dust, suggest a link between cadmium exposure and prostate cancer (Kipling and Waterhouse, 1967; Potts, 1965; Sorahan and Waterhouse, 1983; Sorahan, 1987). Cadmium exposure was estimated to be 600-2800 $\mu g/m^3$ in 1949 (Potts, 1965). After installation of local exhaust ventilation in 1950, cadmium concentrations were reduced to $\leq$500 $\mu g/m^3$ in 1950-1967. Further improvements decreased concentrations to <200 $\mu g/m^3$ 1968-1975, and <50 $\mu g/m^3$ after 1975 (Sorahan and Waterhouse, 1983).

In an early study of this plant, Potts (1965) found three prostate cancer deaths and one lung cancer death among 74 men who had been exposed for at least 10 years, but no comparisons to an unexposed population were conducted. Kipling and Waterhouse (1967) compared cancer incidence among 248 men from this factory who had worked for at least one year at this plant (including the Potts cohort) with incidence rates from a regional cancer registry. They found one new case of prostate cancer, in addition to the three reported by Potts (1965), (Obs/Exp=7, p=0.003), but no significant effect on lung cancer (Obs=5, Exp=4.4, p=0.45).

Sorahan and Waterhouse (1983) expanded the cohort of Potts to 3025 workers (2559 men and 466 women) who were employed at the factory for at least 1 month during the period 1923-1975 (excluding office workers). In comparison with the mortality rates for the general population of England and Wales, a significant increase in respiratory cancer was observed (Obs=89, SMR=127, $p<0.05$). There was also an excess of prostate cancer deaths (Obs=8, SMR=121), but the increase was not statistically significant. To examine the exposure-response relationship, workers were grouped into high, medium, or low exposure by job category, and analyzed by duration of employment, but there was no analysis by cumulative exposure. When analyzed by the method of regression models in life tables (RMLT), duration of employment in the high exposure jobs was significantly ($p<0.05$) related to the incidence of death from prostate cancer, but only when the initial four cases reported by Kipling and Waterhouse (1967) were included. Thus, there was no new evidence supporting a link between cadmium exposure and prostate cancer. The RMLT analysis found that duration of employment in a high-exposure job was not significantly related to increased deaths from cancer of the respiratory system, but a statistically significant relationship was found between respiratory system cancer deaths and duration of employment in medium- or high-exposure jobs.

In a letter to the editor, Sorahan and Waterhouse (1985) identified 15 prostate cancer cases from this population reported to the regional cancer registry. This incidence was not significant

compared to regional incidence rates (Obs=15, Exp=11.02), but workers with little or no exposure to cadmium were included in the cohort. Although a significant increase in prostate cancer incidence was seen in a subgroup of 458 workers who worked for at least 1 year at high exposure jobs (Obs=8, Exp=1.99), this increase was not significant when the original four hypothesis-generating cases of Kipling and Waterhouse (1967) were excluded (Obs=4, Exp=1.78, p=0.21). Workers who had left the region prior to being diagnosed with prostate cancer would have been excluded from the analysis, but the authors estimated that this would have excluded only one case from the entire cohort.

Sorahan (1987) conducted a follow-up of cancer mortality of the entire cohort of 3025 employees during the period 1946-1984. Mortality from cancer of the lung and bronchus was significantly increased in the entire cohort (Obs=110, SMR=130, $p<0.01$). Duration of employment in a high-exposure job was not significantly correlated with cancer mortality, but duration of employment may not have been a sufficient surrogate for dose.

A series of studies (Armstrong and Kazantzis, 1983, 1985; Kazantzis et al., 1992) analyzed worker mortality in a cohort of 6995 men in 17 United Kingdom plants where cadmium was produced or used. The cohort included men born before 1940 and employed for at least one year between 1942 and 1970. The study population was divided into "ever high" exposure (3%), "ever medium" (17%), and "always low" (80%), where exposure for at least a year was required for categorization as "ever high" or "ever medium." Mortality rates were compared to those for the population of England and Wales, accounting for regional variation. Armstrong and Kazantzis (1983) found no significant increase in the number of deaths from lung (SMR=107, CI=92-122) or prostate cancer (SMR=99) in the overall cohort.

Armstrong and Kazantzis (1985) conducted a case-control study of deaths from prostate cancer, renal cancer, bronchitis or emphysema, and nephritis or nephrosis in this cohort, the cohort studied by Sorahan and Waterhouse (1983), and a cohort of copper-cadmium alloy workers. For all groups, the cohort included men born before 1940 and employed for at least one year between 1942 and 1970, and controls were matched by plant, age, and date of birth. As in the Armstrong and Kazantzis (1983) study, workers were divided into groups with "ever high," "ever medium," and "always low" exposure. An elevated odds ratio for prostate cancer deaths was observed for the "ever high" group (1.35) and the "ever medium" group (1.55), but neither of these increases were statistically significant. The only statistically significant increase was for bronchitis and emphysema. In a follow-up of the Armstrong and Kazantzis (1983) cohort through 1989 (Kazantzis et al., 1992), there was a statistically significantly increased risk of lung cancer overall (SMR=1.12, CI=1.00-1.24), with some evidence of increased risk with increased exposure levels or exposure duration, but these relationships did not attain statistical significance. Most of the lung cancer deaths occurred at a zinc-lead-cadmium smelter, where there was also exposure to arsenic. The smelter accounted for 64% of the study population and 70% of the lung cancer deaths, but it included no workers in the "ever high" category. There was no increased prostate

cancer mortality in the overall cohort, or in the high or medium exposure groups. This study is limited by the small relative size of the high-exposure group.

Sorahan et al. (1995) analyzed cancer mortality among a group of 347 male copper-cadmium alloy workers in a rural and an urban factory. Cadmium exposure decreased from ≥480 $\mu g/m^3$ prior to 1935, to 150-360 $\mu g/m^3$ in 1936-1972, and 43-85 $\mu g/m^3$ in 1973-1980, as cadmium oxide fume. They reported that deaths from non-malignant respiratory disease was related to cumulative exposure, but that there was no increase in lung cancer deaths in the cadmium-exposed groups, even in a lagged analysis after adjusting for age. However, no adjustment was made for rural versus urban location.

Elinder et al. (1985c) reported on cancer mortality among 522 male workers in a Swedish cadmium-nickel battery factory who were exposed to cadmium for at least one year between 1940 and 1980. Cadmium oxide dust levels were reported as about 1000 $\mu g/m^3$ prior to 1947, about 300 $\mu g/m^3$ in 1947-1962, about 50 $\mu g/m^3$ in 1962-1974, and about 20 $\mu g/m^3$ after 1975. Nickel hydroxide levels were usually 2-10 times higher for any given period. Mortality in the cohort was compared to expected mortality for the general Swedish population. Although the SMRs for lung and prostate cancer were increased, a statistically significant increase in the number of deaths from these causes was not observed, even when the analysis was confined to workers with at least 5 years of exposure and a 20-year latency period was incorporated into the analysis. However, a significant increase in deaths due to nephritis and nephrosis was observed.

In a case-control study, Van der Gulden et al. (1995) reported a statistically significantly increased age-adjusted risk of prostate cancer associated with occupational exposure to cadmium (SMR=2.76, CI=1.05-7.27). The study included 345 prostate cancer cases and 1346 referents with prostate hyperplasia (an anatomically and morphologically distinct lesion). This study is limited by the small number of cases in the cadmium workers (n=7), and because other occupational exposures in the cadmium group were not reported.

Nonoccupational data on the carcinogenic potential of cadmium is very limited. Abd Elghany et al. (1990) conducted a population-based case-control study based on 358 cases of prostatic cancer newly diagnosed in one year in four urban Utah counties, and 679 age-matched controls. Analyses were conducted based on self-reported exposure, employment in an industry involving cadmium exposure, high dietary intake of cadmium, and smoking. Because some of the controls may have had latent tumors, a separate analysis was conducted for aggressive tumors. There was a borderline significant association with high dietary intake of cadmium (odds ratio=1.4, 95% Confidence Interval =1.0-2.1), but there was no association with jobs with potential cadmium exposure or with cigarette smoking. Increased tumors overall were not observed in the group with occupational exposure, exposure from cigarette smoking, or elevated dietary exposure, but this group did have an increased risk of aggressive tumors (odds ratio 1.7, 95% confidence interval =1.0-3.1).

Noncancer

General

There is extensive epidemiological data as well as numerous occupational studies that demonstrate kidney effects from long-term low level exposure to cadmium from both oral and inhalation routes. esoccupational studies of the effects of cadmium exposure (primarily via the inhalation route), as well as some on the effects of oral exposure to cadmium. In light of the known effects of cadmium, most of the occupational studies only assessed kidney function by measuring the amount of low-molecular-weight protein in urine, typically ß2-microglobulin (β2m), but also lysozyme and retinol binding protein (RBP) and NAG (Jung et al., 1993). These low-molecular-weight proteins are all readily filtered by the glomerulus and are normally reabsorbed in the proximal tubule of the kidney. Therefore, elevated urinary excretion of these proteins is symptomatic of proximal tubular damage. Lung effects have also been observed at somewhat higher cumulative exposures, and postmenopausal women with calcium deficiencies have developed bone disorders following high oral exposure.

Data are available for the incidence of kidney dysfunction based on several measures of exposure, including cumulative cadmium exposure, kidney or liver cadmium levels (a measure of total internal cadmium dose), and urinary cadmium (also a measure of total internal dose, especially of the kidney). As the most sensitive studies of kidney effects reported exposure based on urinary cadmium, the RfC and RfD are based on this measure. However, the other studies are also described for comparison, especially because more detailed exposure-response information is available for the cumulative exposure measure. Key elements of the oral and inhalation studies addressing kidney effects of cadmium are summarized in Table 2.

Consensus has not been reached on the most appropriate marker for cadmium-related kidney effects. Several authors found that effects on NAG activity were more sensitive than effects on β2m (Chia et al., 1989; Fels et al., 1994; Kawada et al., 1990; Roels et al., 1993). However, most of these studies did not report any method for controlling urinary pH, and β2m degrades in acidic urine, so their findings may be more related to instability of β2m. The effects of pH on NAG activity has not been addressed in the cadmium literature, but since activity is assayed (in contrast to RBP, for which amount is measured), it is reasonable to assume that NAG measurements may also be pH sensitive. RBP has been used as a sensitive marker (Fels et al., 1994; Mason et al., 1988; Roels et al., 1993), and has greater stability than β2m. A notable exception is the principal study of Buchet et al. (1990) in which it is specifically stated that the urine sample were buffered (Lauwerys et al., 1990). Effects on other markers, such as urinary calcium (Mason et al., 1988; Thun et al., 1989) and tubular antigens (Fels et al., 1994; Roels et al., 1993) have been reported at lower doses than those causing effects on urinary β2m, but these other parameters have not been well characterized. In a detailed study of 14 parameters related to kidney function in a population of 77 workers exposed to cadmium fume and dust, and 103 age-matched referents, Guthrie et al. (1994) found that NAG was a less sensitive predictor of renal

dysfunction than β2m or RBP. Specificity was similar for all three proteins, and identical sensitivity was observed for β2m and RBP.

A related issue is the levels of urinary proteins that correspond to adverse effects on kidney function. Determination of such levels is problematic, because urinary protein levels are influenced by a variety of factors, including diet, time of day, and physical workload (Mutti et al., 1992). Furthermore, comparisons of urinary β2m levels between studies are complicated by the instability of this protein if the pH is not controlled. In light of these considerations, no attempt was made to determine a uniform measure for adverse levels of urinary proteins. Instead, each study defined adverse levels, usually based on a percentile (e.g. 95th percentile) of the values for the control population.

Because the kidney effects of cadmium are related to cumulative exposure, several investigators have attempted to relate these effects to an internal measure of tissue dose, such as kidney or liver cadmium levels measured using gamma neutron activation analysis. In particular, it has been noted that tubular dysfunction generally develops only after cadmium reaches a minimum threshold level in the renal cortex, a value referred to as the "critical concentration". The critical concentration of cadmium in the renal cortex associated with increased incidence of renal dysfunction in an adult human population chronically exposed to cadmium has been estimated to be about 200 µg/g wet weight by several investigators (Kjellstrom et al., 1984; Roels et al., 1983; Ellis et al. 1985) based on curve fitting to individual data. Although this value is an appropriate estimate of the critical concentration, it includes numerous uncertainties. Much of the basis for this value as presented by Kjellstrom et al. (1984), Roels et al. (1981), and others, comes from liver cadmium data. In reporting their population-based indicator of renal damage, Buchet et al. (1990) calculated that the critical urinary level of 2.7 ug/24 hr urine was associated with a renal cortical concentration of 50 ug/g , close to that obtained by analysis in this assessment of these same data at 41 ug/g..

Cessation of cadmium exposure generally does not lead to any decrease in proteinuria in occupationally-exposed workers (Elinder et al. 1985b; Mason et al. 1988; Thun et al. 1989), possibly because the kidney cadmium level declines very slowly after cessation of exposure. In fact, recent evidence has shown that kidney damage may continue after exposure ceases. Elinder et al. (1985b) observed the development of proteinuria in workers after the cessation of exposure.

Urinary excretion of high-molecular-weight proteins such as albumin has also been reported in occupationally exposed workers (Bernard et al. 1990; Elinder et al. 1985a; Mason et al. 1988; Thun et al. 1989), but there is some debate as to whether this represents glomerular damage (Bernard et al. 1990) or severe tubular damage (Elinder et al. 1985a; Mason et al. 1988).

Inhalation exposure results are presented throughout this section in terms of cumulative occupational exposure although when possible these values are converted to human equivalent concentrations (HECs) as per Section 5.3.3. These HEC values are also shown in Table 3.

Oral (population-based)

As part of the Cadmium in Belgium (CadmiBel) study, Buchet et al. (1990) conducted a cross-sectional study from 1985 to 1989 of a stratified random sample of 2327 people from two high exposure areas (one urban and one rural) and two low exposure areas (one urban and one rural). Cadmium intake by this population occurred primarily via ingestion of contaminated water and contaminated food, but also via direct inhalation of cadmium. The experimental protocol of the field study (described in Lauwerys et al., 1990) was for each participant to complete a questionnaire on their medical history, current and past occupations, smoking habits, consumption of alcohol, locally grown vegetables and well water and drug intake, including analgesics. Each participant was also characterized by 10 blood pressure readings, and two determination each of pulse rate, height and body weight. Twenty-four hour urine samples and venous blood were also collected from each participant. For evaluation of urinary enzyme activities and protein excretion fresh urine samples were collected, buffered to pH 7.6, and stored at 4 degrees C. To minimize confounding by factors that could also influence kidney function subjects who were outside the age range of 20-80 years, those who had been occupationally exposed to heavy metals, those 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 leaving 1699 individuals. Multiple regression analysis procedures showed that RBP (retinol binding protein) and NAG (N-acetyl-beta-D-glucosaminidase), β2m, amino acids, and calcium were significantly associated with urinary cadmium excretion. Multivariate correlation analysis revealed interactions between cadmium body burden and the presence of diabetes for both NAG and β2m excretion, suggesting that diabetics are a sensitive subpopulation. The study population was then divided into quartiles for each of the five variables according to 24 hr urinary excretion and compared using analysis of variance procedures. Each variable showed a significant dose-response relationship. A logistic regression model was then applied to these data to examine the probability of individual subjects having abnormal renal variable values as a function of urinary cadmium excretion. This procedure was used to estimate urinary cadmium levels at which >10% of the population would have abnormally high excretion of these markers (i.e., abnormal kidney function). They estimated that this would occur at urinary cadmium levels of 1.9 µg Cd/24 hours for calcium, 2.74 ug Cd/24 hr for NAG, 2.87 ug Cd/24 hr for RBP, 3.05 ug Cd/24 hr for β2m and 4.29 ug Cd/ 24hr for amino acids. Abnormal values were defined as $\geq$338 µg/24 hr for RBP, $\geq$283 µg/24 hr for β2m, and $\geq$2.74 µg/24 hr for NAG. (These values can be converted to µg/g creatinine by noting that normal creatinine excretion is 1-1.8 g/24 hours [Dorland's, 28th Edition, 1988]).

Using 2 µg cadmium/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, Buchet calculated that 2 µg/24 hr corresponds to ~50 ppm (ug/g) cadmium in the renal cortex, or 50 years of oral intake of about 1 µg/kg/day. The modified model of Oberdorster (1990) used in this assessment (Appendix B) projected that a urinary excretion of 2.7 µg Cd/day

corresponded to a daily lifetime intake of 0.84 µg/kg/day if all of the cadmium intake is via the oral route, and 0.59 µg/m^3 if all cadmium intake (save for 0.14 mg/kg-day oral background) is via the inhalation route, with the corresponding renal cortex concentration being 41 ug/g (renal concentration of 33 ug/g x 1.25). This value for renal cortical concentration is much lower than the 200 ppm estimated from occupational studies (Friberg et al.,1974). 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.

In other reports of the CadmiBel population, Staessen et al. (1992) reported that measures of indicators to cadmium exposure in the CadmiBel study population did not correlate with increases in blood pressure, prevalence of hypertension or other cardiovascular diseases. Staessen and Lauwerys (1993) reported on the significant and positive correlation of urinary cadmium with both serum alkaline phosphatase and urinary cadmium. The contributions or exacerbation of findings concerning calcium metabolism and homeostasis to morbidity outcomes such as osteoporosis or osteomalacia requires further investigation.

Nogawa et al. (1989) evaluated kidney function and cadmium exposure in a group of 1850 cadmium-exposed subjects (878 males and 972 females) and 294 controls in Japan. The exposed subjects lived in an area in which the river water is contaminated with cadmium from a mine, leading to cadmium contamination of rice grown in that area. Cadmium intake in rice (based on cadmium concentration in the rice and length of residence in the exposed area) was used by the study authors to calculate dose, because more than 70% of the total cadmium intake in that region has been reported to be derived from rice. β2-microglobulinuria was defined as >1000 µg/L, or as >1000 µg/g creatinine, and the incidence of microglobulinurea was presented as a function of grouped total cadmium intake. It is noted that only the percent with kidney dysfunction were reported in this study and that the definition of kidney dysfunction is much less conservative than that used by investigators of effects of cadmium following inhalation exposure to cadmium (typically 200-600 µg/g creatinine for β2-microglobulinuria). It is unclear why such a high cutoff was chosen for this study, although it may be based on a level at which kidney effects become irreversible. Nogawa and Kido (1993) reported that the incidence of β2-microglobulinuria in exposed subjects with urinary cadmium levels of 3.8-4 µg Cd/g creatinine was comparable to the incidence in controls. A BMD of about 0.001 mg/kg/day was estimated, based on the incidence of β2-m levels >1000 µg/g creatinine (Appendix C). Cumulative doses in mg/kg were estimated from the reported doses in mg using a default body weight of 70 kg which is likely an overestimate of the actual body weight, and hence an underestimate of the actual dose. An additional factor in the underestimation of the dose was that cadmium intake that was not in rice, which may have accounted for as much as 30% of the total cadmium intake, was not included in the dose estimates.

Hayano et al. (1996) examined the dose-response relationship of urinary cadmium concentrations with respect to age in a general population of 3178 individuals > 50 years old (exposed) including 1134 individuals who lived in nonpolluted areas (nonexposed). The summary statistics for overall prevalence rate for abnormal β_2-m (> 1000 ug/g creatinine) was 4-6.3% in the

nonexposed group as compared to 14.3-18.7% for the cadmium-exposed groups. The increased prevalence of β_2-microglobulinurea in the nonpolluted areas was found to be associated with 1.6 - 3.0 ug/g creatinine for men and a slightly higher range for women at 2.3-4.6 ug/g creatinine. Other statistics for the nonexposed populations showed that urinary cadmium concentrations were greater for women (geometric mean of 3.60 ug/g creatinine) than for men (geometric mean of 2.29 ug/g creatinine) and that when stratified with age, levels tended to increase in males and approach the levels in females which were relatively unchanged with respect to age. Bivariate analysis showed that both age and urinary cadmium were positively associated with the prevalence rate of abnormal β_2-microglobulinurea, defined by the authors as > 1000 ug/g creatinine. Although this study assumed an abnormally large cut-off value for β_2-microglobulinurea and did not consider smoking, the urinary cadmium levels associated with increased β_2-microglobulinurea prevalence in the nonexposed general population is comparable with the range of 2-4 ug Cd/ 24 hr urine reported by Buchet et al., (1990) that was associated with a 10% probability of exceeding a number of abnormal renal variables including β_2-microglobulinurea.

Nakashima et al. (1997) examined various urinary indicators in relation to the concentration of cadmium in rice in a population of 1703 (832 men and 871 women) who had consumed home grown rice and had lived in the same hamlet in Japan for at least 30 years. Measurements were made of several urinary indicators and of cadmium levels in rice. Average cadmium levels in rice (ranging from 0.11 to 0.67 ppm.) were positively and significantly correlated with prevalence of abnormal β_2-m (abnormal, > 1000 ug/L), metallothionein (abnormal, 550 ug/L), and amino acids (abnormal > 251-348 mg/L). The maximum allowable urinary concentration of cadmium calculated with β_2-m as an indicator of health effects was reported as 1.6 - 3.0 ug/g creatinine in men and 2.3-4.6 ug/g in women. Using 1-1.8 g of creatinine excreted/day (Dorland's 28th Ed, 1988) as a conversion factor these levels correspond to about 1-5.4 ug/24 hr urine in men and 2.3-8.3 ug/ 24 hr urine in women which are both in the range reported in the Buchet et al. (1990) study.

Ikeda et al. (1995) found no correlation between urinary cadmium and β2m or RBP levels in 378 nonsmoking, nondrinking Japanese women with no known occupational exposure to heavy metals, and cadmium exposure primarily from food. The range of urinary cadmium levels was approximately 0.4 to 7.4 µg/g creatinine and are within the ranges reported by the larger study of Hayano et al. (1996).

Bone disorders, including osteomalacia (softening of bones), osteoporosis, and spontaneous bone fracture, have been observed following chronic ingestion of high levels of cadmium in food (Kjellstrom, 1992). In a cadmium-contaminated area of Japan, osteomalacia most often affected women with poor nutrition and who had borne several children; this disease is called Itai-Itai disease (Nagawa and Kido, 1993). These changes appear to be secondary to disruption of vitamin D metabolism in the kidney, and resulting imbalances in calcium absorption and excretion. Although overt effects on the bone occur at doses much higher than those causing kidney effects, 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 comparable to those that cause minimal kidney effects. However, the contributions or exacerbation of findings concerning calcium metabolism and homeostasis to morbidity outcomes such as osteoporosis or osteomalacia requires further investigation.

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Inhalation (Occupational Studies)

Mason et al. (1988) evaluated a group of 75 current and retired male copper-cadmium alloy workers in the U.K. who had been exposed to cadmium for up to 39 years, and an equal number of controls matched for age and employment status. Cadmium exposure decreased from $\geq$480 μg/m^3 prior to 1935, to 150-360 μg/m^3 in 1936-1972, and 34-85 μg/m^3 in 1973-1983, as cadmium oxide fume. Based on data provided by the authors, individual cumulative exposure ranged from 30 to 13,277 μg/m^3 x years. Smoking status was reported as comparable in the two groups. Cadmium intake from smoking was not included in the analysis, but typical liver cadmium levels in smokers (2 ppm) were much lower than those in most of the exposed workers (typically 2.7-90 ppm). Detailed work histories were available on the exposed workers, and cumulative exposure was calculated on an individual basis. Liver cadmium levels were determined and correlated well with the cadmium exposure index ($r=0.64$, $p<0.0001$). Kidney cadmium was also determined, but the correlation between kidney cadmium and exposure index (0.43) is less informative, because kidney cadmium decreases in cases of kidney dysfunction usually as a consequence of increased urinary cadmium output. In addition, both the kidney and liver cadmium levels did not fully reflect the cumulative exposure. These measurements, as well as blood and urine cadmium, were negatively correlated with years since exposure ended (after allowing for the effect of cumulative exposure). Significant differences were observed between the exposed and control groups in numerous measurements of kidney function (e.g., urinary total protein, albumin, RBP, fractional excretion of calcium and urate), and most of these endpoints correlated with both the cadmium exposure index and liver cadmium. Data were reported as the difference in RBP from the matched control, versus individual exposure level, and as the incidence of proteinuria for grouped exposure levels, with proteinuria defined as urinary RBP >95th percentile for the referent population. Based on the individual data provided by the authors, the response was 3/28 in the <500 μg/m^3 x years group (average 242 μg/m^3 x years), 1/16 among those exposed to 501-1000 (average 719) μg/m^3, and 6/9 in the 1001-1500 (average 1301) μg/m^3 x years group. The data based on the individual differences is a better reflection of the kidney effects of cadmium, because it corrects for the natural deterioration of kidney function with age. Significant differences between the exposed and control groups were also reported for urinary N-acetyl-β-D-glucosaminidase (NAG) and albumin, and measures of kidney function, such as creatinine clearance, but no dose-response data were presented for these endpoints. Based on the grouped data, the NOAEL is 719 μg/m^3 x years, and the LOAEL is 1301 μg/m^3 x years. A BMC of 181 μg/m^3 x years was calculated based on the grouped data. Based on the individual data (and

assuming a background response rate of 5%), BMCs of 251 and 1340 μg/m^3 x years were calculated using the Weibull model and Power model, respectively, using the hybrid modeling approach (Appendix C). The corresponding NOAEL(HEC) was 3.7 ug/m^3 and BMC(HEC) based on the same 5% response was 0.93 ug/m^3. (By contrast, a BMC of 2090 μg/m^3 x years and BMC[HEC] of 11 ug/m^3 can be calculated from the data of Davison et al. [1988] on lung effects in the same cohort.)

Kjellstrom et al. (1977) and Jarup et al. (1988) evaluated kidney function in men and women who had worked at a battery factory for at least 3 months, where exposure was to cadmium oxide (and nickel hydroxide) dust. The nickel exposure was not considered to contribute significantly to any kidney effects, based on a rabbit study with nickel hydroxide from that plant. Area sampling found cadmium concentrations of 300-700 μg/m^3 in the 1950's, and <100 μg/m^3 in the 1960's. During the 1970's the geometric mean exposure measured with personal air samplers was 53 μg/m^3. Kjellstrom et al. (1977) examined 185 male and female cadmium workers, and compared them with 87 unexposed male workers. Tubular proteinuria was defined as 290 μg/L (290 μg/g creatinine), based on the upper 95% tolerance limit for the control group, and was observed in 3.4% of the reference group. A significant increase in proteinuria was observed in those exposed for 6-12 years or more. Jarup et al. (1988) evaluated cumulative cadmium exposure, cadmium blood levels, and urinary β2-m levels in 326 men and 114 women employed for at least 3 months in the same factory; there was no control group. β2-m levels exceeding 35 μg/mmol creatinine (310 μg/g creatinine) was defined as tubular proteinuria. This value was chosen based on the upper 2.5 percentile in "populations without tubular dysfunction" in the Kjellstrom et al. (1977) and other studies, but appears to be based on unexposed controls that were not screened for kidney function. Only the grouped data were reported, with groups ranging from <359 μg/m^3 x years to >15,000 μg/m^3 x years. The incidence of proteinuria was 3/264 (1.1%), 7/76 (9.2%), and 10/43 (23.3%) in the groups with cumulative exposures of <359, 359-<1710, and 1710-<4578 μg/m^3 x years (means of 131, 691, and 3460 μg/m^3 x years), respectively. The Jarup study is limited because there is no method for controlling for variability in sampling methodology or subject age. However, the authors noted that similar dose-response functions were observed for the exposed subjects >60 years old and <60 years old. The NOAEL for this study was 131 μg/m^3 x years, and the LOAEL was 691 μg/m^3 x years. A BMC of 1030 μg/m^3 x years was calculated, based on the incidence data. The corresponding estimates for the NOAEL(HEC) was 0.69 ug/m^3 and for the BMC(HEC) for 10% response was high at 5.2 ug/m^3.

Thun et al. (1989) evaluated kidney function in 45 male workers at a cadmium recovery plant and 32 age-matched male controls. Exposure levels at this plant were previously described in the cancer section (Smith et al., 1980; Thun et al., 1985). Cumulative exposure was estimated based on historical air sampling data, adjusted for respirator use. After controlling for age, blood pressure, and body size, cadmium exposure was associated with increased β2m and RBP in urine, as well as with other measures of renal function, such as tubular resorption of calcium and serum creatinine, but not to urinary NAG. No control for smoking was conducted, but a smaller percentage of the exposed group were current or former smokers. Individual data were presented

for several measures of renal function versus cumulative exposure. The study authors used a logistic regression model to calculate that a threshold for renal dysfunction is approximately 300 mg/m^3 x days (822 µg/m^3 x years) (using a definition of abnormal β2m as >486 µg/g creatinine, or RBP>321 µg/g creatinine). Using the hybrid model and a background incidence of 5% to model the individual β2m data, the BMC based on β2m is 1838-1964 µg/m^3 x years. Based on the RBP data, a BMC of 646 µg/m^3 was calculated using the Weibull model, and a BMC of 1975 µg/m^3 x years was calculated using the Power model (Appendix C). The authors also estimated that a urinary cadmium concentration of 3.2 µg/g cadmium corresponded to a 1% prevalence of abnormal β2m, using 5000 µg β2m/L (~5000 µg/g creatinine) as the definition of abnormality. The BMC(HEC) value was estimated at 3.3 - 10 ug/m^3 based on the 5% response of β2m.

Elinder et al. (1985a, 1985b) evaluated β2m levels in 58 males and 2 females exposed to cadmium in cadmium-containing solders for 4-24 years. Personal air sampling in 1976 showed solderers were exposed to 95-1958 µg/m^3, and other workers were exposed to average levels of 140-200 µg/m^3. Exposure for all workers had ceased 5 years prior to examination. Cumulative exposure was calculated on an individual basis by classifying each person's activities as high, medium, low, or no exposure, and estimating exposure levels for each category based on the 1976 measurements. Subjects ingested bicarbonate prior to urine sampling in order to maintain pH above 5.6. Based on data from the same study group and from other authors (Kjellstrom et al., 1977; Kowal and Zirkes, 1983), tubular dysfunction was defined as 300 µg β2m/g creatinine, or "the upper 95 or 97.5 percentile." The lowest exposure group (<1000 µg/m^3 x years) was a LOAEL, with a response rate of 3/16, and response increased with increasing cumulative exposure (Elinder et al., 1985a). Based on the quantalized data presented by the authors, a BMC of 293-304 µg/m^3 x years was calculated (Appendix C). The corresponding BMC(HEC) estimate (10% response) was 1.5 ug/m^3. This study is limited because the estimate of cumulative exposure was based only on measurements during one year, and by the broad range in average exposure in the lowest cumulative exposure group.

In the 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. In a 5-year follow-up of 16 workers from this cohort with marked tubular proteinuria (530 mg β2m/g creatinine) at the initial analysis, the glomerular filtration rate declined more than would be expected based on normal aging (Jarup et al. 1993). These results support the irreversibility of functional changes at this level of proteinuria.

Ellis et al. (1985) evaluated the effect of cadmium exposure on kidney function in 82 male workers, including 40 active and 21 retired cadmium production workers, 8 active and 4 retired office workers (unexposed), and 3 active and 6 retired nonproduction workers, many of whom had earlier prior exposure to cadmium. Individual cumulative exposure estimates were based on area measurements, personal monitoring, and respirator usage, and ranged from 1 to >10,000 µg/m^3 x

years. Liver and kidney cadmium levels were measured, and urinalysis was conducted, including β2m, total protein, creatinine, and cadmium. Abnormal kidney function was defined as β2m levels >200 µg/g creatinine or total protein >250 µg/g creatinine, to be consistent with the definitions used by Roels et al. (1981). The incidence of kidney dysfunction was 0/9, 1/10, 2/9, and 6/15 in the groups with cumulative exposures of ≤20, 20-100, 100-500, and 500-1000 µg/m^3 x years, respectively. Based on individual exposure levels shown in plots of cumulative exposure versus liver and kidney cadmium concentrations, the corresponding average cumulative exposures were 7.5, 54, 315, and 684 µg/m^3 x years. This study identified a NOAEL of 7.5 µg/m^3 x years, a LOAEL of 54 µg/m^3 x years, and a BMC of 116 µg/m^3 x years, based on modeling of the quantal data, and a 10% response rate (Appendix C). The corresponding NOAEL(HEC) value was estimated at 0.036 ug/m^3 and the BMC(HEC) for the same 10% response rate was 0.57 ug/m^3.

In a small study, Smith et al. (1980) evaluated kidney function in 16 cadmium workers exposed for at least 6 years to cadmium concentrations commonly greater than 200 µg/m^3 (cumulative exposure 700-~20,000 µg/m^3 x years) and 12 workers exposed to low levels elsewhere in the plant (cumulative exposure <700 µg/m^3 x years). This was the same plant investigated by Thun et al. (1985) regarding cadmium carcinogenicity, and the same cohort examined for pulmonary effects by Smith et al. (1976). Urinary β2m levels correlated with cumulative exposure, and was significantly elevated in the high exposure group. Creatinine clearance was markedly lower and fractional excretion of uric acid was markedly higher (no statistical tests were conducted) in a group with urinary β2m >300 µg/g creatinine, compared to a group (apparently including unexposed controls) with urinary β2m <300 µg/g creatinine. Benchmark modeling was not conducted, due to the small size of the cohort. There was no effect of cadmium exposure on hypertension or blood pressure.

Falck et al. (1983) examined urinary protein levels in 33 male cadmium-exposed workers and 41 male controls. The control group was not age-matched to the exposed group. The average age of the control group was 40 years, while that of the exposed group was 50 years. This difference was significant, introducing a source of bias into the results, since kidney function declines with age. Individual data for the exposed group were reported for cumulative exposure and β2m levels. The study authors calculated a reference value of 629 µg β2m/g creatinine, based on the "0.95 tolerance limits" for the control population, and the exposed population with abnormal values was identified based on this reference value, but the method for calculating the tolerance limit was not further defined. The average cumulative exposure was significantly higher in the group with abnormal values than in the exposed subjects with normal values. All eight subjects with abnormal values in the spot urine sample were retested using 24-hour urine samples. The β2m concentrations in the 24-hour urine samples differed from those in the spot urine samples by as much as a factor of 200, and only three subjects were considered to have abnormal values in the 24-hour sample. These differences were not addressed by the study authors. Due to these quantitative concerns and the availability of higher-quality data from other studies, no BMC was calculated for this study.

A number of other studies presented dose-response data for kidney effects of cadmium in terms of urinary cadmium levels. Urinary cadmium levels reported as µg/g creatinine can be converted into µg/24 hours for comparison with the Buchet et al. (1990) study by noting that creatinine excretion is 1.0-1.8 g/24 hours (Dorland's, 28th Edition, 1988). As part of a collaborative European project, Fels et al. (1994) analyzed a panel of 26 urinary analytes related to various nephron segments in a German study population. The study included cadmium oxide workers, people working nearby in other factories, and people living in areas without environmental exposure to cadmium. The subjects were classified by urinary cadmium levels, into controls (<1.5 µg Cd/g creatinine, N=31 males, 24 females), moderate body burden (1.5-5 µg Cd/g creatinine, mean 2.35; N=30 males, 18 females), and high body burden (>5 µg Cd/g creatinine, mean 11.5; N=29 males, 40 females). Statistically significant elevations in urinary levels of proximal tubule antigens and glycosaminoglycans were observed in the moderate-exposure group. In the high-exposure group, statistically significant increases in urinary levels of several tubular and glomerular markers were observed, and there were significant increases in the prevalence of abnormal values (defined as values beyond the 95th percentile of the controls). The largest increases in the average values compared to controls were observed for RBP (88 vs. 53 µg/g creatinine), NAG (3.1 vs. 1.6 U/g creatinine), α1-microglobulin (4.8 vs. 1.9 mg/g creatinine), and alkaline phosphatase (1.02 vs. 0.33 U/g creatinine).

In an earlier phase of the collaborative European project, Roels et al. (1993) investigated a panel of markers of kidney function among exposed and control male workers in Belgian zinc and cadmium smelters. After eliminating workers whose renal function might be altered for reasons other than exposure to cadmium, there were 43 men in the control group and 37 in the exposed group. Because urinary creatinine was significantly higher ($p<0.05$) in the control group than the exposed group, normalization of urinary parameters by creatinine resulted in different values than normalization by volume; analyses were conducted based on normalization by volume. To determine urinary cadmium levels corresponding to altered renal function, the study authors defined the 95th or 5th percentile of the reference group (defined as subjects excreting <1 µg Cd/g creatinine) as the limits of normal. Workers were grouped by urinary cadmium level: <1, 1-<2, 2-<10, and >10 µg/g creatinine, and the probability of abnormal values was modeled using a logistic regression model. They reported that the "threshold for a significantly higher probability of change" (not further defined) fell into approximately 3 groups, with one at 2 µg Cd/g creatinine for biochemical alterations, one around 4 µg Cd/g creatinine for high molecular weight proteins (e.g., albumin) and some tubular antigens (e.g., NAG), and one around 10 µg Cd/g creatinine for other tubular markers, including β2m. The value for NAG is generally consistent with the value of 2.7 µg Cd/24 hours reported by Buchet et al. (1990) for an effect on NAG in the general population.

Kawada et al. (1990) examined the excretion of the urinary proteins β2m, NAG, and metallothionein in 79 workers exposed to low levels of cadmium pigment dust at a cadmium pigment factory, with exposure to cadmium sulfide and cadmium selenide. Urinary cadmium was low (<10 µg/g creatinine) in all workers, perhaps due to low absorption of cadmium sulfide, as described in Section 3.0. Urinary metallothionein and NAG were correlated with urinary Cd, with

a statistically significant increase in the group with an average urinary cadmium level of 2 µg/g creatinine. However, there was no significant correlation with β2m, suggesting that urinary NAG may be a more sensitive and reliable indicator protein than β2m in populations with low cadmium exposure. Van Sittert et al. (1993) reported on a very small study of 14 male cadmium production workers in the Netherlands. Four of the workers had worked in the plant for an average of 22 years, including periods of higher exposure prior to 1973. The others had been employed at the plant for an average of 12 years. Exposure levels after 1976 were 4-25 µg/m^3, and personal samplers during periods of high exposures measured average levels of 11-29 µg/m^3. Urinary cadmium levels ranged from 0.64-9.2 µg/g creatinine. There was no statistically significant difference between the exposed group and referent groups used in earlier studies in renal function, as measured by RBP, β2m, or NAG, although β2m levels tended to be higher in workers with higher urinary cadmium levels. The significance of the absence of an effect is limited by the very small sample size.

Chia et al. (1989) studied four measures of urinary function in a cohort of 65 women who had worked in a nickel-cadmium battery factory in Singapore for 1-14 years (mean 3.7 years). Nine female office workers served as controls. Cadmium exposure during the study was estimated at 7-39 µg/m^3. No estimate of cumulative exposure was provided, but average urinary cadmium was 1.7 µg/g creatinine, suggesting low exposure. Age-adjusted values of both urinary β2m and NAG were higher than those of the controls, but a significantly elevated value was found only for urinary NAG. To examine the dose-response relationship, the study population was grouped into the control group, and groups with <1, 1-<3, and >3 µg cadmium/g creatinine in urine. There was a clear, statistically significant increase in NAG with increasing urinary cadmium. Age-adjusted NAG activity in the 1-<3 µg Cd/g creatinine group fell just short of a significant increase compared to the controls (p=0.055). The average NAG activity in this group (about 250 nmol/hr/mg creatinine) was also well above the levels considered by the study authors to be adverse (>139 or >147 nmol/hr/mg creatinine). Although β2m levels tended to be higher at higher urinary cadmium levels, there was no clear concentration-related trend, possibly as a result of the wide variability in response. This study suggests that a LOAEL for altered tubular function is about 3 µg Cd/g creatinine in urine, although the clinical significance of the changes seen at this level is unclear.

In a study of 97 exposed workers (52 females) and 122 unexposed workers (80 females), Chia et al. (1992) found significant increases in urinary NAG and α1-microglobulin in workers with urinary cadmium levels >5 µg/g creatinine, and urinary levels of these proteins increased with both urinary cadmium and exposure duration. However, the number of workers in the high exposure groups was not reported, and it is unclear if the observed elevated level of NAG (168 nmol/hr/mg creatinine in the group with >10 µg Cd/g creatinine) has any clinical significance. There was no effect on urinary β2m.

Jarup and Elinder (1994) used probit analysis of data from 394 Swedish battery workers to estimate a 10% incidence of proteinuria at a urinary cadmium level of 3 µg/g creatinine. However, their definition of proteinuria was much more sensitive than that used by many other studies, 221

µg/g creatinine. They found that urinary cadmium correlated with cumulative exposure, but the workers with proteinuria tended to have higher urinary cadmium levels for a given cumulative exposure level. In a study of a 29 men and 43 women living near a rural cadmium battery plant, Jarup et al. (1995) found a markedly higher prevalence of tubular dysfunction among those with urinary cadmium $\geq$0.5 µg/g creatinine (40%) than among those with lower urinary cadmium levels; the mean urinary cadmium was not reported in the higher exposure. Tubular dysfunction was defined as NAG >4.4 U/g creatinine.

In a study of 58 male workers exposed to cadmium at a non-ferrous smelter and 58 age-matched controls, Bernard et al. (1990) found that the incidence of abnormal values of urinary markers (β2m, NAG, RBP, albumin, and transferrin) was significantly increased compared to controls in the group with urinary levels >10 µg Cd/g creatinine. Normal values were defined based on the mean +2 SD of the control group values. Because larger changes, and changes at lower urinary cadmium levels, were observed for albumin and transferrin, the study authors suggested that the subtle changes in glomerular barrier function may occur prior to tubular changes.

Lung effects were also observed in several occupational studies, at levels somewhat higher than those that result in kidney effects. Davison et al. (1988) evaluated lung function and chest radiographs in the same cohort in which Mason et al. (1988) investigated kidney function. This pair of studies allows a direct comparison based on cumulative exposure. Lung function measurements were conducted on 97 or 75 exposed subjects (depending on the endpoint), and 71 controls. The endpoints measured were forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), carbon monoxide transfer factor (TLCO), carbon monoxide transfer coefficient (KCO), radiographic total lung capacity (RTLC), and residual volume (RV). (Carbon monoxide diffusion is used as a measure of the diffusion of oxygen across the air-blood interface, since both gases have similar diffusion coefficients, and carbon monoxide binds more strongly to hemoglobin, minimizing technical problems related to back-diffusion). Because the controls were not matched for height or smoking, expected values were calculated based on the referents, taking into account age, height, and pack years smoked. Significant decreases (compared to the expected value) were observed in FEV_1, FEV_1/FEV%, TLCO, and KCO, and significant increases were observed in RTLC, RV, and RV/RTLC%. When the exposed subjects were grouped by cumulative exposure index or liver cadmium levels, a significant trend was observed for TLCO and KCO, but not for FEV_1 or FEV_1/FVC%. However, these data could not be modeled, because no information on variability was provided. Emphysema was reported in 19% of the exposed workers and 7% of the controls. These data can not be modeled because no information on exposure levels were provided. Of the 14 cadmium workers with emphysema, 2 had never smoked, while none of the 5 control workers had never smoked. Moderate or severe emphysema was reported in 7 exposed and 1 control worker, all of whom had TLCO or KCO 1.96 SD or more below the predicted value. The data were not reported in a form that allowed the determination of a LOAEL. However, a BMC of 2090 µg/m^3 x years was calculated based on individual data for the observed minus expected (O-E) KCO versus cumulative exposure (Appendix C).

Smith et al. (1976) evaluated lung function in 17 cadmium workers exposed for at least 6 years to cadmium concentrations commonly greater than 200 μg/m^3, 12 "low exposure" workers exposed to low levels elsewhere in the plant and matched to the exposed group for age and cigarette smoking status, and 17 similarly matched unexposed controls. The study authors estimated that most of the individuals in this study were exposed to freshly generated cadmium fume (respirable cadmium oxide particles <1.0 μm in diameter). Based on data presented for these cohorts by Smith et al. (1980), cumulative exposure for the low exposure group ranged from about 20 to 700 μg/m^3 x years, and the high exposure group ranged from about 800 to 20,000 μg/m^3 x years. The average urinary cadmium concentrations in the low- and high-exposure groups were 13.1 μg/L and 45.7 μg/L, respectively. FVC (absolute and as a percent of predicted value) was significantly decreased in the high-exposure group. No dose-response data based on cumulative exposure were presented. However, a BMC of 32.8 μg Cd/day (occupational exposure) was calculated for urinary excretion of cadmium corresponding to a 10% increase in the probability of adverse FVC, assuming a 1% background response rate and 1.4 L urine/day (Gearhart et al., 1995; Appendix C). A toxicokinetic model was also used to convert the reported urinary cadmium levels to exposure levels, resulting in a BMC(HEC) of 8.7 μg/m^3 for continuous lifetime exposure. This should be compared with the modeled levels in this assessment that are associated with renal dysfunction at 0.59 ug/m^3 (in addition to 0.14 mg/kg-day for dietary background). Elinder et al. (1985b

Edling et al. (1986) found no effect on lung function in a group of 57 male workers exposed to 50-500 μg/m^3 cadmium from cadmium-containing solders, compared to a group of 31 unexposed male controls from a nearby company. The exposed group included 35 workers who were retired or working elsewhere, and thus no longer exposed to cadmium. Cumulative exposure was estimated at 340-9900 μg/m^3 x years (median 1700 μg/m^3 x years). Measured endpoints included single breath washouts (closing volume) and a variety of spirometric endpoints, including FVC, FEV at 1 second (FEV_1), and maximum mid-expiratory flow (MMF). This is the same cohort as that studied by Elinder et al. (1985b), in which kidney dysfunction was observed, supporting the conclusion that the kidney is more sensitive than the lungs.

One 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 μg/m^3, depending on the job task, and the average urinary cadmium concentration was 17 μg/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, few studies have specifically assessed neurological effects. Hart et al. (1989) found decreased performance on measures of attention, psychomotor speed, and memory in a cohort with urinary cadmium >25 µg/24 hours, compared to a group with urinary cadmium levels <11 µg/24 hours. The limited number of men studied makes it difficult to evaluate the significance of this effect. Viaene et al. (1999) reported a greater incidence of peripheral polyneuropathy among retired long-term cadmium workers (7/13, 54%) when compared with nonexposed age-matched controls (11%, 2/19).

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). Staessen et al. (1992) reported that measures of indicators to cadmium exposure in the CadmiBel study population did not correlate with increases in blood pressure, prevalence of hypertension or other cardiovascular diseases. Roels et al. (1990), however, 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.

Oral

As for inhalation exposure, the kidney is the most sensitive organ following oral exposure. As discussed above, Buchet et al. (1990) conducted a sensitive study relating kidney function and urinary cadmium levels in the general population in an area where cadmium exposure was via both the oral and inhalation routes.

There are no studies investigating reproductive or developmental effects of ingested cadmium in humans.

4.2 Pre-chronic, chronic studies and cancer bioassays in animals - oral and inhalation

Cancer

Inhalation

The results of inhalation studies conducted in rats support the human data in indicating an association between cadmium exposure and lung cancer (Glaser et al., 1990; Oldiges et al., 1989; Takenaka et al., 1983). The data of Takenaka et al.(1983) are further analyzed and used in quantitative analysis in Section 5.4.2. Species-related differences have been observed. No evidence was found for an association between cadmium inhalation exposure and lung cancer in hamsters (Aufderheide et al., 1989; Heinrich et al., 1989), and the evidence in mice (Heinrich et al., 1989), is inconclusive. However, study design and reporting inadequacies limit the conclusions of the studies conducted in these species. Increased incidences of testicular cancer and leukemia have been reported in animals following oral administration of cadmium (Waalkes and Rehm, 1992) although subsequent work gives firm scientific evidence that the testicular tumors are endocrine-mediated.

Takenaka, S., H. Oldiges, H. Konig, D. Hochrainer, and G. Oberdorster. 1983. Carcinogenicity of cadmium chloride aerosols in Wistar rats. J. Natl. Cancer Inst. 70: 367-373.

Groups of 40-41 male Wistar rats were exposed to nominal concentrations of 0, 12.5, 25, or 50 $\mu g/m^3$ cadmium, as cadmium chloride aerosol (actual concentrations, 13.4, 25.7, and 50.8 $\mu g/m^3$) for 23 hours/day, 7 days/week for 18 months, and observed for an additional 13 months. Only rats that survived at least 18 months were examined histologically. Concentration-related increases in the incidence of adenocarcinomas, squamous cell (epidermoid) carcinoma, and mucoepidermoid carcinoma were observed. The total incidence of lung carcinomas in rats examined histologically was 0/38, 6/39, 20/38, and 25/35, at 0, 12.5, 25, and 50 $\mu g/m^3$, respectively. The majority of lung carcinomas were adenocarcinomas (0/38, 4/39, 15/38, and 14/35, respectively). The corresponding incidences for epidermoid carcinoma were 0/38, 2/39, 4/38, and 7/35. Mucoepidermoid carcinoma was observed in 3 high-concentration animals, but not in the other groups. No exposure-related increases in the incidence of tumors in other tissues, or cadmium-related increases in non-neoplastic lesions were reported. (See Section 5.3.2 for further analysis of these data and calculation of an inhalation unit risk.)

Glaser et al (1990) and Oldiges et al. (1989) both report on a later study from the same laboratory, in which male and female Wistar rats (20 /sex/group) were exposed to clean air or cadmium chloride aerosol at 30 or 90 $\mu g\ Cd/m^3$, cadmium sulfate aerosol at 90 $\mu g\ Cd/m^3$, cadmium sulfide at 90 $\mu g\ Cd/m^3$, cadmium oxide dust at 30 or 90 $\mu g\ Cd/m^3$, or cadmium oxide fume at 10 or 30 $\mu g\ Cd/m^3$. The exposure protocol was the same as in the Takenaka study, except when high toxicity forced a reduction in the duration of exposure. Except for a markedly lower response with cadmium oxide fume, similar lung tumor responses were observed for all of the compounds, with increased levels of brochio-alveolar adenomas, adenocarcinomas, and squamous cell carcinomas. The existence of a concentration-related response could not be evaluated, because survival was lower at the higher concentrations, but no time-to-tumor analysis was conducted. Non-neoplastic lesions among rats exposed to cadmium oxide dust included bronchiolo-alveolar hyperplasia, squamous metaplasia, interstitial fibrosis, and focal inflammatory cell infiltration.

Male and female Wistar rats (39-40/sex/group) were exposed to clean air or cadmium oxide dust at 30 or 90 µg Cd/m^3 for a maximum of 18 months (Takenaka et al., 1990). Six to eight animals from each group were sacrificed at 6 months, with the exception of the 90 µg/m^3 group. In the 90 µg/m^3 group, exposure was terminated at 7 months, due to increased mortality in the animals. Morphological changes progressed from inflammation and bronchiolo-alveolar hyperplasia at 6 months, to abnormal epithelial proliferation (including basophilic foci of cuboidal epithelia and adenomatous proliferation of epithelia, and squamous metaplasia) at 18 months. Lung tumors (bronchiolo-alveolar adenomas and carcinomas, benign and malignant squamous cell tumors, and an adenosquamous carcinoma) occurred in 72% and 31% of the low- and high-concentration groups, respectively, but in none of the controls. The lack of a concentration-related response was due to the decreased survival at the high concentration.

In a similar experiment Heinrich et al., (1989) exposed groups of 38-47 female Han:NMRI mice to cadmium chloride aerosol at 30 or 90 µg Cd/m^3, cadmium sulfate aerosol at 30 or 90 µg Cd/m^3, cadmium sulfide at 90, 270, or 1000 µg Cd/m^3, cadmium oxide dust at 10, 30, or 90 µg Cd/m^3, or cadmium oxide fume at 10, 30, or 90 µg Cd/m^3. Exposures were generally for 19 hours/day, 5 days/week, for up to 64 weeks, although some groups were exposed for 8 hours/day. All animals were sacrificed 6-12 months after the termination of exposure. An unspecified number of male and female Syrian hamsters were exposed under similar conditions, and concurrent controls were used for both species. Reporting of the study is incomplete, with no information on tumor types, and there was wide variation in the incidence of lung tumors in the control groups (15-37%). Toxic effects in the respiratory tract resulted in significantly decreased survival in mice exposed to cadmium concentrations as low as 30 µg/m^3, and hamsters exposed to levels as low as 90 µg/m^3. Life table analysis indicated a significantly increased probability of dying with a lung tumor in most groups of mice exposed to the various cadmium compounds, but the high mortality, lack of increase in numbers of mice with tumors in these groups, and high variability among the control groups make it difficult to interpret these results. A significant concentration-related increase in lung tumor incidence was reported in mice exposed to cadmium oxide fume (9/43, 13/44, and 16/47 at 10, 30, and 90 µg/m^3, compared to 9/45, 9/45, and 6/41 in the corresponding controls). Significantly increased incidences of alveolar lipoproteinosis, interstitial fibrosis, and bronchoalveolar hyperplasia were observed in "most" exposed groups. The authors reported no effect of cadmium on cancer incidence in hamsters, but presented no supporting data. Significant concentration-related increases in bronchiolar-alveolar hyperplasia, thickening of septa, and proliferation of connective tissue were found with all tested cadmium compounds.

Similar results were observed in an inhalation experiment with hamsters. Aufderheide et al. (1989) exposed groups of 24 Syrian golden hamsters (sex not reported) to filtered air, cadmium oxide aerosol at 10, 90, or 270 µg Cd/m^3, cadmium sulfide aerosol at 90 or 270 µg Cd/m^3, cadmium chloride at 30 or 90 µg Cd/m^3, or cadmium sulfate 30 or 90 µg Cd/m^3 for 8 hours/day, (19 hours/day for high-concentration cadmium chloride or sulfate) 5 days/week for about 65 weeks. Animals were held after exposure until they died, and the lungs and trachea were examined. Proliferative lesions (bronchiolization, consisting of proliferation of bronchiolar

epithelium into the alveolar ducts) were reported in groups exposed to the high concentrations of cadmium oxide or cadmium sulfide, but it appears that only 5 animals/group were examined. The study authors concluded that inhalation of cadmium oxide and cadmium sulfide by hamsters results in hyperplasia, but no tumor development. However, the conclusion is limited by the lack of a complete histopathological examination.

Groups of 22-28 male Wistar (WF/NCr) rats were provided 0, 25, 50, 100, or 200 ppm cadmium in the diet as cadmium chloride for 77 weeks with either sufficient (60 ppm) or deficient (7 ppm) dietary zinc (Waalkes and Rehm, 1992). The goal of this study was to examine whether dietary zinc influenced cadmium toxicity via metallothionein. Only the results from the zinc sufficient animals are discussed further. Based on a body weight of 350 g and food consumption of 18.5 g/day (estimated from graphs for the high-dose group), the corresponding doses were estimated at 0, 1.32, 2.65, 5.3, and 10.6 mg/kg/day. Doses of cadmium were sufficient to markedly decrease body weights relative to controls both at 200 ppm (12-17%) and 100 ppm (about 10%). Proliferative prostatic lesions were noted to be increased over controls (2%) but only at 50 ppm (12%). Focal atypical hyperplasia and adenomas were observed in the ventral prostate but with no clear dose-response, the only significant increase (for the combined incidence of hyperplasia and adenomas) occurring at 50 ppm. There were no lesions observed in the dorsolateral prostate lobes (where prostate cancer is seen in humans) and no prostatic carcinomas were observed. No association between testicular atrophy and cadmium exposure was observed, but moderate to severe testicular atrophy was observed in about 50% of the males in all dose groups. A statistically significant increase in the incidence of interstitial (Leydig) cell tumors of the testes was observed at the highest dose (which was also one of the doses at which body weight decreases were decreased > 10% relative to controls); the incidences were 2/56 in controls, 2/27 at 25 ppm, 1/25 at 50 ppm, 1/24 at 100 ppm and 6/27 at 200 ppm. Large granular lymphocytic leukemia was observed in 1/28 controls, 4/27 animals at 25 ppm, 5/24 animals at 50 ppm, 5/24 animals at 100 ppm but only 1/27 animals at 200 ppm, the latter decrease probably due to cadmium toxicity. These results indicate that oral cadmium exposure is associated with tumors of the testes and the hematopoietic system in rats.

In a follow on study from the oral cancer study with rats (Waalkes and Rehm, 1992), Waalkes et al. (1997) conducted a chronic rat study designed to elucidate the role of cadmium in perturbating the hypothalamic-pituitary-testes axis. Several organic compounds known to disrupt this axis (e.g., antiandrogens) also induce the type of benign testicular tumors, Leydig cell tumors, that were observed in animals exposed to 200 ppm cadmium in Waalkes and Rehm (1992). Male Fisher 344 rats were divided into 4 groups of 50 each as follows: group 1, noncastrated controls with no cadmium treatment; group 2, castrated controls with testosterone implants and no cadmium treatment; group 3, noncastrated rats with cadmium treatment; group 4, castrated rats with testosterone implants and cadmium treatment. Cadmium or saline treatment (0.02 mmole $CdCl_2$ / kg, subcutaneous, 5 times at intervals of one week for a total of 0.1 mmole/kg) was initiated 2 weeks after castration. Ten animals per treatment group were sacrificed at experimental week 10 to define testosterone status. The remaining 40 animals per group were sacrificed either

when significant clinical signs developed or at experimental week 104. The 10 week interim sacrifice showed dramatic testicular weight loss relative to control (> 50% in all groups, including the testosterone implant group). Testosterone levels (and prostate weights) comparable to controls were maintained in all groups save for group 3. At 104 weeks it was shown that cadmium alone (group 3) resulted in an incidence of 34/40 for Leydig cell neoplasia (versus 24/40 in group 1 controls) and an incidence of 39/40 for chronic testicular degeneration (versus 0/40 in group 1 controls). Testesterone implantation abolished both cadmium-induced (group 4) and spontaneously occurring (group 2) Leydig cell tumors but had no effect on cadmium-induced chronic testicular degeneration (33/37 for group 4). These results clearly indicate that cadmium induction of Leydig cell tumors (such as those occurring in Waalkes and Rehm, 1992) is endocrine-mediated and that the occurrence of such tumors appears to depend on reduced circulating testosterone levels stemming from cadmium-induced testicular hypofunction, most likely through perturbation of the hypothalamic-pituitary-testes axis.

There was no evidence of cadmium-related cancer in a 2-year study with groups of 50 male and 50 female Wistar rats administered 1, 3, 10, or 50 ppm cadmium in the diet as cadmium chloride (approximately 0.05, 0.15, 0.5, or 2.5 mg/kg/day, assuming a food factor of 0.05) (Loser, 1980). One hundred rats of each sex served as the controls. Body weights in high-dose males were significantly reduced, but no further information on the extent or timing of this decrease was provided.

Noncancer

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).

NTP (1995) exposed male and female F344/N rats (10/sex/concentration) to 0, 25, 50, 100, 250, or 1000 $\mu g/m^3$ cadmium oxide aerosol (0, 22, 44, 88, 219, or 875 $\mu g\ Cd/m^3$) for 6 hours/day, 5 days/week for 13 weeks. The respiratory tract was the most sensitive target in both sexes, with significantly increased lung weight at $\geq$100 $\mu g/m^3$, and increased incidences of lung lesions (alveolar histiocyte infiltrate, alveolar epithelial hyperplasia) at $\geq$50 $\mu g/m^3$ in both sexes, larynx lesions (epithelial degeneration) at $\geq$25 $\mu g/m^3$ in both sexes, and nose lesions (inflammation of the respiratory epithelium) at $\geq$100 $\mu g/m^3$ in females and $\geq$250 $\mu g/m^3$ in males. Relative kidney weight was significantly increased in both sexes at $\geq$250 $\mu g/m^3$, but the only effect on urinalysis parameters was a slight, but statistically significant increase in aspartate aminotransferase in females at $\geq$250 $\mu g/m^3$. The study authors noted that the kidney cadmium levels were lower than the concentration estimated to be toxic to the rodent kidney (200 ppm) in a study by Goyer et al. (1989) of subcutaneous cadmium administration. Spermatid count was significantly decreased and estrous cycle length was significantly increased at 1 mg/m^3.

In a related experiment, NTP (1995) exposed male and female B6C3F1 mice (10/sex/concentration) to target levels of 0, 25, 50, 100, 250, or 1000 µg/m^3 cadmium oxide aerosol (0, 22, 44, 88, 219, or 875 µg Cd/m^3) for 6 hours/day, 5 days/week for 13 weeks. Significantly increased kidney weight was observed at ≥25 µg/m^3 in both sexes, and significantly increased absolute and relative lung weight was observed at ≥50 µg/m^3 in both sexes. Respiratory tract lesions were observed at all exposure levels. Alveolar histiocytic infiltration of the lungs occurred in almost all males and females low-concentration, with fibrosis, inflammation, and alveolar epithelial hyperplasia occurring at higher concentrations. All low-concentration mice had squamous metaplasia of the larynx, and degeneration of the olfactory epithelium was observed in males at ≥100 µg/m^3 and females at ≥250 µg/m^3.

Glaser et al. (1986) exposed male Wistar rats to 100 µg Cd/m^3 as cadmium chloride or cadmium oxide, or to 1000 µg Cd/m^3 as cadmium sulfide, for 22 hours/day, 7 days/week for 30 days, and assessed urine protein at the end of the exposure period and 2 months later, but found no effects. Although cadmium deposition in the lung was documented, urinary cadmium increased only in the rats exposed to cadmium sulfide, consistent with the relatively low exposures for the other compounds. Bronchoalveolar lavage (BAL) analysis revealed increased macrophages, leucocytes, and lactate dehydrogenase levels in all three exposed groups.

Prigge (1978a) exposed female Wistar rats continuously to 25 or 50 µg Cd/m^3 for 90 days, or 100 µg Cd/m^3 for 63 days, all as cadmium oxide aerosols. Controls were exposed to clean air. There was no evidence of proteinuria and no exposure-related kidney lesions. There was, however, a concentration-related decrease in body weight gain at ≥50 µg/m^3, and an increase in the incidence and severity of lung lesions, including emphysematic areas, cell proliferation of the bronchi, bronchioli and alveoli, and histiocytic cell granulomas at all concentrations. Lung lesions (bronchoalveolar hyperplasia, proliferation of connective tissue, and interstitial fibrosis) were observed in rats exposed for 22 hours/day, 7 days/week to 30 or 90 µg Cd/m^3 as cadmium oxide (Takenaka et al. 1990), as described above in the section on carcinogenicity.

High exposure levels were tested in the one animal inhalation study that observed kidney toxicity. Rabbits exposed to 4100 or 5700 µg Cd/m^3 as cadmium oxide developed proteinuria after 4 months of inhalation exposure, and histologic lesions were found after an additional 3-4 months of exposure (Friberg 1950).

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 (Kotsonis and Klaassen 1978; Mangler et al., 1988; Prigge 1978a).

Prigge (1978a) administered 0, 25, 50, or 100 ppm cadmium in drinking water as cadmium chloride to female Wistar rats for 90 days. Body weight gain was significantly decreased at ≥50 ppm, serum alkaline phosphatase was significantly decreased at all doses, and statistically significant increases in urinary protein were observed at ≥50 ppm. The kidney cadmium

concentration was 27 ppm and 36 ppm (wet weight) in rats administered 50 ppm and 100 ppm in water, respectively. However, proteinuria was not observed in a parallel study in rats that had similar kidney cadmium concentrations following inhalation exposure. In a study of female Sprague-Dawley rats exposed for 6-18 months to 31.5 ppm cadmium in drinking water as cadmium chloride, and then sacrificed 0-12 months after the end of exposure, renal histopathology was observed in all groups except one (Mangler et al., 1988). Kidney cadmium concentrations were 120-367 ppm (dry weight). However, apparently some time is required for the development of kidney histopathology, because no lesions were observed in the group exposed for 6 months and sacrificed immediately after exposure, even though the kidney cadmium concentration was 150 ppm. Kotsonis and Klaassen (1978) observed a decrease in inulin clearance with increasing kidney concentration in rats administered cadmium chloride in drinking water.

In groups of 5 rats given 0, 10, 50, 100, or 200 ppm cadmium in drinking water for 37 weeks as an unspecified compound, kidney lesions (interstitial fibrosis) were observed at $\geq$100 ppm (Kawai et al., 1976). Spontaneous nephropathy was reported at 0, 10, and 50 ppm in 3/5, 1/5, and 3/5 animals, respectively, possibly reducing the sensitivity of the study to detect other kidney lesions at lower doses. Kidney function was not measured. It is interesting to note that femur atrophy was observed at $\geq$50 ppm, and a dose-related decrease in cortical thickness occurred in all groups, although no statistical comparisons were conducted.

Rhesus monkeys (*Macaca mulatta*) were given 0, 3, 10, 30, or 100 ppm cadmium in their feed as cadmium chloride for 9 years (Masaoka et al., 1994). There were 5, 8, 8, 8, and 6 monkeys/group, respectively, but animals were sacrificed periodically, beginning at 39 weeks, so only 1-2 monkeys/group were kept until the end of the study. High-dose monkeys gained weight more slowly, and had an increased incidence of proteinuria and glycosuria.

Perry and Erlander (1974) reported statistically significant ($p<0.005$) increases in blood pressure in rats fed diets containing 1, 2.5, or 5 ppm cadmium, inconsistent results have been reported and NTP (1995) found no effect on any cardiovascular function in rats or mice exposed to cadmium oxide via the inhalation route. The contradictory findings with regard to the effect of cadmium on blood pressure may be explained by the report of Kopp et al. (1982) that the dose-response curve for the effect of cadmium on blood pressure and other parameters related to cardiac function in rats follows an inverted U-shaped curve. The maximum effect was at 0.5 ppm in drinking water (approximately 0.05 mg/kg/day, based on the calculations of Perry and Kopp, 1983).

4.3 Reproductive/developmental studies (with emphasis on neurodevelopmental effects) - oral and inhalation

The design of many developmental studies in this section, both oral and inhalation exposure, is inclusive of neurotoxicological testing and examination in young animals. When usual

indicators for developmental toxicity of cadmium such as birth weight, various malformations and variations are conducted in parallel with evaluation of neurodevelopmental effects, the latter are more sensitive, i.e., neurodevelopmental effects extend to lower doses. Both inhalation and oral studies show that cadmium may also be a developmental toxin, with effects such as decreased fetal weight occurring at higher doses than neurodevelopmental effects, and teratogenic effects occurring at levels concomitant with severe maternal toxicity.

In a rare study on reproductive effects in humans, Gennart et al (1992) studied reproductive effects of occupational exposure to cadmium in a group of 83 married male cadmium workers and 138 married male controls who worked in other factories but also 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 $\mu g/m^3$ x years), and the reference population consisted of age-matched unexposed workers from the same plant.

The cadmium database is replete with studies of near lethal doses of cadmium to male laboratory animals that show extensive damage to testicular tissues (see Jarup, 1998). Long-term multigenerational reproductive studies are, however, missing from the data base with only a few indirect studies (such as developmental studies involving a preexposure period) that may have relevance to reproductive function. A recent study (Corpus and Antonio, 1998) does present experimental evidence that oral doses of cadmium may produce structural alterations in the reproductive organs of pups born from dams exposed to cadmium at as little as 1 mg/kg-day. It should be noted, however, that even these effects are well above those causing indications of renal damage in the human population.

NTP (1995) exposed groups of 32 sperm-positive Sprague-Dawley rats and groups of 33 Swiss (CD-1) mice to cadmium oxide at 0, 44, 438, or 1750 µg Cd/m^3 for 6 hours/day, 7 days/week on gestation days 4-19 (rats) or gestation days 4-17 (mice). Developmental parameters monitored included number of implantations/dam, litters with resorptions, resorptions/litter, live fetuses/litter, fetal weight, and fetal malformations. Maternal body weight and body weight gain were significantly decreased in high-exposure rats. Developmental toxicity in rats was observed at the high concentration, as indicated by significantly decreased pup weight of males and females, and a significant increase in the percent of fetuses/litter with decreased ossification of the pelvis and sternebrae. However, no significant effect was reported on a per litter basis. In mice, the pregnancy index was significantly decreased at $\geq$438 $\mu g/m^3$, and four pregnant high-concentration

females died. Significantly decreased fetal body weight also occurred at 438 μg/m^3. Other effects at 1750 μg/m^3 were significantly increased resorptions/litter and increased incidence of decreased ossification of the sternebrae. The NOAEL for maternal rat and mice and fetal rat toxicity is 170 ug/m^3. The NOAEL for fetal mouse toxicity is 44 ug/m^3.

In a developmental and reproductive (partial) study and Baranski (1984) exposed female rats to 20 or 160 μg Cd/m^3 as cadmium oxide aerosols for 5 hours/day, 5 days/week for 5 months, and during mating and gestation. Females exposed to air served as controls; half of the inseminated females were killed on day 21 of gestation to assess embryonic and teratogenic effects. The remainder delivered and reared the pups. The study authors reported no effect on fertility at either exposure level, but sensitivity was low, since less than half of the inseminated control females became pregnant. The low gestation index was attributed to the age of the mothers at mating (approximately 8 months). Viability of the pups in the high-exposure group was significantly ($p<0.05$) reduced. Cd exposure also resulted in significant ($p<0.05$) reduction of motor activity in 3-month-old female pups from the high exposure group and both male pups from both groups. Other behavioral tests (open field, avoidance acquisition) also indicated that central nervous system dysfunction occurred in female offspring of dams exposed to $\geq$20 μg/m^3 cadmium, the LOAEL of this study.

In another developmental (partial) reproductive study, Baranski (1985) exposed Wistar rats to cadmium oxide aerosol at 0, 20 or 160 μg/m^3 for 5 hours a day, 5 days a week for 5 months, or to a cadmium oxide aerosol of 1000 μg/m^3 for 4-6 months; the exposure period included the mating and gestation periods. An increased maternal death rate at 1000 μg/m^3 prevented accurate analysis of fetal effects for that group. Retarded fetal growth and delayed ossification were noted at 160 and 1000 μg/m^3. The viability index but not the death rate index was affected by exposure to 160 μg/m^3. No congenital abnormalities were observed. Statistically significant effects on motor skills tests were observed at 160 and 20 μg/m^3, the LOAEL of this study.

Kutzman et al. (1986) reported no decrement in reproductive success, as measured by viable embryos and preimplantation losses, in male and female rats exposed to 0, 300, or 1000 μg Cd/m^3 as cadmium chloride for 6 hours/day, 5 days/week for 62 days and subsequently mated with unexposed controls although no data were shown. Maternal weight gain and fetal weight were reduced in pregnant rats exposed continuously during gestation to cadmium chloride aerosols at concentrations of 200, 400, or 600 μg Cd/m^3 (Prigge 1978b), with the decrease in fetal weight reaching statistical significance at 600 μg/m^3.

Ali et al. (1986) exposed groups of 10 pregnant Wistar rats during gestation to 0, 4.2, or 8.4 ppm cadmium in drinking water as cadmium acetate. The calculated doses of cadmium were 0, 0.71, and 1.2 mg/kg/day. There was no effect on litter size or somatic markers of development (e.g., eye and ear opening). However, the birthweight of the high-dose pups was significantly decreased, and pup weight was significantly decreased in both groups at several postnatal time points. In addition, a consistent, dose-related effect was observed in a cliff aversion test (a

measure of sensory motor coordination) and in development of swimming behavior on postnatal days 3-12, with significant differences in pairwise comparisons at both doses at several time points. This study identified a LOAEL of 0.71 mg/kg/day, with no NOAEL.

Baranski et al. (1983) administered 0, 0.04, 0.4, or 4 mg Cd/kg/day as cadmium chloride by gavage to female Wistar rats for 5 weeks prior to mating, and then during mating and gestation. Dosing was 5 days/week. The dams were allowed to deliver, and pups (8/sex/dose) were tested at 2 months for spontaneous locomotor activity and performance on the rotarod test. The study authors reported no effect on reproductive and developmental indices, including implantations, copora lutea, resorptions, fetal length and body weight, and external, visceral and skeletal examination of fetuses. However, no data were presented. Although the marked variability in spontaneous activity and rotarod performance made it difficult to identify a NOAEL for these endpoints, significant effects were consistently seen at doses as low as 0.4 mg/kg/day, and occasionally at 0.04 mg/kg/day. In a related experiment (Baranski, 1985), female Wistar rats were administered 2, 12, or 40 mg Cd/kg/day by gavage as cadmium chloride on gestation days 7-16. Fetal weight was significantly decreased at $\geq$12 mg/kg/day, and decreased live fetuses, developmental anomalies (sirenomelia; fused lower limbs and no feet, and amelia; absence of limbs) and retarded bone ossification were observed at the high dose. All dose groups had significant decreases in maternal body weight gain during pregnancy. Based on neurodevelopmental effects, 0.4 mg/kg/day is considereda LOAEL and 0.04 mg/kg/day a marginal NOAEL for this study.

Baranski (1987) observed a dose-related statistically significant decrease in fetal weight in the offspring of Wistar rats given 60 or 180 ppm (estimated at 9 and 29 mg Cd/kg/day) cadmium as cadmium chloride in drinking water on gestation days 1-20. There was no effect on resorptions or live fetuses/litter, but significant decreases in maternal body weight gain were observed. Sutou et al. (1980) administered cadmium to male and female Sprague-Dawley rats at 0, 0.1, 1.0, or 10 mg/kg/day for 6 weeks (form not specified), and mated the exposed animals. Females continued to receive the same doses during gestation, and were sacrificed on gestation day 20. Statistically significant decreases in total implants, live implants, fetal body weight and length, and increases in delayed ossification were observed at the high dose. There were no statistically significant changes at the lower doses. All of these studies by Baranski and colleagues are limited by incomplete data reporting.

Machemer and Lorke (1981) treated mated groups of 19-20 fertilized FB 30 (Long Evans) rats with 0, 1.2, 3.5, or 12.5 mg Cd/kg/day as cadmium chloride in feed, or 1.8, 6.1, 18.4, or 61.3 mg Cd/kg/day as cadmium chloride by gavage. The highest gavage dose was severely toxic, causing deaths of 15 dams, and resorptions of all embryos in the surviving dams. One dam administered 18.4 mg/kg/day also died, and the mothers lost weight during dosing. Significantly decreased maternal body weight gain also occurred at 6.1 mg/kg/day by gavage. A significant increase in stunted rats, and in fetuses with malformations (primarily dysplasia of facial bones and rear limbs, and general edema) were also observed at 18.4 mg/kg/day by gavage; no statistical

comparisons were conducted based on affected litters. There was no evidence of any reproductive or developmental effect in the animals administered cadmium chloride in feed.

Popieluch et al. (1995) exposed groups of 8 pregnant Wistar rats to tap water or water containing 5 ppm cadmium chloride on gestation days 0-14. Based on the reported water intake, this corresponds to 0.36 mg Cd/kg/day, assuming the reported doses were actually as cadmium chloride, rather than as cadmium. Male pups were tested beginning at 3 months in a conditioned avoidance reflex task. In this task, the rats were trained to avoid a shock administered 5 seconds after a light was turned on. The pups were trained for 14 consecutive days, and then tested weekly or biweekly until 70 days of follow-up. Learning was significantly delayed in the cadmium-exposed group, responses not reaching control levels until day 34 of the experiment.

Using treatment regimes in combination, Dési et al. (1998) investigated the role of pre and postnatal cadmium exposure in development of neurotoxicological changes. Groups of pregnant Wistar rats were administered either water or 3.5, 7, or 14 cadmium chloride mg/kg during days 5-15 of pregnancy (P) or days 5-15 of pregnancy + 4 weeks of lactation (P + L). Additional groups were formed from administering cadmium to male offspring from the P+L groups for 8 weeks postweaning (P+L+8). Male offspring from each of these groups were tested for behavioral (open-field exploration) and electrophysiological (electrocorticogram, evoked potentials, and peripheral nerve function) at 12 weeks. Electrophysiological changes were significant ($p < 0.05$) only in the P+L+8 group and only at the highest dose. Behavioral effects were inconsistent with this effect as they were not seen in the P+L+8 groups but in the P+L group. These results indicate that fetal exposure to cadmium *in utero* and through breast milk during weaning was not effective in producing a consistent pattern of neurotoxicological effects. Neither the route of administration (presumed water gavage from earlier reports, Nagymajtényi et al., 1997) nor the group size (noted as a total of 280 rats in the study) were reported in this study. A LOAEL of 7 mg/kg (and NOAEL of 3.5 mg/kg) is could be judged from this study based on effects of peripheral nerve function although the preponderance of effects were seen at the highest dose level of 14 mg/kg.

Antonio et al. (1998) examined the effects of gestational and early lactational exposure to cadmium in the brain in comparison with other organs with both liver and kidney mentioned. Pregnant Wistar rats (n=4/group) were exposed to cadmium acetate in drinking water (1.13 mg/kg-day) from initiation of pregnancy to parturition or until postnatal day (PND) 5 at which time brains were excised and examined. Neurotransmitter levels (DA, dopamine; SE, seritonin and metabolites of both) were increased in brain tissues but to different levels and in different areas in the brain. SE was increased 2 to 3-fold throughout whereas DA levels were increased 86% over controls in the mesencephalon only. However, cadmium administration did not result in a change to other biochemical parameters in brain tissues including protein and lipid content. The authors mention that brain was less affected than other tissues (i.e., liver and kidney) although no data were shown. The functional significance of the perturbations in monoamine levels is unclear although these results indicate that the alterations depend on the specific area of the brain that may be related to the overall development of the brain.

Unlike the effects observed in pups from females exposed to cadmium during gestation, exposure of males to cadmium does not appear to result in neurobehavioral effects in the progeny. Zenick et al. (1982) exposed groups of 5 male Long-Evans rats to 0, 17.2, 34.4, or 68.8 ppm cadmium in drinking water (~0, 2.4, 4.8, or 9.6 mg/kg/day, assuming water intake of 0.14 L/kg/day) as cadmium chloride for 70-80 days, and then mated each male to three females. A semipurified diet was used to preclude zinc inhibition of cadmium-related toxicity. There was no effect on exploratory activity of the pups at 21 days, or on acquisition or reversal of a visual discrimination learning task. There was also no effect on reproductive function in the males (as measured by litter size, or by implantations, resorptions, and corpora lutea in the single female/male sacrificed on gd 20), or on sperm count, number of normal sperm, testes weight, or testes histopathology in the treated males.

In an evaluation of cadmium effects on reproductive organs, Corpus and Antonio (1998) observed that exposure to cadmium in drinking water (1.13 mg/kg-day) during gestation until postnatal day 5 damaged pup reproductive systems. In male pups this was noted in the testes as a 3-fold decrease in seminiferous tubule diameter (from 49 um to 18 um); in the ovaries of female pups the DNA/RNA ratio was significantly reduced indicative of altered cell division processes.

Sutuo et al. (1980) reported that at 10 mg/kg-day (gavage) but not 1 mg/kg-day during a 6 week period prior to gestation period significantly decreased the number of copulating males and pregnant female rats.

4.4 Other studies - Neurotoxicity, Genotoxicity and Other Data on Mode of Action

Neurotoxicity

Behavioral and electrophysiological endpoints were measured in three consecutive generations of male Wistar rats that had been exposed to cadmium *in utero* and by gavage from weaning (week 4) to week12 when these endpoints were examined (Nagymajtényi et al., 1997). Cadmium was adminstered as cadmium chloride in water at either 3.5, 7 or 14 mg/kg on a 5 day per week schedule beginning when the pups were 4 weeks of age. For females producing the F1, F2 and F3 generations, treatment was daily from the beginning of mating until separation of the offspring at their age of 4 weeks. The main behavioral outcomes were alterations in exploration activities (open field and vertical) that were described as being dose-dependent but without interactions among generations. Electrophysiological findings (increased mean frequencies in electrocorticograms) were shown to be significantly increased over controls at the high dose in all 3 generations for auditory, sensory, and visual focus. However, in the third generation differences significant from controls extended downward to the next dose level (7 mg/kg) for both visual and sensory focus. These results suggest that low level multigenerational exposure to cadmium can

affect functions of the nervous system. However, it is not possible to compare the neurotoxicological effects with anticipated renal effects as no renal histopathology was reported. The dose level of 3.5 mg/kg would appear to be a NOAEL for this study.

Genotoxocity

Cadmium has been extensively tested in genotoxicity assays, with mixed and often contradictory results. Exposure of isolated DNA to cadmium does not consistently result in production of direct DNA damage, such as DNA adducts or strand breaks. As a consequence, it has been proposed that the observed genotoxic effects of cadmium are mediated by oxidative damage (Rossman et al., 1992) However, some positive results, including mutations and chromosomal aberrations, have been observed *in vitro*, in mammalian and bacterial cells, and *in vivo*, in mice (reviewed in IARC, 1993).

An increase in chromosome aberrations that correlated with cumulative cadmium exposure level was observed in peripheral blood lymphocytes from factory workers who were also exposed to zinc, copper, and silver alloys (Forni et al., 1990). A number of other studies conducted in workers exposed to cadmium and in people with high environmental exposure to cadmium reported small, and occasionally statistically significant, increases in the incidences of chromosomal aberrations and sister chromatid exchanges or no effect (IARC, 1993). Most of the studies did not control for exposure to other mutagenic agents.

Conflicting results regarding the mutagenesis of cadmium compounds in bacteria were resolved by the work of Pagano and Zeiger (1992). Using a preincubation protocol, they found that cadmium chloride was reproducibly weakly mutagenic in *Salmonella typhimurium* strain TA97 when distilled water was the buffer, but that mutagenesis was lower in Hepes buffer, and not observed in phosphate buffer. They suggested that certain buffers and components of the medium can inhibit metal mutagenesis by chelating the metals.

Micronucleated polychromatic erythrocytes (PCEs) were significantly increased in mice administered 3-12 mg/kg cadmium as cadmium chloride, although there was no clear dose-response relationship (Marrazzini et al. 1994). The incidence of structural chromosome aberrations were also significantly increased at the high dose. Cadmium is a suspected spindle poison, and induction of aneuploidy was observed (based on the results of a trend test) in spermatocytes of mice injected i.p. with 1-6 mg/kg cadmium as cadmium chloride, and harvested 6-22 hours after dosing (Miller and Adler, 1992). Mixed results were obtained for cadmium chloride in a multi-laboratory analysis of a battery of *in vivo* tests for aneuploidy, but the predominance of the results were negative, except in one laboratory (Adler, 1993).

Rita Misra et al. (1998) evaluated the genotoxic potential of cadmium (as Cd chloride) in four different rodent cell lines; Chinese hamster ovary cells, L6 myoblast cells, rat Clone 9 liver

cells, and rat TRL 1215 liver cells. Cultures of these cells were exposed to 0, 1, 5, 10, 50, or 100 uM Cd for 24 hours and cells monitored for % DNA strand breaks and % DNA-protein crosslinks. Metallothionein synthesis was also monitored as was cellular toxicity (decrease colony forming ability and mitochondrial function) which was observed to occur in a dose-related manner. Although variability in sensitivity to DNA damage was evident between the different cell lines, in all of the cell lines tested, increases in DNA damage were observed only at cadmium l doses that completely arrested cell growth. Metallothionein preinduction, thought to mediate metal toxicity such as Cd, was observed to have no protective effect in 3 of the 4 cell lines tested. Taken together, these cellular tests indicate that cadmium is not directly genotoxic.

A number of mechanisms have been proposed for the development of mutations from exposure to cadmium. Although cadmium can destabilize DNA by binding to the bases and phosphate groups, exposure of isolated DNA to cadmium does not result in production of direct DNA damage, such as DNA adducts or strand breaks. Therefore, it has been proposed that the observed genotoxic effects of cadmium are mediated by oxidative damage (reviewed by Rossman et al., 1992). Cadmium treatment reduces cellular glutathione levels, and catalase (a scavenger of hydrogen peroxide) inhibited production of chromosome aberrations by cadmium. Insoluble cadmium particles may cause oxidative damage *in vivo* via inflammatory mechanisms, such as the hydrogen peroxide released by polymorphonuclear leukocytes (PMNs) exposed to cadmium sulfide. Alternatively, an altered DNA conformation could lead to decreased fidelity of DNA replication or repair, or cadmium could affect the activity of a zinc-binding regulatory protein (reviewed in Waalkes et al., 1992). Cadmium has been observed to increase the mutagenic activity of other chemicals, suggesting that it can act by inhibiting DNA repair.

The sensitivity of certain tissues to cadmium carcinogenesis may be related to the poor inducibility of metallothionein in these tissues (Cherian et al., 1994). For example, tumors have been observed in the testes and ventral prostate in rats, and metallothionein levels are low in these tissues. Higher metallothionein production in the lungs of mice compared to rats has been proposed as an explanation for the apparent resistance of mice to cadmium-induced lung cancer (Oberdorster et al., 1994).

Animal data indicate that it is unlikely that cadmium would cause lung cancer via the oral route. Indeed, Oberdorster (1990) noted that ingested cadmium is likely to have an effect on the induction of lung cancer different from that of inhaled cadmium. In the case of cadmium inhalation, lung cells on the alveolar/air side of the lung are exposed to cadmium, while lung cells on the vascular side of the lung are exposed following cadmium ingestion. No lung tumors were observed in rats exposed to cadmium in the diet for 77 weeks, although prostatic and testicular tumors were observed (Waalkes and Rehm 1992). The production of lung tumors following ingestion of a metal appears to be limited to cases where there is significant distribution to the lung following oral dosing. For example, arsenic ingestion has been reported to cause lung cancer (Chen et al. 1992). By contrast, ingested cadmium is distributed primarily to the liver and kidney, with small amounts deposited in other organs.

4.5 Weight of Evidence Evaluation and Cancer Classification -

Under the proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), it is concluded that cadmium should be considered *a probable human carcinogen* by *inhalation exposure*. The weight of evidence of human carcinogenicity from cadmium exposure via the inhalation route consists of problematic epidemiological evidence associating occupational cumulative inhalation exposure to cadmium with the development of lung cancer, demonstrated induction of lung cancer in two independent rat inhalation studies and equivocal mutagenicity and chromosome aberration induction in *in vivo* and *in vitro* test systems, coupled with several plausible mechanisms by which mutagenicity might occur other than by direct DNA alkylation. Under the current Risk Assessment Guidelines (U.S. EPA, 1987), cadmium would be assigned carcinogen category B1, probable human carcinogen.

The weight-of-evidence for cancers occurring from cadmium exposure via the oral route is considered inadequate. The sole tumor types observed in an oral study with Cd, testicular Leydig cell, were benign, already present at a high rate in control animals, occurred only in Cd treated groups that were at or in excess of the maximum tolerated dose (> 10% weight loss), and for which there exists solid experimental evidence for indirect causation (disruption of the hypothalamic-pituitary-testes axis as a consequence of cadmium-exacerbated testicular degeneration). Other well conducted animal bioassays in rats (e.g., Loser, 1980) showed no evidence of a carcinogenic response.

The mechanisms of cadmium carcinogenesis are not known. Some studies have found that cadmium is genotoxic *in vitro* and *in vivo* whereas others have not. Several plausible mechanisms for mutagenic effects of cadmium have been postulated, some of which may operate via thresholds. For example, the potential effect of cadmium on DNA repair, the inability of cadmium to directly bind to DNA, and the role of oxidative damage in cadmium-related genotoxicity are suggestive of nonlinearity or indirect mechanisms for carcinogenicity. In addition, the suggestion that metallothionein levels play a role in tissue susceptibility could also provide reason for support of a nonlinear dose-response relationship for cancer via the inhalation route. On the other hand, several different mechanisms may be operative simultaneously, thereby obscuring contributions by linear mechanisms which may also be present. Good dose-response data are not available for the nontumor endpoints that may be related to nonlinear mechanisms of carcinogenicity. The dose-response assessment should, therefore, be conducted using both default approaches, linear and nonlinear extrapolation.

This overall classification is not substantially changed from the former IRIS inhalation assessment for cancer which was based on an earlier study (Thun et al., 1985) of the same cohort used by Stayner et al. (1992) and Sorahan and Lancashire (1997). The principal animal evidence to support the occurrence of lung cancer remains the rat study of Takenaka et al. (1983) that are now reinforced by the work of Oldiges et al. (1989) and Glaser et al. (1990). What is changed is the segregation of classification based on route of exposure.

4.6 Synthesis and evaluation of major noncancer effects and mode of action - oral and inhalation

There are extensive human data documenting kidney effects following oral environmental and inhalational occupational exposures to cadmium. In both cases, toxicity is related to cumulative exposure. Because exposure via both routes affects the kidneys and toxicity is related to total internal dose, intake from all routes should be considered in evaluating the potential health effects of cadmium exposure. Cumulative exposure has been measured as total intake (oral dose or exposure duration x concentration in air), or as urinary cadmium levels or kidney cadmium levels. Because cadmium accumulates in the kidney and urinary excretion is related to total body burden, both of these measures can be used to assess total dose.

The kidney is more sensitive than the liver to cadmium toxicity, despite higher cadmium levels in the liver, probably as a result of the lower capacity for cadmium binding by metallothionein in the kidney, and resulting higher concentrations of free cadmium in the kidney (Goyer et al., 1989; Kotsonis and Klaasen, 1978; NTP, 1995; Squibb and Fowler, 1984). Cadmium toxicity is related to the amount of cadmium not bound to metallothionein. Cadmium-metallothionein filtered by the glomerulus and reabsorbed by the proximal tubule cells undergoes proteolysis in kidney lysosomes, releasing free cadmium.

Respiratory effects from cadmium exposure have been noted so far only in the occupational setting, apparently due to the direct irritative effects of the cadmium particles. Davison et al. (1988) and Smith et al. (1976) reported decrements in pulmonary function in workers exposed to cadmium. These results are supported by findings in animal studies. Respiratory tract lesions were observed by NTP (1995) in a subchronic study in rats and mice, and by Prigge (1978a) in a subchronic rat study. Glaser et al. (1986) also reported increased BAL findings in rats continuously exposed for 30 days. Kidney effects, on the other hand , have been observed on a large scale in general populations exposed orally to cadmium. Quantitative comparison in the same cohort of the cumulative exposure levels that result in kidney and lung effect also indicates that the kidney is more sensitive (Davison et al., 1988; Mason et al., 1988). Also, reversal of respiratory effects has been observed in workers (Chan et al., 1988), whereas limited if any reversal of kidney effects has been observed after the discontinuation of exposure (Elinder et al., 1985b; Mason et al., 1988; Thun et al., 1989; McDiarmid et al., 1997). Thus, respiratory effects would not be expected to be manifest antecedent to renal effects even in an occupational scenario. It should be kept in mind, however, that measures of renal toxicity are also much more sensitive than those currently available for respiratory effects.

Effects of high levels of cadmium ingestion on the bone have been observed to be catastrophic as with the Itai-itai incident with lesser but still high cadmium intakes associated various other bone disorders (Kjellstrom, 1992). Subtle changes in calcium metabolism have been observed at low doses comparable to those associated with increased urinary proteins (Buchet et

al., 1990). Jarup et al. (1998) state that there is increasing evidence that cadmium may act independently on bone tissue and that persons without previous renal lesions may be affected. In general, however, current evidence indicates that such effects are probably secondary to renal damage as changes in the renal metabolism of vitamin D and/or calcium, or changes in collagen metabolism (Kjellstrom, 1986, 1992) have been observed concurrent with bone effects. It has been demonstrated in large populations and under similar exposure conditions urinary excretion of cadmium is higher in women than men (Hayano et al., 1996) and therefore imply higher internal doses. The report of Tsuritani et al. (1992) showing a decrease in women but not in men of vitamin D levels concomitant with an increase in urinary microglobulin concentrations indicates that women may be susceptible to bone damage that occurs with renal damage whereas males are not.

Assay for and reports of neurodevelopmental toxicity of animals exposed via oral or inhalation routes either *in utero* or during lactation occur frequently in the data base of cadmium. Relative to more standard measures of developmental toxicity, neurodevelopmental effects are reported to occur at lower doses. Baranski (1984) observed behavioral effects offspring of dams exposed to $\geq$0.02 mg/m^3, Ali et al. (1986) observed dose-related effects in sensory motor coordination and swimming behavior on postnatal days 3-12 at 0.71 mg/kg/day, with no NOAEL. Popieluch et al. (1995) noted significant learning delays in pups from dams who were exposed to 0.36 mg/kg-day during gestation. Although a NOAEL was difficult to identify due to variability in neurotoxicological measures, data from Baranski et al. (1983) indicated that significant effects were present at 0.4 mg/kg-day and occasionally at 0.04 mg/kg-day. On the other hand, Dési et al. (1998) and Nagymajtényi et al. (1997) reported no behavioral and electrophysiological effects observable in 12 week old rats who were exposed *in utero* and/or through milk at lactation to cadmium at levels as high as 3.5 mg/kg-day. The inconsistency of dose at which these effects occur limits any meaningful evaluation relative to other known and well characterized effects such as renal dysfunction that are already observable in humans. There are, however, reports on cadmium as a possible etiological factor in excess peripheral neuropathies observed in among retired cadmium workers when compared to nonexposed age-matched controls (Viaene et al., 1999).

4.7 Susceptible Populations

4.7.1 Possible Childhood Susceptibility

Animal studies are somewhat equivocal in indicating the nature of the effect cadmium may have on newborn and young animals as compared to adult. A study of cadmium absorption in juvenile rats indicated increased absorption of up to 12% in neonates at 2 hours after birth (Sasser and Jarboe, 1977; see Section 3.2). Despite this increased potential for uptake of cadmium, Goering and Klaassen (1984) report that immature rats are more resistant to cadmium toxicity than are mature rats, ostensibly due to the higher content of metallothionein in their livers (up to 20-fold; Klaassen and Wong, 1982) as compared to adult animals. Other reports, however, report a

minor role for this surfeit of metallothionein and give evidence that age-associated changes in liver histiocytes and infiltrating neutrophils are alternative and more important determinants of cadmium-induced hepatotoxicity in rats (Yamano et al., 1998). Wong and Klaassen (1982) also report an increased susceptibility to neurotoxicity in newborn rats. In Nagymajtényi et al. (1997) neurotoxicological effects (evaluated at 12 weeks) were seen in rats treated by gavage from 8-12 weeks of age but not in rats that were exposed via milk during lactation.

Neurotoxicological studies of young animals (discussed in 4.3 and 4 .6) give an inconsistent view of the sensitivity of children to this endpoint that may be related to analytical methods or possibly kinetic differences due to different dosing strategies. At present this endpoint cannot be reliably evaluated.

An obscure report (Schumann, 1990; abstract only) claims that chronic toxic intake of cadmium causes a microcytotic hypochromic anemia in young rats at lower exposure levels and after shorter exposure periods than in adult animals. This report also claims that in 3 year old children, cadmium concentrations in the kidney can reach up to 1/3 of those found in adults.

Also, it should be noted that although the CadmiBel study was cross-sectional, it is not unreasonable to presume that a proportion of this study population had resided in the areas examined and therefore had been exposed to similar levels of cadmium for their entire lives, including childhood although this has yet to be confirmed through the study authors. Thus, this assessment may be considered to be inclusive of specific childhood toxicological considerations.

4.7.2 Possible Gender Differences

Berglund et al. (1998) write that women show higher concentrations of cadmium in body tissues than do men and consider that this difference may be related to reduced iron stores such as occurs during pregnancy and menarche. Reduced iron stores are known to lead to increased gastrointestinal absorption of cadmium both in humans and experimental animals. Berglund et al. (1994) noted that in a group of 57 nonsmoking women aged 20-50, 67% had subadequate iron stores (serum ferritin > 30 ug/L) which was highly and inversely associated with blood cadmium; women with depleted iron stores had blood cadmium levels which ranged up to 0.8 ug/L as compared to a maximum value of 0.3 ug/L among women with adequate iron stores.

Women may also exhibit specific cadmium toxicities such as bone abnormalities. The Itai-Itai cases in the Jinzu river basin were mostly women over 40 years of age who had lived in this area for more than 30 years. Although it is not totally clear, bone effects in women seem to manifest in concert with renal effects implying that effects on bone would be secondary to renal effects. It is clear that urinary excretion levels of cadmium are higher in women than in men even when measured in large control populations that have been stratified by age (e.g., 3.6 vs 2.29 ug/g creatinine; Hayano et al.,1996). Tsuritani et al. (1996) conducted ultrasonic examinations of the

heel bone in 17 males and 18 females in a cadmium polluted area and compared the results with 23 males and 45 females from a nonpolluted area. These abnormalities in women were reported to correlate with renal tubular damage (urinary beta 2-microglobulin) indicating concurrent adverse effects occurring in bone and kidney. 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. The population in the principal study of Buchet et al. (1990) included adult women who had been exposed throughout their lives. Although effects on bone were not reported in this study, urinary Ca levels, which may well be a predictor of bone effects, was elevated at urinary cadmium levels about the same as for NAG, 1.9 ug Cd/24 hr urine for Ca and 2.7 ug Cd/ 24 hr urine for NAG.

5. Dose Response Assessments

5.1 Oral Reference Dose (RfD) -

5.1.1 Choice of Principal Study and Critical Effect - with rationale and justification

Human epidemiology studies have shown the kidney is the primary target of oral exposure to cadmium, and have quantified the dose-response relationship (Buchet et al., 1990; Nogawa et al., 1989). Nogawa et al. (1989) reported on a study in a Japanese population that consumed high levels of cadmium in drinking water and in rice prepared with that water. The study was conducted with a large number of subjects, and incidence of kidney dysfunction was determined as a function of cumulative cadmium intake. However, the study uses a relatively insensitive measure of kidney dysfunction, β2m levels in urine greater than 1000 µg/g creatinine, while other authors typically use values of 200-300 µg β2m/g creatinine (Ellis et al., 1985; Elinder et al., 1985a, 1985b; Jarup et al., 1988) or a totally different more sensitive measure. Therefore, neither this study nor a similar one reported by Hayano et al. (1996) were used as the primary basis for the RfD. However, as noted in Section 6.1, these studies and that of Nakashima et al. (1997) lend both qualitative and quantitative support for the study of Buchet et al. (1990). The BMD for daily intake estimated from the Nogawa study (0.001 mg/kg-day) is very close to the daily intake estimated using the principal study described below and a toxicokinetic model (0.00084 mg/kg-day).

Buchet et al. (1990) conducted an epidemiology study in a Belgian population that was exposed to cadmium via the oral and inhalation routes. The authors related urinary cadmium levels with abnormal urinary levels of various kidney markers of dysfunction including retinol binding protein, amino acids, β-microglobulin, NAG and calcium. For NAG, the most sensitive and relevant marker, they reported that a 10% increase in the incidence of abnormal responses would be expected at a urinary cadmium level of 2.7 µg/day. Th study was reasonably well conducted in

a population that included sensitive subpopulations (diabetics, people up to 80 years old and presumably individuals that were exposed throughout childhood). Therefore, this study was considered the most appropriate basis for the RfD. Occupational inhalation studies with exposure reported in terms of urinary cadmium or kidney cadmium levels were also considered as the basis for the RfD, but it was preferred to use the more relevant general population study. Table 2 summarizes critical features of the oral and inhalation studies of kidney function.

5.1.2 Methods of Analysis - Logistic Regression and Toxicokinetic Model

Buchet et al. (1990) demonstrated the dose-response relationships between urinary cadmium levels and various urinary markers of renal effects in a general human population. They estimated that the urinary cadmium levels at which >10% of the population would have abnormally high excretion of these markers was 1.9 µg Cd/24 hours for calcium, and 2.74, 2.87, 3.05, and 4.29 µg Cd/24 hours for NAG, RBP, β2m, and amino acids, respectively. Urinary excretion of calcium was not designated as the basis for the RfD. Although increased calcium excretion is hypothesized to eventually lead to an adverse effect, i.e., bone weakening especially in women, increased calcium excretion by itself does not necessarily indicate dysfunction and is therefore not regarded as an adverse effect. On the other hand increased levels of NAG are very likely associated with tubular breakdown. Bernard et al. (1994) demonstrated two isozymes of NAG and found the form associated with tubular breakdown to be predominate in the urine of cadmium workers and nonexposed healthy subjects. This finding also suggests that cadmium produces cellular alterations at exposures commonly found in the general population. Too, there exists ample evidence that even minor renal damage is probably irreversible. The RfD was therefore calculated based on excretion of cadmium associated with abnormal levels of NAG excretion at 2.7 µg Cd/24 hr urine.

Benchmark dose modeling could not be conducted on the data, because only very broadly grouped data were provided, but the modeling conducted by the authors resembles BMD modeling in fitting a mathematical model to dose-response data. However, the study authors only reported the urinary cadmium level at which 10% of the values would be abnormal. This value is a best estimate of the 10% response. By contrast, the 95% lower bound (analogous to the BMD) can not be calculated from the data presented. It may be noted that the study authors used 2.0 µg Cd/24 hours in urine as the basis for their calculations of the critical cadmium concentration in the kidney, based on their most sensitive marker. For the calculation of the RfD, the dose corresponding to the minimal adverse effect has been chosen, with allowances made for the fact that the best estimate, rather than the lower bound, was used.

As discussed above, urinary cadmium is reflective of the internal body burden of cadmium, which is related to the cumulative cadmium dose. A modification of the Oberdorster (1990) model was used to calculate the lifetime daily oral intake of cadmium that would result in a urinary excretion of 2.7 µg Cd/day. This model is described in greater detail in Appendix B. As in the Oberdorster model, absorption from the gastrointestinal tract was estimated at 5%, with the other

95% of the ingested dose being eliminated in feces. A half-life of 20 years was used for the main analysis, as the mid-point in the range of values (10-30 years) reported in the literature for the whole body half-life of cadmium (Friberg et al., 1974). Analyses were also conducted using a half-life of 10 years, to determine the sensitivity to the size of the half-life. Because these values for the half-life are large relative to the human lifespan, a steady-state assumption (which would simplify the calculations) can not be made. Therefore, a simple 1-compartment model was used to calculate the daily intake. The model includes information on the fraction of the cadmium body burden that is present in the liver and kidney that can be related to the concentration of cadmium in these organs. Calculation of the daily intake from the urinary concentration reported by Buchet et al. (1990) was based only on the absorption fraction and the half-life, and did not involve any estimates of the cadmium deposition in specific tissues or the use of any other pharmacokinetic parameters. In accordance with Svartengren et al. (1986), a conversion factor of 1.25 is used to estimate the cadmium concentration in the kidney cortex concentration from data reported as whole kidney concentration.

5.1.3 RfD derivation - including consideration of background levels (dietary) and application of uncertainty factors (UF) and modifying factors (MF)

Buchet et al. (1990) calculated that a 10% incidence of abnormal urinary excretion of NAG would occur at a urinary cadmium level of 2.7 µg/day. Using a modification of the Oberdorster (1990) model, and a half-life of 20 years, a urinary cadmium level of 2.7 µg/day corresponds to a daily oral intake of 0.84 µg/kg/day assuming that all cadmium intake is via the oral route (and a corresponding renal cortical concentration estimated at 41 ug/g).

The critical effect level elucidated by Buchet et al. (1990) is not a NOAEL, but rather an estimate of a circumstance at which 10% of a general population would be affected with abnormal urinary indicators. Further, the value presented by Buchet et al. (1990) is the maximum likelihood rather than a lower bounds estimate. 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 (such as smokers, females, and diabetics) 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.

No uncertainty factors (UF) are proposed for this estimate for several reasons. This study is based on a sensitive endpoint and a chronic lifetime exposure in a general population which included sensitive populations. The absence of UF is not meant to imply that the value would not change. General population studies with larger cohorts may yield a different estimate. Future elucidation of sensitive subpopulations may also give reason to alter the estimate.

The intake in attaining this critical urinary cadmium level is nonspecific for source and therefore should be inclusive of routes of exposure and also inclusive of background levels. As discussed in Section 3.5, the principal background source of cadmium is dietary with the current generally applicable estimate being 0.14 ug/kg-day. This level of dietary intake should be adjusted for in all oral assessments, including the RfD Therefore the modeled value would be corrected for this background to arrive at the RfD:

RfD = 0.84 µg/kg-day - 0.14 ug/kg-day = 0.7 ug/kg-day (7E-4 mg/kg-day).

This amount would total to an oral intake of 59 ug/day for a 70 kg person, inclusive of diet and exclusive of smoking.

The cadmium RfD is intended to accommodate different backgrounds such that larger backgrounds would result in a smaller net intake. With known cadmium intake from shellfish eaters, for example, the background level could be as high as 0.30 ug/kg-day and the corresponding RfD would be:

RfD = 0.84 µg/kg-day - 0.30 ug/kg-day = 0.54 ug/kg-day (5E-4 mg/kg-day)

There is clear evidence in humans (Chung et al., 1986; Jarup,1998) that smoking increases cadmium intake by as much the daily dietary intake. This assessment acknowledges and stresses 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.

5.2 Inhalation Reference Concentration (RfC) -

5.2.1 Choice of Principal Study and Critical Effect - with rationale and justification

A number of studies, primarily studies of occupational exposure, show kidney effects resulting from inhalation exposure to cadmium. A variety of exposure measures were used for these studies, including the external measure of cumulative exposure (µg/m^3 x years), or internal measures of liver/ kidney cadmium levels or urinary cadmium levels. Urinary cadmium levels or cumulative exposure were preferred over liver or kidney cadmium levels, because fewer assumptions are required to determine a cadmium intake level corresponding to the observed effects. As noted in section 5.1.1 above, a study in the general population (Buchet et al., 1990) elucidated and demonstrated dose-response on urinary markers of kidney function at low urinary

cadmium levels. The urinary cadmium concentration corresponding to kidney effects reported by Buchet et al. (1990) is supported by recent sensitive studies on urinary markers and urinary cadmium levels in occupationally exposed populations (Fels et al., 1994; Kawada et al., 1990; Roels et al., 1993). These studies are summarized in Table 4.

The Buchet et al. (1990) study was chosen as the basis for the RfC for several reasons. It used a large sample size from a general population that was exposed both by oral and inhalation routes and that included sensitive subpopulations, such as women and diabetics and used measures to control confounders from affecting the study results. The results of this study also were consistent with estimates regarding urinary cadmium excretion rates and corresponding proteinurias made from occupational studies. Use of this study also allows greater consistency between the RfC and the RfD, since both are derived from the same urinary cadmium concentration. In the Buchet et al. (1990) study, 2.7 µg Cd/day in urine was estimated to correspond to a 10% incidence of abnormal urinary levels of NAG.

It was considered whether lung effects (e.g., decreased FVC) of cadmium exposure might be the critical effect, or a co-critical effect. Several lines of evidence indicate that the kidney may be considered to be more sensitive than the lung. First, the kidney effects of chronic exposure 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). Second, comparison of benchmark concentrations calculated based on urinary protein excretion (Mason et al., 1988) and pulmonary function tests (Davison et al., 1988) in the same population shows that effects on pulmonary function occur at higher cumulative exposures. A BMC(HEC) of approximately 1 µg/m^3 was calculated for the kidney effects, whereas a BMC(HEC) of 11 µg/m^3 was calculated for the lung effects (see Table 3). Analysis of the data of Smith et al. (1976) on cadmium exposure and pulmonary function also shows that the kidney is more sensitive than the lung. Gearhart et al. (1995) calculated a BMC of 32.8 µg Cd/day for the urinary cadmium level corresponding to decreased FVC, based on the data of Smith et al. (1976). Adjusted for discontinuous exposure, this BMC corresponds approximately to a BMC(HEC) for urinary cadmium of 7.5 µg Cd/day, a value almost 3-fold higher than the value calculated by Buchet et al. (1990) for kidney effects at 2.7 ug Cd/24hr. The difference between the kidney and lung sensitivity is somewhat larger than implied by these numbers, since the BMC is based on the lower confidence limit, while the value reported by Buchet et al. (1990) is the best estimate from logistic regression analysis. However, it should be noted that pulmonary function tests are relatively insensitive measures of damage, compared to the sensitivity of urinary protein markers for kidney damage. Therefore, it is possible that sensitive measures of effect could identify lung effects at exposures comparable to those at which kidney effects occur. Table 3 summarizes the cadmium inhalation epidemiology studies in which exposure was calculated based on cumulative exposure, and shows the BMC(HEC) estimates for these studies, after adjustment for discontinuous exposure as per Section 5.3.3.

5.2.2 Methods of Analysis - the Toxicokinetic Model and and BMC

As for the RfD, the RfC was calculated from a urinary cadmium level of 2.7 µg/day (Buchet et al., 1990), using the modified toxicokinetic model of Oberdorster et al. (1990) and a whole-body half-life of 20 years. Exposure in the Buchet study was both via the oral and inhalation routes. Because the RfC is based on systemic toxicity, there is no portal-of-entry effect, and a dose measure related to internal dose (urinary cadmium) was used, and critical parameters are known or can be reasonably estimated, the toxicokinetic model is used to calculate both the RfC and RfD. A fractional pulmonary deposition of 0.21 in humans was calculated (U.S. EPA, 1994) based on the particle sizes reported by Dorn et al. (1976) for ambient air, and was used to determine exposure levels. Absorption from the lung was assumed for a worse-case scenario and is therefore based on readily solubilized cadmium oxide at 90%, from the monkey data of Oberdorster and Cox (1989).

5.2.3 RfC derivation - including application of uncertainty factors (UF) and modifying factors (MF)

Buchet et al. (1990) calculated that a 10% incidence of abnormal urinary excretion of NAG would occur at a urinary cadmium level of 2.7 µg/day. Using a modification of the Oberdorster (1990) model, and a half-life of 20 years, a urinary cadmium level of 2.7 µg/day corresponds to a daily inhalation exposure of 0.65 $\mu g/m^3$. This calculation includes a concomitant oral dietary intake of 0.14 mg/kg-day, equivalent to 10 ug/person-day (Section 3.5).

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RfC = 0.65 $\mu g/m^3 \div 1$ = 7E-4 mg/m^3 (inclusive of a oral background rate of 0.14 mg/kg-day).

Neither and UF or an MF is applied to this RfC as per the rationale in the RfD (Section 5.1.3). As normal environmental air levels of cadmium are considered negligible (Section 3.5.2) no adjustment for background is considered necessary.

5.2.4 RfC Determination with Different Dietary Intakes

The inhalation RfC for cadmium of 7E-4 mg/m^3 is inclusive of a background level of 0.14 ug/kg-day (1.4E-4 mg/kg-day) to account for typical dietary sources of 10 ug/person-day (FDA, 1993). However, other backgrounds may be more appropriate for different populations with different dietary composition such as those that may contain much higher cadmium levels, e.g., shellfish eaters (see Sections 3.5). As with the RfD, a different dietary background would imply a different guidance value as dietary cadmium contributes equally with exogenous sources to the total kidney cadmium

Different dietary levels of cadmium would alter the RfC. For the RfD, this contribution could be subtracted directly from the oral intake value such that, for example, total daily oral

intake remained at 0.84 ug/kg-day. For the inhalation RfC, however, an extra oral dietary contribution would have to be accommodated for with the toxicokinetic model. Consequently, the model was run to generate ranges of dietary intake that would result in changes to the RfC. These results are presented below.

Dietary intake in ug/person/day and (ug/kg/day)	RfC (mg/m^3)
10 (0.14)	7E-4
11-18 (0.16 - 0.26)	6E-4
19 - 25 (0.27 - 0.36)	5E-4
26 - 33 (0.37 - 0.47)	4E-4
34 - 40 (0.49 - 0.57)	3E-4

The intake ranges were generated by simulating runs on the rounding points of the RfC. For example, for the RfC designated at 5E-4, the model was run at 5.4E-4 mg/m^3 (where the oral component was 0.27 ug/kg-day) and at 4.5E-4 mg/m^3 (where the oral component was 0.36 mg/kg-day). The model run was for a 70 kg human for 70 years at a half life of 20 years.

5.3 Cancer Assessment

5.3.1 Choice of Study/Data with rationale and justification

Stayner et al. (1992) conducted the highest quality epidemiology study of lung cancer risk in humans exposed to cadmium, following up an earlier study by Thun et al. (1985). The study used an adequate-sized cohort (602 white men, with 162 deaths), and characterized exposure as well as possible on an individual basis using duration worked in a given job category and the average exposure level for that category. An exposure-response relationship between lung cancer mortality and cumulative cadmium exposure was observed. The study also attempted to address potential confounding by smoking and by concurrent exposure to arsenic. Some other studies (Kazantzis et al., 1992; Sorahan, 1987) have found statistically significant increases in lung cancer related to cadmium exposure, but the exposure-response relationship was not well-characterized, and the evidence for an association with cadmium (rather than confounding factors) was less strong. Also, a recent study of this cohort based on a more definitive accounting of individual worker exposures suggests that the groups used by Stayner may not be appropriate (Sorahan and Lancashire, 1997). However, because exposure and confounding were addressed as well as possible with the information available in the Stayner et al. (1992) study, the inhalation cancer risk was based on this study.

Some studies (Kipling and Waterhouse, 1967; Lemen et al., 1976; Potts, 1965) have suggested a relationship between cadmium exposure and prostate cancer, but later studies (Sorahan and Waterhouse, 1985; Thun et al., 1985) have not supported this finding. Although a relationship between cadmium exposure and prostate cancer can not be completely ruled out, the lung cancer data are more appropriate as the basis for the inhalation risk, because there is a

stronger association, good exposure-response data are available, and lung cancer is more deadly than prostate cancer.

Support for an association between lung cancer and inhalation of cadmium compounds comes from animal studies in rats (Takenaka et al., 1983; Glaser et al., 1990; Oldiges et al., 1989) and possibly mice (Heinrich et al., 1989), but not hamsters (Heinrich et al., 1989; Aufderheide et al., 1989). The best exposure-response data comes from the study of Takenaka et al. (1983), in which concentration-related increases in adenocarcinomas, squamous cell (epidermoid) carcinoma, and mucoepidermoid carcinoma were observed in response to exposure to cadmium chloride aerosol. These data were used to calculate an inhalation unit risk, for comparison with the occupational data. However, since good-quality occupational data are available, the cadmium form in the occupational studies are more environmentally relevant (cadmium oxide and fume vs. cadmium chloride in the animal study), and there are uncertainties in the dosimetric extrapolation from animals to humans, the occupational study was used as the basis for the inhalation unit risk.

There are inadequate data to suggest that orally administered cadmium is carcinogenic to animals. No data exists assessing cancer in humans orally exposed to cadmium. Waalkes and Rehm (1992) exposed groups of 22-28 male rats to 0, 25, 50, 100, or 200 ppm cadmium in the diet for 77 weeks, and observed a statistically significant increase in the incidence of benign interstitial cell tumors of the testes at the high dose. Support for an association between cadmium and testicular cancer comes from studies of animals administered cadmium subcutaneously (IARC, 1993). Statistically significant increases in leukemia were also observed in the Waalkes and Rehm (1992) study, but there was no increase at the high dose, and this finding is not supported by other studies. In addition, the tumor response as well as the testicular toxicity seen in this study was present only in those exposure groups where the maximum tolerated dose, (as indicated by body weight losses of 10% or greater) were observed. These data are not compelling or rigorous enough to raise a carcinogenic concern by the oral route for cadmium.

5.3.2 Dose-response data

The inhalation unit risk was calculated based on the epidemiological study of Stayner et al. (1992), which is an update of the Thun et al. (1985) cohort previously used for the cancer assessment. The assessment shown here is that used by OSHA (1992) for its cadmium rulemaking, adjusted for differences between occupational and environmental exposure (see Section 5.4.3).

Cumulative Exposure (mg/m^3-day)	Median Exposure ($\mu g/m^3$-year)	Adjusted for Continuous Exposure ($\mu g/m^3$-year)	Expected Lung Cancer Deaths	Observed Number of Lung Cancer Deaths

≤584	795	182	3.35	1
585-1460	2466	566	2.64	7
1461-2920	5699	1308	1.55	6
>2921	10,836	2488	2.41	7

For this assessment, the expected number of deaths was calculated based on the mortality experience of U.S. white males. The median exposure, as presented by OSHA (1992), was used in the curve fitting. To convert these exposures to environmental exposure, the human equivalent exposure level for continuous exposure can be calculated as described in the RfC guidance (U.S. EPA, 1994b), and shown in section 5.4.3. These calculations are shown for illustrative purposes only; all adjustments were conducted on the final risk, as described in Section 5.4.4.

For comparison, the inhalation unit risk was calculated based on the incidence of the lung carcinomas, including adenocarcinomas, squamous cell (epidermoid) carcinoma, and mucoepidermoid carcinoma, in male Wistar rats (Takenaka et al., 1983).

Actual Exposure Level ($\mu g/m^3$)	Human Equivalent Concentration ($\mu g/m^3$)	Tumor Incidence
0	0.0	0/38
13.4	4.07	6/39
25.7	7.80	20/38
50.8	15.42	25/35

Due to the problematic nature of the tumors observed in the oral studies (benign testicular tumors) and the evidence that the tumors were most likely endocrine-mediated (Section 4.2), no oral slope factor is derived.

5.3.3 Dose conversion

Oral doses were converted to human equivalent doses using the equation human dose = animal dose x $(0.35/70)^{1/4}$, where 0.35 kg is the body weight of the high-dose rats as estimated from graphical data, and 70 kg is the default human body weight.

Adjustments were made in calculating the environmental exposure levels from the occupational inhalation exposure. First, if given as cumulative exposures, the values were divided by the occupational lifetime of 45 years to get an average occupational lifetime exposure. Second, these occupational lifetime exposures were converted to continuous lifetime exposures using the following:

Exposure (continuous) = Exposure (average occup lifetime) x 10/20 x 5/7 x 45/70

where the default occupational minute volume is 10 m^3/8 hours, and the default ambient minute volume is 20 m^3/24 hours. Occupational exposure of 5 days per week was assumed for the occupational unit risk, while exposure for 7 days/week was assumed for environmental exposure. This exposure value was adjusted to a 70 year lifetime exposure based on 45 years of occupational exposure by using the appropriate factor of 45/70.

Differences in pulmonary deposition resulting from differences in particle distribution in the occupational and environmental settings were also considered. Data on these particle distributions is quite limited. In fact, none of the numerous epidemiology studies on cancer or noncancer effects of cadmium exposure did any particle size measurements. Smith et al. (1980) described the cadmium production facility used for the Stayner et al. (1992) study. At this facility there was exposure to cadmium oxide dust and cadmium oxide fume. Oberdorster (1989) estimated that a median particle size for cadmium oxide dust would be about 2-3 μm, and that for cadmium oxide fume would be in the submicron range, but the size dispersion was not estimated. A sensitivity analysis was conducted for this assessment to determine how deposition varied with particle size. Particles sizes (values for the mass median aerodynamic diameter, or MMAD) of 0.5 μm (fume), and 2 or 3 μm (dust), and geometric standard deviations (σ_g values) of 1.1 (monodisperse) and 3.0 (highly polydisperse) were used. Based on these values, estimates of pulmonary deposition fractions for occupational exposure ranged from 0.18 to 0.28. Deposition under environmental conditions was estimated using the particle sizing of Dorn et al. (1976), following the lead of Oberdorster (1989). These authors reported that a typical industrial setting has an MMAD of 1.3 μm and a σ_g of 2.6 μm, and that a typical rural setting has an MMAD of 2.6 μm and a σ_g of 3.6 μm. The corresponding pulmonary deposition fractions based on the procedures in U.S. EPA (1994) are 0.24 and 0.18, respectively. Although the deposition ranges under both the occupational and environmental scenarios are both rather broad, the midpoint of the occupational range (0.23) is quite close to the average of the pulmonary deposition fractions for rural and industrial settings (0.21). Therefore, no adjustment for deposition under different conditions was made.

The human equivalent concentration (HEC) was calculated for the animal inhalation study (Takenaka et al., 1983) by a three step procedure. The exposure was first adjusted for discontinuous exposure. Next, the regional deposited dose ratio (RDDR) was calculated for the particle characteristics used in the animal study (MMAD of 0.55 μm, σ_g of 1.8 μm). Finally, the calculated deposition was multiplied by the ratio of (1) the fractional pulmonary deposition in humans under the conditions of the animal study (0.265) to (2) the fractional pulmonary deposition in humans under the ambient scenario (0.21).

Thus, HEC = Exp(adj) x RDDR x (Human fractional deposition for particles in animal study)/(Human fractional deposition under ambient scenario)
= Exp(adj) x 0.251 x (0.265/0.21)

5.3.4 Extrapolation Method

Three methods were used to extrapolate to low doses. In accordance with the proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), a linear extrapolation from the 95% lower bound on the ED10 was conducted for this genotoxic carcinogen. Extrapolation was also conducted using the Margin of Exposure (MOE) approach, to determine the effect of potential nonlinear mechanisms of cadmium carcinogenicity on the risk estimate. The dose-response assessment was conducted using both default approaches, linear and nonlinear extrapolation, because cadmium may act both via linear, genotoxic mechanisms, and via nonlinear mechanisms. In addition, extrapolation of the animal data was conducted using the linearized multistage model (extra risk), in accordance with the current Risk Assessment Guidelines (U.S. EPA, 1987). For the occupational data, an epidemiological model, a Poisson regression model, was used with relative risk.

Estimates of the ED10 and LED10 for the epidemiology data were not available directly. However, good estimates can be obtained from Table VI-12 of OSHA (1992). OSHA calculated that the maximum likelihood estimate (MLE) risk at 200 $\mu g/m^3$ is 112.1/1000 and the upper bound on risk at 100 $\mu g/m^3$ is 95/1000. (For comparison, the upper bound at 200 $\mu g/m^3$ was 177.9/1000, and the MLE risk at 100 $\mu g/m^3$ was 58.3/1000.) The MLE and upper bound at 200 and 100 $\mu g/m^3$, respectively, are sufficiently close to a 1/10 risk that a linear extrapolation to a 1/10 risk can be made from these data with little error, even though risk is slightly nonlinear in this exposure range. This extrapolation is conducted by multiplying the exposure by the desired risk per 1000 (i.e., 100) over the observed risk per 1000:

$ED10 = 200\ \mu g/m^3 \times (100/112.1) = 178\ \mu g/m^3$
$LED10 = 100\ \mu g/m^3 \times (100/95) = 105\ \mu g/m^3$

Note that these are the ED10 and LED10 under occupational exposure scenarios. Because they are not in the linear range, the ED10 and LED10 for environmental exposure scenarios can not be calculated by adjusting for discontinuous exposure. However, risk is linear in the 1-10 $\mu g/m^3$ and lower range (see Table VI-12 of OSHA, 1992). Therefore, risk under continuous exposure conditions was calculated from the occupational risk after low-exposure extrapolation:

Continuous exposure risk = Occupational risk x 20/10 x 70/45 x 7/5

The risk using the Poisson regression model was also calculated using the data in Table VI-12 of OSHA (1992), which reported that, at a TWA exposure of 1 $\mu g/m^3$, the 95% upper confidence limit on the risk is 1.0 per 1000. (The risk at this exposure level is erroneously shown in Table VI-12 as 10, due to a typographical error resulting in a misplaced decimal point.) Thus, the unit risk is 10^{-3} per $\mu g/m^3$ under the occupational exposure scenario. This risk was converted to the risk under continuous exposure using the above equation.

5.3.5 Inhalation Unit Risk

The inhalation unit risks calculated using various extrapolation methods from data on the incidence of lung cancer in exposed workers (Stayner et al., 1992), and the incidence of lung carcinomas in inhalation exposed rats (Takenaka et al., 1983) are shown in Table 5. Risks calculated from the epidemiology study for the occupational exposure scenario are shown, in addition to the risks for the continuous, environmental exposure scenario, for ease of tracking the calculations. Based on the data reported in Table VI-12 of OSHA (1992), the 95% upper bound for the risk under the occupational scenario at 1 $\mu g/m^3$ is 1.0 per 1000, or 1.0×10^{-3} $(\mu g/m^3)^{-1}$. A risk of 4.2×10^{-3} $(\mu g/m^3)^{-1}$ was calculated based on the epidemiology study using the ED10 method, and a risk of 4.4×10^{-3} $(\mu g/m^3)^{-1}$ was calculated from this study using the Poisson regression model. Risks calculated from the animal study were about 10-fold higher, with a unit risk of 3.9×10^{-2} $(\mu g/m^3)^{-1}$ calculated using the ED10 method, and 4.1×10^{-2} $(\mu g/m^3)^{-1}$ using the LMS method.

Application of the MOE methodology was also considered. The LED10 value used as the point of departure was 105 $\mu g/m^3$ (based on the occupational data). This discussion is based on tumor response as the point of departure, because sufficient dose-response information are not available for any nontumor endpoints that may be related to a nonlinear mechanism of carcinogenicity. An acceptable MOE on the order of 10 might be considered for the occupational data, to account for human variability. Because the LED10 for the occupational study was in the slightly nonlinear range, adjustment for discontinuous exposure should be applied after consideration of an acceptable MOE. An MOE of 10 for the occupational data would lead to an environmental level of 2.4 $\mu g/m^3$, after adjustment for discontinuous exposure, as described in Section 5.3.3.

6.0 Major Conclusions in Characterization of Hazard and Dose-Response

6.1 Hazard Identification

Cadmium and its various compounds are ubiquitous in the environment in amounts sufficient to warrant inclusion of a dietary intake component in these assessments.

The various cadmium compounds vary widely in their solubility and availability, from freely soluble salts such as cadmium chloride to nearly insoluble complexes such as cadmium sulfide. Adverse effects of cadmium are nearly always associated most closely with the metal ion, not in the other part of salts or complexes. Quantitative analyses in this assessment are made on the basis of freely soluble cadmium in which the metal ion would be maximally available for any given dose. This practice would be considered conservative from the perspective of public health.

In humans chronically exposed to low levels cadmium, nephrotoxicity is the principal adverse effect. This has been confirmed with a sensitive measure (proteinuria) with several studies of large diverse populations in different parts of the world exposed to cadmium orally and with occupational cohorts in which cadmium was inhaled. Renal dysfunction of the specific type caused by cadmium has been demonstrated to occur in the general population at background levels of exposure (Bernard et al. (1994).

Animal studies have confirmed these results and aided in elucidating the mode-of-action for this endpoint. The mode-of-action of cadmium involves in a sequential fashion, cadmium absorption, transport to the liver, binding to and stimulation of metallothionein (MT) synthesis (a low-molecular-weight protein with a high binding capacity for cadmium and other metals), release of MT-Cd complex back into the blood, transport to the kidney, filtration by the glomerulus and reabsorption by the renal proximal tubule cells (Foulkes, 1978). Proteolysis of the MT-Cd may then occur in kidney 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 re-bound to MT, probably due to an excessive concentration of cadmium (Goyer et al., 1989; Kotsonis and Klaasen, 1978).

Other nonrenal effects have been associated with cadmium exposure. Bone effects and abnormal calcium excretion, observed mostly in women, appear to be secondary to renal effects. Developmental and testicular effects are produced in animals at exposure concentrations much greater than those producing renal effects. Lung effects have been observed in occupational settings at exposure levels that have already caused renal effects.

Sensitive subgroups exist for cadmium toxicity. Subgroups sensitive for reasons of increased exposures include those with high cadmium diets (such as shellfish eaters) and smokers and possibly women or others with fluctuating or inadequate iron stores. Subgroups sensitive due to an increased response would be those with an inadequate renal reserve such as diabetics or those with a genetic deficiency for the binding protein (MT). The evidence for children as a sensitive subgroup is unclear. Contradictory results are reported for neurobehavioral effects in neonatal animals. As neonatal animals are reported to have greater amounts of MT than adults, neonates could be relatively resistant to cadmium toxicity. The inclusion of sensitive subgroups in the Principal Study (and several supporting studies) is a principal reason for not applying typical uncertainty factors such as that for sensitive subgroups.

The noncancer assessments have high confidence. Both assessments are derived from modeling of urinary cadmium excretion, an reliable accurate indicator of internal cadmium body burden. Both the RfD and RfC are based on and supported by human studies with large cohorts whose exposures extended over a significant portion of the subjects' lives. Although multigenerational reproductive studies are not available, suspect effects (testicular degeneration) was observed in rats only at high doses and the placenta appears to act as a barrier to fetal exposure. Too, the large populations studies which form the basis of both noncancer assessments

involved both men and women over a good portion of at least their adult lifetimes and would therefore likely have revealed any robust significant reproductive effects.

Several occupational epidemiology studies show a relationship between inhalation exposure to cadmium and lung cancer. These data are supported by observations of lung cancer in inhalation studies in rats although no tumor responses were observed in hamsters and results in mice were inconclusive. Overall, the occupational studies show a relationship between occupational exposure to cadmium and lung cancer that is related to cumulative exposure but problematic due to confounding factors. Early reports of an association between cadmium exposure and prostate cancer have not been supported by more recent follow-ups with the same cohorts. There are no data on the relevance to humans of the tumors observed following cadmium dosing via the oral route and the animal evidence for a direct effect of cadmium in tumor formation is not convincing.

The process of synthesizing these assessments have revealed limitations, both about the data base and the interpretation of existing information. The significance of the the calcium effects reported in women and their potential relationships to more serious bone diseases remains obscure. Resolution of this issue may alter the assessment strategy for cadmium significantly. The controversy of the contribution of confounding factors (smoking and arsenic exposure) to lung cancer is yet to be clearly elucidated; the resolution of this point will provide justification for more firm classification of cadmium as either a “probable “ or a “known” carcinogen. Several cadmium toxicokinetic models have been developed, including the one in this assessment and comparison of model simulations against outcomes from large occupational cohort and population studies indicate that these models are performing in a consistent manner. However, there exist few and limited human data sets specific enough to test the models against and no available bases exist for assigning variability to input parameters to attain ranges and limits on model solutions.

6.2. Dose Response

The level of cadmium intake forming the basis of the noncancer assessments, in oral equivalents, is 59 ug/person-day inclusive of a dietary background level of 10 ug/person -day. level of cadmium intake. This level of daily intake is consistent with the maximum tolerable weekly intake of about 60 ug/person/day for a 60 kg person recommended by the World Health Organization/Food and Agricultural Organization (WHO/FAO, WHO, 1989) and the maximum tolerable daily intake figure of 55 ug/person/day suggested by FDA (1993).

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 presumably due to the direct irritative effects of the cadmium particles. Human occupational studies where pulmonary and renal effects were reported in the same cohort

showed kidney effects occurring at lower exposure levels than did lung effects although it is acknowledged that measures of renal toxicity are more sensitive than those currently available for respiratory effects

This assessment has also revealed differing scientific opinions about the levels of urinary protein excretion (NAG, β2m) considered to be indicative of adverse effects in the kidney. Most studies, including the Principal Study of Buchet et al. (1990) used β2m levels in the range 200-300 µg/g creatinine, while others (e.g., Nogawa et al. 1989) defined an adverse response as >1000 µg/g creatinine. The level at which these protein levels are adverse is important as the protein level that is designated as adverse may affect the calculated incidence of affected people. However, Kowal and Zirkes (1983) provided data on the frequency distribution of urinary β2m in the general population. These data indicate that there is a bimodal distribution, with a low background incidence of people in the range of 200-350 µg β2m per liter. This suggests that small changes within this range in the level chosen as an effect would be expected to have a relatively small effect on the incidence of response, and therefore would have a small effect on the ultimate choice of NOAEL/LOAEL/BMD. It is not clear whether a bimodal distribution is also present for occupationally exposed populations. Frequency distribution data for NAG are not available, but similar arguments may hold for that protein.

Buchet et al. (1990) used their data and a toxicokinetic model to calculate a critical kidney cadmium level that was 1/4 the value, about 50 mg/kg versus 200mg/kg, calculated by Kjellstrom et al. (1984) and others based on occupational exposure. The toxicokinetic model used in this assessment also yields this lesser value. The reason for this difference is unclear, but may be related to differences in toxicokinetic parameters used or the nature of the populations studied. Recent occupational studies have observed effects on urinary excretion of kidney marker proteins at cadmium excretion rates comparable to those reported in the Principal Study (Chia et al., 1989; Elinder et al., 1985a; Fels et al., 1994; Kawada et al., 1990). Thus, the apparent differences in critical kidney cadmium levels may be more related to differences in toxicokinetic assumptions than differences in population sensitivity.

The previous cadmium assessment included separate RfDs for cadmium in water and in food, based on 5% absorption of cadmium from water, and 2.5% absorption of cadmium from food. However, separate RfDs for cadmium in water and food are not supported by the available data. Ruoff et al. (1994) conducted a detailed analysis of animal studies, and 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 in less than 4 mg/kg/day (a dose much higher than the RfD). Bioavailability was found to be more influenced by the contents of the gastrointestinal tract than by the exposure medium.

The amount of cadmium absorbed from the lung is another area of uncertainty. As discussed in Section 3, the lung absorption of different cadmium compounds would be expected to differ markedly depending on the chemical form. The chemical constitution of cadmium in ambient

air is not well characterized. It has been proposed, however, that cadmium in ambient air is present as cadmium oxide, elemental cadmium, and cadmium sulfide (Oberdorster, 1989). The assumption that all inhaled cadmium will be absorbed with a 90% efficiency as for cadmium oxide is, as stated above, a conservative health-protective assumption. Absorption would be lower for the other major forms of cadmium in air.

A source of uncertainty in the calculation of the dose-response from the epidemiology data is in the comparison between deposition under occupational and ambient exposure scenarios. For that comparison, it was assumed that the estimated median particle size could be directly converted to an MMAD. If the reported value were actually a different type of median (e.g., count median aerodynamic diameter, area median), the MMAD would be larger. A second uncertainty relates to the appropriate region of the respiratory tract for calculation of deposition. It is likely that the cadmium-containing particles under ambient exposure conditions are smaller than those in the occupational setting. If that is correct, relative deposition in the pulmonary region compared to the tracheobronchial (TB) region would be higher for ambient exposure than for occupational exposure. If bronchogenic cancers result from occupational exposure but ambient exposure would lead to cancers in the pulmonary region, it is unclear what the most appropriate dose metric for extrapolation from occupational to ambient exposure would be.

Several different mechanisms have been proposed for cadmium carcinogenicity, and it is likely that cadmium exerts its effects via several different modes of action. Cadmium is mutagenic, but this mutagenicity may be due to cadmium-related oxidative damage, or altered DNA repair activities rather than direct interaction with DNA. Along these lines, Waalkes et al. (1997) have demonstrated a endocrine-mediated cause for testicular cancer observed in rats treated orally with cadmium. No single unifying mechanism of cadmium carcinogenicity has been proposed, and it is possible that cadmium may act via multiple modes of action which would dictate use of nonlinear extrapolation method as was done with cadmium in this assessment. Because both genotoxic and nongenotoxic mechanisms are plausible, both types of extrapolations were considered for this assessment.

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8.0 Appendices

A- External Review Comments

B - Cadmium Toxicokinetic Model

C - Benchmark dose modeling

D - Cancer Risk Output

Table 2. Summary of Studies Evaluating Kidney Effects of Cadmium Exposure

Study	Size	Cum. exposure	Urinary Cd	Controlled for urine pH?
Bernard et al. 1990	58 exposed 58 control	NR; ave. 10.4 yr duration	β2m, NAG, RBP, albumin, sig inc at >10 µg/g creatinine	collected into phosphate buffer
Buchet et al. 1990	1699 (primarily oral, environmental exposure)	NR	effect estimated at 2.7-4.3 µg Cd/24 hours	NR
Chia et al. 1989	65 female exposed 9 female control	NR, but duration 1-14 years and estimated exposure during study 7-39 µg/m^3	effect on NAG at about 3 µg Cd/g creatinine	no control
Chia et al. 1992	97 exposed (52 females), 122 controls (80 females)	NR	significant increases in urinary NAG and α1-microglobulin at urinary cadmium levels >5 µg/g creatinine	NR
Elinder et al. 1985a, 1985b	60 (2 females)	1985b: LOAEL at lowest exposure group (<1000 µg/m^3 x years) BMC of 293-304 µg/m^3 x years, all based on β2m	1985a: β2m >500 µg/g creatinine was 25% in the group with 2-≤5 µg Cd/g creatinine, compared to 7% in the group with ≤2 µg Cd/g creatinine	subjects ingested bicarbonate to neutralize urine
Ellis et al. 1985	70 exposed 12 control	NOAEL of 7.5 µg/m^3 x years LOAEL of 54 µg/m^3 x years, BMC of 116 µg/m^3 x years, based on β2m	NR	pH adjusted
Falck et al. 1983	33 male exposed 41 male controls	individual data reported for β2m, but poor reproducibility	NR	adjusted above 5.5

Table 2. Summary of Studies Evaluating Kidney Effects of Cadmium Exposure (continued)

Study	Size	Cum. exposure	Urinary Cd	Controlled for urine pH?
Fels et al. 1994	control: 31 males, 24 females moderate: 30 males, 18 females high: 29 males, 40 females	NR	Biochemical markers elevated at 1.5-5 µg Cd/g creatinine, proteinuria in group with >5 µg Cd/g creatinine, mean 11.5	no control
Ikeda et al. 1995	378 oral	NR	No correlation with β2m or RBP at 0.4 to 7.4 µg Cd/g creatinine	no control
Jarup et al. 1988	326 men and 114 women (exposed) no controls	NOAEL 131 µg/m^3 x years LOAEL 691 µg/m^3 x years. BMC 1030 µg/m^3 x years, based on β2m	NR	no control
Jarup et al. 1995	29 men, 43 women, varying levels of environmental exposure	NR	Tubular dysfunction based on NAG elevated among those with urinary cadmium ≥0.5 µg/g creatine than among those with lower urinary cadmium levels.	NR
Kawada et al. 1990	26 exposed 53 control	NR; estimated maximum of 3 µg/m^3 for 20 years, but exposure at one area was 3-350 µg/m^3	NAG correlated with urinary Cd, but β2m wasn't statistically significant increase at 2 µg Cd/g creatinine in urine	No control
Kjellstrom et al. 1977	185 male and female exposed 87 male controls	NR--dose-response based on duration of employment	NR	Measured, not controlled

Table 2. Summary of Studies Evaluating Kidney Effects of Cadmium Exposure (continued)

Study	Size	Cum. exposure	Urinary Cd	Controlled for urine pH?
Mason et al. 1988	75 male exposed 75 male controls	NOAEL 719 µg/m^3 x years, LOAEL 1301 µg/m^3 x years BMC of 181 µg/m^3 x years calculated based on the grouped data, and BMCs of 251 and 1340 µg/m^3 x years based on individual data, all based on RBP	NR	Not applicable
Nogawa et al. 1989	878 males and 972 females exposed (oral) 294 controls	BMD of about 0.001 mg/kg/day was estimated, based on the incidence of β2-m levels >1000 µg/g creatinine (much higher than the definition of adversity used for the occupational studies)	NR	not controlled
Roels et al. 1993	43 male exposed 37 male control	NR	"threshold for a significantly higher probability of change" at 2 µg Cd/g creatinine for biochemical alterations, 4 µg Cd/g creatinine for HMW protein and some tubular antigens (e.g., NAG), and 10 µg Cd/g creatinine for other tubular markers.	no control

Table 2. Summary of Studies Evaluating Kidney Effects of Cadmium Exposure (continued)

Study	Size	Cum. exposure	Urinary Cd	Controlled for urine pH?
Smith et al. 1980	16 workers 12 controls	exposed group cumulative exposure 700-~20,000 µg/m^3 x years No attempt at dose-response analysis	NR	no control
Staessen and Lauwerys 1993	1699 (primarily oral, environmental exposure)	correlation between urinary cadmium and serum alkaline phosphatase	NR	NR
Thun et al. 1989	45 exposed males 32 control males	study estimated threshold at 822 µg/m^3 x years (based on β2-m >486 µg/g creatinine, or RBP>321 µg/g creatinine) BMC base on individual β2m data is 1838-1964 µg/m^3 x years. Based on grouped RBP data, BMCs were 646-1975 µg/m^3 x years, depending on the model	NR	No control
Van Sittert et al. 1993	14 exposed	no; exposure 4-25 µg/m^3	0.64-9.2 µg/g creatinine no statistically sig effect on RBP, β2m, NAG, or β2m	No control

NR = not reported

Table 3. Summary of Inhalation Epidemiology Studies of Cadmium
based on Cumulative Exposure

Study	Endpoint/BMR definition	NOAEL ($\mu g/m^3$ x years)	LOAEL ($\mu g/m^3$ x years)	NOAEL(HEC)[1] ($\mu g/m^3$)	BMC ($\mu g/m^3$ x years)	BMC(HEC) ($\mu g/m^3$)
Ellis et al. 1985	Incidence of kidney dysfunction, based on β2-microglobulin >200 µg/g creatinine or total protein >250 mg/g creatinine	7.5	54	0.036	116	0.57
Jarup et al. 1988	Incidence of kidney dysfunction, based on β2-microglobulin >310 µg/g creatinine, derived from upper 2.5 percentile among unexposed populace	131	691	0.69	1030	5.2
Elinder et al. 1985a, 1985b	Incidence of kidney dysfunction, based on β2-microglobulin >300 µg/g creatinine, derived from upper 2.5-5 percentile among unexposed populace	None	1000	None	293-304	1.5
Mason et al. 1988	Incidence of tubular proteinuria, defined as urinary RBP >95th percentile of referent population. Estimated by OSHA (1992) as corresponding to ~650 µg β2-microglobulin/g creatinine Difference from matched referent for urinary RBP, $p_0 = 0.05$	~719	~1301	~3.7	181 251 (Weibull) 1340 (Power)	0.93 1.3 (Weibull) 6.8 (Power)
Davison et al. 1988	(Observed - Expected) for carbon monoxide transfer coefficient, $p_0 = 0.05$	N/A[2]	N/A	N/A	2090	11
Thun et al. 1989	β2-microglobulin, $p_0 = 0.05$ RBP, $p_0 = 0.05$	N/A N/A	N/A N/A	N/A N/A	1838-1964 646 (Weibull) 1975 (Power)	9.3-10 3.3 (Weibull) 10 (Power)

[1]Exposure (continuous) = Exposure (occup) x 10/20 x 45/70 x 5/7
[2]N/A = Not available; cannot be determined based on the provided data

Table 4. Summary of Urinary Cadmium Levels Corresponding to Abnormal Values of Various Markers

Reference	Population	Result	Marker	Critical Level (µg Cd/g creatinine)	Critical Level (µg Cd/day)[1]
Buchet et al. (1990)	General population	10% incidence of "abnormals," based on logistic regression	calcium NAG β2m	Not reported	1.9 2.74 3.05
Fels et al. (1994)	Workers and general population	Increased levels	tubular antigens tubular markers	1.5-5, mean 2.35 >5, mean 11.5	mean 1.3-2.3 mean 6-11.5
Roels et al. (1993)	Workers	Threshold for higher probability of change, based on logistic regression	albumin, NAG, and some other tubular antigens β2m, other markers	~4 10	2.2-4 5.6-10
Kawada et al. (1990)	Workers exposed to CdS	Significant increase	NAG	2	1.2-2
Chia et al. (1989)	Women in Ni-Cd factory	Near-significant (p=0.055) increase	NAG	1-<3 group	0.6-3 group
Chia et al. (1992)	Female workers	Increased prevalence compared to controls	NAG	>5	>2.8->5
Jarup and Elinder (1994)	Workers	10% incidence of proteinuria, based on probit analysis	protein	3	1.7-3
Jarup et al. (1995)	M&F general population	Increased prevalence of tubular dysfunction	NAG>4.4 U/g creatinine	≥0.5 (mean not reported)	>0.3->0.5
Bernard et al. (1990)	Male workers	Increased incidence of abnormals	β2m, NAG, RBP	group >10	>5.6->10
Elinder et al. (1985a)	Mostly male, some female workers	7% incidence of elevated β2m 25% incidence	β2m	≤2 2-≤5	≤1.1-≤2 1.1-≤5
Thun et al. (1989)	Male workers	1% prevalence of abnormal β2m, using 5000 µg β2m/L (~5000 µg/g creatinine) as the definition of abnormality	β2m	3.2	1.8-3.2

[1]Ranges are shown to account for daily excretion of creatinine of 1-1.8 g/day.

Table 5. Inhalation Cancer Risk

Basis for Risk	ED10 ($\mu g/m^3$)	LED10 ($\mu g/m^3$)	Risk from Poisson Regression Model (occupational) or LMS (animal) $(\mu g/m^3)^{-1}$	Risk based on ED10 $(\mu g/m^3)^{-1}$	
				MLE	95% Upper bound
Occupational Exposure, Based on Stayner et al. (1992)	178	105	1.0×10^{-3}	5.62×10^{-4}	9.52×10^{-4}
Continuous Exposure, Based on Stayner et al. (1992)	Not calculated	Not calculated	4.4×10^{-3}	2.45×10^{-3}	4.15×10^{-3}
Continuous Exposure, Based on animal study (Takenaka et al., 1983)	4.27	2.59	4.1×10^{-2}	2.34×10^{-2}	3.86×10^{-2}

Appendix A
External Review
Peer Reviewer Instructions, General and Specific Questions and Recommendation

General

The U.S. EPA is conducting a peer review of the scientific basis supporting the health hazard and dose response assessments for cadmium and compounds (CAS No. 7440-43-9) that t will appear on the Agency's online database, the Integrated Risk Information System (IRIS). Materials to be reviewed include the summary information that will appear on IRIS (the inhalation reference concentration [RfC], oral reference dose [RfD], and cancer assessment) and the supporting document, the Toxicological Review. All of these documents in their curretn draft form have been made available to the public.

A listing of Agency Guidelines and Methodologies that were used in the development of these hazard and dose-response assessments included the following: The Risk Assessment Guidelines (1986), the (new) Proposed Guidelines for Carcinogen Risk Assessment (1996), Guidelines for Developmental Toxicity Risk Assessment, (proposed) Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity, (proposed) Guidelines for Neurotoxicity Risk Assessment, Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, Recommendations for and Documentation of Biological Values for Use in Risk Assessment and Use of the Benchmark Dose Approach in Health Risk Assessment. Copies of these documents (and/or their relevant sections) will be made to the reviewer upon request.

Guidelines for Peer-Reviewing

Peer review is meant to ensure that science is used credibly and appropriately in derivation of these dose-response assessments. You have been chosen as an expert on the chemical under consideration, on a scientific discipline related to at least one of the assessments, or in the field of risk assessment. At least three peer reviewers per chemical are being chosen to review the scientific basis of these draft dose-response assessments before they are forwarded on to the EPA's Consensus Process for final approval and adoption by the EPA. These hazard and dose-response assessments will then appear on IRIS and become available as Agency consensus health effect information.

The primary function of the peer reviewer should be to judge whether the choice, use, and interpretation of data employed in the derivation of the assessments is appropriate and scientifically sound. This review is not of the recommended Agency risk assessment guidelines or methodologies used to derive cancer or RfD/C assessments as these have been reviewed by external scientific peers, the public, and EPA Science Advisory Boards. The reviewer's comments on the application of these guidelines/methodologies within the individual assessments is, however, welcomed and encouraged. For example, the reviewer may ascertain whether or not there is data sufficient to support use of other than default assumptions for areas such as sensitive subpopulations or linear cancer extrapolation. The reviewer may also have opinions on other areas of uncertainty such as subchronic to chronic duration (when only a subchronic study is available) or an incomplete data base but should focus on the specific area of uncertainty rather than on the magnitude of the overall estimate.

Tasking - General Questions

The following set of general questions are meant to guide the reviewer through the review in evaluating the overall validity and soundness of the assessment. It is not imperative that each question of this group be answered.

1. Are you aware of any other data/studies that are relevant (i.e., useful for the hazard identification or dose-response assessment) for the assessment of the adverse health effects, both cancer and noncancer, of this chemical?

2. For the RfD and RfC, has the most appropriate critical effect been chosen (i.e., that adverse effect appearing first in a dose-response continuum)? For the cancer assessment, are the tumors observed biologically significant? relevant to human health? Points relevant to this determination include whether or not the choice follows from the dose-response assessment, whether the effect is considered adverse, and if the effect (including tumors observed in the cancer assessment) and the species in which it is observed is a valid model for humans.

3. Have the noncancer and cancer assessments been based on the most appropriate studies? These studies should present the critical effect/cancer (tumors or appropriate precursor) in the clearest dose-response relationship. If not, what other study (or studies) should be chosen and why?

4. Studies included in the RfD and RfC under the heading "Supporting/Additional studies" are meant to lend scientific justification for the designation of critical effect by including any relevant pathogenesis in humans, any applicable mechanistic information, any evidence corroborative of the critical effect, or to establish the comprehensiveness of the data base with respect to various endpoints (such as reproductive/developmental toxicity studies). Should other studies be included under the "Supporting/Additional" category? Should some studies be removed?

5. For the noncancer assessments, are there other data that should be considered in developing uncertainty factors or a modifying factor?

6. Do the Confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the studies chosen, the relevancy of the effects (cancer and noncancer) to humans, and the comprehensiveness of the data base? Do these statements make sufficiently apparent all the underlying assumptions and limitations of these assessments? If not, what needs to be added?

Tasking - Chemical Specific Questions

The following group of questions are specific to the cadmium assessment and are meant to address areas of uncertainty and controversy that have arisen during previous reviews processes or from analysis of the literature. These questions have been generated from issues present in the data base or arising from prior reviews, including internal Agency review. It is acknowledged that definitive answers to many if not all of these queries may not be possible to formulate. Nevertheless, the Agency may have to make a judgment based on available scientific evidence. Therefore, reviewer input to this set of questions is considered vital to the entire assessment in making judgments in the full light of limitations.

7. The current draft cancer assessment for cadmium via the inhalation route is based on limited evidence from occupational studies. This evidence is considered limited by the presence of possible confounding factors, arsenic and smoking in particular. It is principally for this reason that cadmium is considered a "probable" rather than a "known" human carcinogen via the inhalation route. Do you agree with this assessment or do you consider that these confounding factors have been dealt with adequately?

8. This current draft cancer assessment states that the evidence for cadmium via the oral route is inadequate. Is the weight-of-evidence presented for this position adequate? Should cadmium instead be treated as with other endocrine-mediated animal cancers, such as with a MOE (margin of exposure) approach?

9. Typically RfD/Cs are derived from animal evidence where exposures are known and uncertainty factors applied to address the various extrapolations. The RfD and RfC in this assessment are based on human evidence with only generally known exposures but with which extrapolations are minimized. Is this approach sound and defensible?

10. Has the current principal study of Buchet et al. (1990) been adequately characterized with respect to its limitations (e.g., the number and distribution of subjects)? Are the cohort inclusion criteria in this study (e.g., smoking and occupational information, reliable 24-hr urine sample) sufficient to address the major confounders that could affect the study results? Should general conclusions about other populations be made based on this study?

11. The noncancer RfD and RfC assessments do not use an uncertainty factor for human variability principally because of the characteristics of the population studied in Buchet et al. (1990) that are considered to be inclusive of potential susceptible subgroups. Do you agree with this action and justification? (Proposed RfD intakes, at 0.70 ug/kg-day, are not far removed from dietary intake levels of 0.14 ug/kg-day.)

12. Has the development and applicability of the toxicokinetic model used in this assessment been adequately documented? (Including the issue of different renal cortical concentrations predicted from similar urinary outputs, 200 ug/g historically but around 50 ug/g in this assessment's and Buchet's model?)

13. Are the issues of cadmium effect and gender adequately addressed? Has the evidence and issues surrounding the elevated excretion of calcium concomitant with cadmium been considered appropriately?

14. Have the issues of cadmium effects on the young and children been adequately addressed in this assessment?

Recommendations

Based on your reading and analysis of the information provided, please identify your OVERALL recommendation for the IRIS materials you have reviewed from among the following choices:

- acceptable as is
- acceptable with minor revision (as indicated)
- acceptable with major revision (as outlined)
- not acceptable

Appendix B
Cadmium Toxicokinetic Model

This Appendix describes the adaptation of the Oberdorster (1990) toxicokinetic model used to calculate exposure levels corresponding to the critical urinary cadmium levels calculated by Buchet et al. (1990). Oberdorster (1989) developed a model to evaluate the deposition and retention of cadmium particles of varying size distributions in the lungs of humans and animals. This model was then developed further to compare the systemic dose of cadmium following inhalation and ingestion exposure (Oberdorster, 1990). The inhalation portion of the model used the lung deposition model of Yeh and Schum (1980) to estimate cadmium deposition in the lung after inhalation of cadmium with a given particle size distribution. Retention in the lungs for different cadmium compounds was based on data from monkeys (Oberdorster and Cox, 1989; Oberdorster et al. 1987), and included parameters for mechanical clearance and absorption. The systemic dose from cadmium inhalation was then calculated based on the air concentration, volume inhaled, deposition fraction in the lung, respiratory tract absorption fraction, and mechanical lung clearance fraction. For cadmium ingestion, the systemic dose was based on the amount ingested and the intestinal absorption fraction.

The approach used here was a modification of the Oberdorster (1990) model. Although the concentration of cadmium not bound to metallothionein is the toxicologically relevant form of cadmium, the kinetics of cadmium-metallothionein interaction in the blood and tissues is insufficiently characterized to accurately describe the concentration of unbound cadmium. Therefore, the simplified one-compartment toxicokinetic model shown in Figure B-1 was used to describe cadmium toxicokinetics.

For the present analysis, the Oberdorster model was simplified by considering inhalation and oral exposures separately, as shown. The 10% of the cadmium deposited in the lung that is transferred to the gastrointestinal tract and eliminated in the feces was not included, because only urinary concentration (and not fecal elimination) was used to back-calculate the exposure level. Oberdorster (1990) modeled 5% of the material in the gastrointestinal tract as being absorbed systemically. Because this route (clearance to the gastrointestinal tract and fecal elimination) would account for only 0.5% of the cadmium deposited in the lung, this fraction was not considered to be significant, in light of the magnitude of uncertainty and variability associated with the parameter values accounting for larger portions of the deposited dose.

Other parameters used in the model were chosen as follows. The ventilation rate (Vent) was assumed to be 20 m^3/day in accordance with EPA standard values. The fractional deposition (fDep) was calculated using the U.S. EPA particle deposition model (RDDR) (U.S. EPA, 1994), using the particle size distributions considered by Oberdorster (1989) in the modeling of lung tumors from cadmium exposure. Oberdorster (1989) considered distributions typical of industrial settings (MMAD of 1.3 and σ_g of 2.6) and of rural settings (MMAD of 2.6 and σ_g of 3.6) as described by Dorn et al. (1976). For these two distributions, the fDep was 0.24 and 0.18, respectively. The average fDep of 0.21 was used in the current assessment. Oberdorster estimated that 90% of deposited cadmium oxide is solubilized from the lung to the body compartment (fAbs), and 10% is mechanically cleared to the gastrointestinal tract. This value for fAbs was chosen based on absorption of cadmium oxide by monkeys, and is a health-protective assumption as this form of cadmium is highly soluble and bioavailable. As discussed in Section 3 of the main document, the degree of solubilization is highly dependent on the form of cadmium. Cadmium oxide was chosen for this analysis also because it is representative of environmentally-relevant cadmium exposure. Although the chemical form of cadmium in ambient air is not well characterized, Oberdorster (1989) suggested that it is reasonable to assume that cadmium oxide is present, perhaps along with elemental

cadmium and cadmium sulfides. As described in Section 3.0 of the main document, approximately 5% of the intestinal dose is absorbed (fUptake), with the rest being excreted in the feces. The actual absorption depends on such factors as diet, trace nutrients, and the amount of food in the stomach (Ruoff et al., 1994).

The elimination rate constant for excretion from the body is shown in the model as kUrine. Cadmium is excreted from the body with a long half-life, with values in the literature ranging from 10 to 30 years (Friberg et al., 1974). Values in individual studies vary considerably within this range, probably due to such factors as inter-individual variability, small sample size, and the effect of trace metal intake on cadmium metabolism. Oberdorster (1990) used a half-life of 10 years. Different values for the whole body half-life of cadmium were used in this analysis. Oberdorster (1990) assumed a whole body half-life of 10 years, while the parameter value chosen by Kjellstrom and Nordberg (1985) was approximately 13.5 years. For the main analysis, a half-life of 20 years (corresponding to an hourly urinary excretion constant, kUrine, of 4.0e-6/hr, from 0.693 / 175200 hrs) was used, as falling in the middle of the 10-30 year range reported by Friberg et al. (1974). To determine the sensitivity of the analysis to the size of the half-life, analyses were also conducted using a half-life of 10 years (8.0e-6/hr), based on the value used by Oberdorster (1990). Figure B-1 also shows the liver and kidney as containing a fixed fraction of the cadmium body burden. These parameters were included to allow for calculations based on liver or kidney cadmium levels, but deposition in the liver or kidney was not included in the calculation of oral dose or inhalation exposure corresponding to specific urinary cadmium levels.

The exposure was then calculated using the equation:

$$dA(body)/dt = kDose - kUrine*A(body)$$

where:

A(body) = the amount of cadmium in the body
kDose = the intake rate of cadmium, i.e., the amount of cadmium taken up by the body each day from both oral (ug/kg-day) and inhalation (ug/m^3) routes of exposure
kUrine = the urinary excretion rate constant based on a half-life of 20 years, 4.0e-6/hr.

Results

Using this model, the cadmium accumulation in the body was modeled to determine the exposure level that would result in the critical urinary excretion of 2.7 µg cadmium/day (from Buchet et al., 1990) after 70 years of exposure.

Figure B-2 shows the results for the human daily oral intake rate of 0.84 ug/kg-day in attaining the critical urinary excretion (CE) at 70 years. A half-life of 20 years was used for the urinary excretion rate. The oral intake of 0.84 ug/kg-day includes a dietary background component of 0.14 ug/kg-day whose source is explained in the main document. The RfD is defined from this figure as 0.84 - 0.14 ug/kg-day = 0.7 ug/kg-day. Different backgrounds of the dietary component would give different values for the net component, i.e. the RfD, such that the total daily oral intake would always equal no more than 0.84 ug/kg-day (and the critical urinary concentration would always equal no more than 2.7 ug Cd/day).

Figure B-3 shows the results of a continuous human exposure to a concentration of 0.65 ug/m^3 cadmium (at the particulate parameters described above) in attaining the critical urinary excretion (CE) at 70 years. A half-life of 20 years was used for the urinary excretion rate. The model was simultaneously run with an oral input for the same dietary background component used for the RfD in Figure B-2, 0.14 ug/kg-day. The RfC is defined from this figure at 0.65 ug/m^3, 7E-4 mg/m^3. Different background of the dietary component would necessarily yield different air concentrations of cadmium to limit the critical urinary concentration to no more than 2.7 ug Cd/day. Unlike the situation with the RfD, where the background component may simply be subtracted from the total allowable intake, the effect of different background dietary intake components on the RfC would have to be determined by the model. Thus, a series of RfC values that would result from a range of dietary backgrounds was calculated with the model and are presented in the main document in Section 5.3.2. When sufficient information is available to use different dietary levels indicated in this section, the corresponding RfC would apply.

Validation

The validity of the model was examined utilizing both animal and available human data. Revis and Osborne (1984) examined the effect of low and hi protein diets on the effects of cadmium disposition in male Sprague-Dawley rats. Experimental data on the concentration of cadmium in the kidneys and liver were extracted. The cadmium model in Figure B-1 was parameterized for rats and the concentration in the kidney (CKID) and liver (CLIV) calculated and compared to the data. Bernard et al. (1990) also examined liver and kidney concentrations of cadmium after administering 200 ppm cadmium to female Sprague-Dawley rats. The experimental versus model simulations for both of these data sets were quite comparable and are presented in Figures B4-9.

Information with which to test the human parameterized model is limited. Oberdorster (1990) states that a daily ingested dose of 10 ug/person would produce a whole body retained dose of 2.55 mg over a 50 year period. The output of the model (Abody) configured to these durations and doses ranged from 2.48 mg - 4.23 mg, within this stated range.

The draft ATSDR Toxicological Profile for cadmium (1998) cites a data set in which urinary excretion was reported from an estimated oral intake of 16 ug/day (0.229 ug/kg-day) for 50 years and cigarette exposure totaling 2-4 ug/day (assumed 0.15 ug/m^3) starting at 20 years of age. The model outputs estimating the urinary output obtained either by summing 50 years of oral intake alone plus 30 years of inhalation intake alone (1 ug/24 hr) or by modeling oral and inhalation simultaneously for 30 years plus oral alone for 20 years (1.3 ug/24 hr) somewhat overstimated the range observed, 0.56 - 0.8 ug/24 hrs.

The draft ATSDR profile also cites a data set for an average 45-year-old Japanese person whose daily intake of cadmium is 40 ug from food (40 ug / 60 kg = 0.66 ug/kg-day) and 2.7 ug via the inhalation route (0.135 ug/m^3) from the cigarette smoking beginning at age 20. The model outputs estimating the concentration in the liver (CLIV) obtained either by summing 45 years of oral intake alone plus 25 years of inhalation intake alone (4.8 mg/kg) or by modeling oral and inhalation simultaneously for 25 years plus oral alone for 20 years (6.4 mg/kg) both somewhat overstimated the reported value of 3.4 mg/kg. The corresponding values for Cd in the urine at 24 hrs were 1.9 ug/24 hr and 2.4 ug/24 hr as compared to the measured value of 1.3 ug/24 hr.

Comparison to Nordberg-Kjellström Model

The Nordberg-Kjellström model (Kjellström and Nordberg, 1978; Nordberg and Kjellström, 1979) is a linear multicompartmented model that describes cadmium disposition via oral and inhalation routes. For inhalation exposure the model accommodates differential exposure of the respiratory tract based on particulate aerodynamic diameter. The oral route of exposure is described by cadmium entering into three different blood compartments folowed by distribution to either the liver, kidney or "other tissues". Elimination is either via the feces or urine. Parameterization of the model requires 21 coefficients/parameters besides some basic physiologic parameters.

As discussed above, the model used in this assessment in Figure B-1 is a simplified version of the Oberdorster models (1989,1990). This model is parsimonious with respect to parameters. Fraction absorbed (fAbs) via inhalation (with fDep calculated from available methods), fractional uptake (fUptake) for the oral route, a urinary excretion rate (kUrine), a final estimate of the amount in the liver (ALiv) and kidney (Akid) only are required to generate outputs. Comparison of outputs generated by these models from the same data listed in the ATSDR draft Toxicological Profile for Cadmium showed that the Nordberg-Kjellström simulations were closer to the measured observations. As variability estimates are absent from both models, however, it is not possible to judge if these differences were significant. Also, limited human data currently restrict the possibility for any extensive and meaningful comparison among various models. Based on both its parsimonious nature and ability to generally match and simulate both animal and human data, the modified Oberdorster model is preferred for use in this assessment.

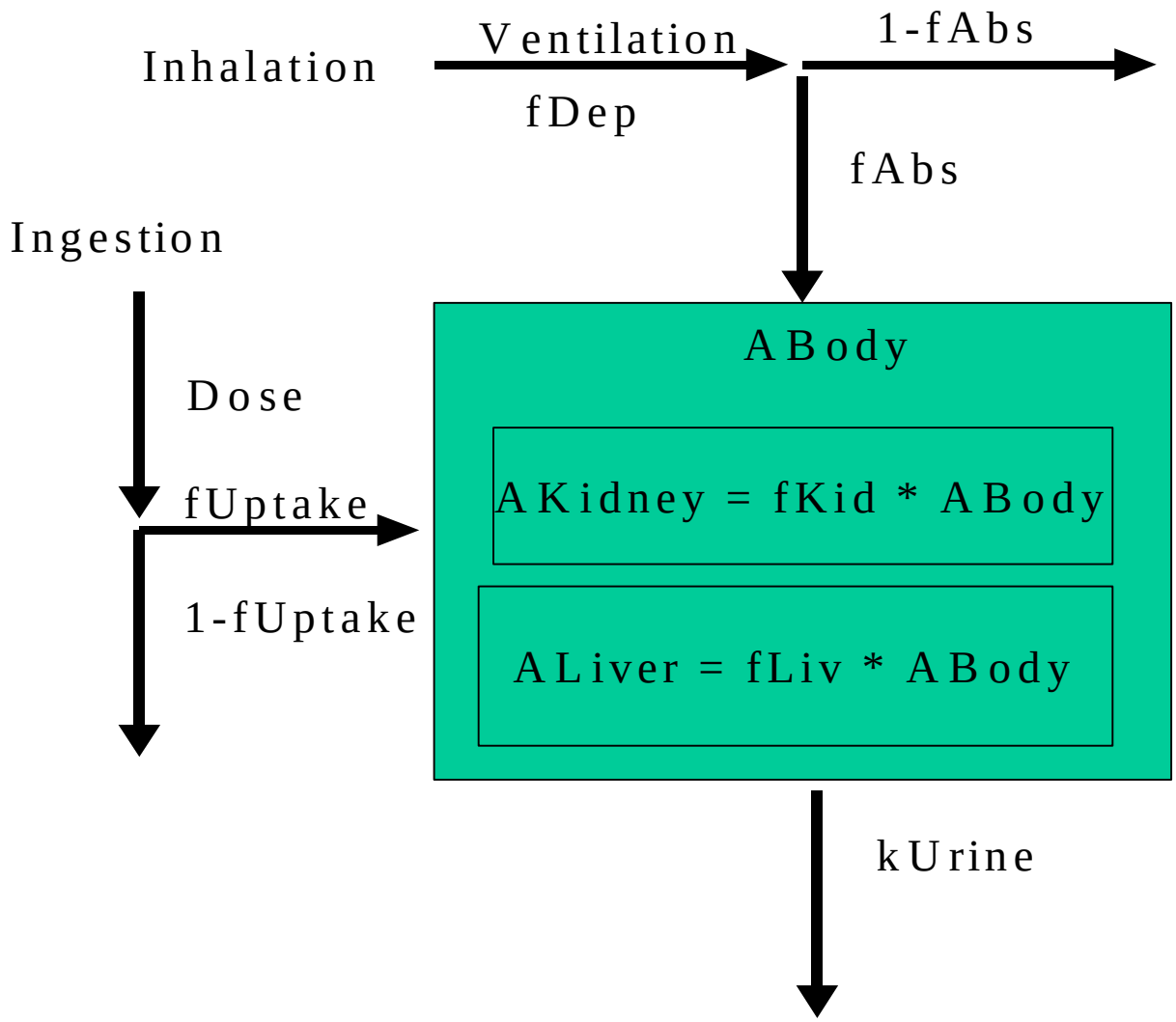


Figure B-1. Pharmacokinetic model for cadmium. This model has been synthesized from the toxicokinetic model used by Oberdorster to evaluate disposition of cadmium particles in lung (1989) and in calculation of critical urinary cadmium levels (1990).

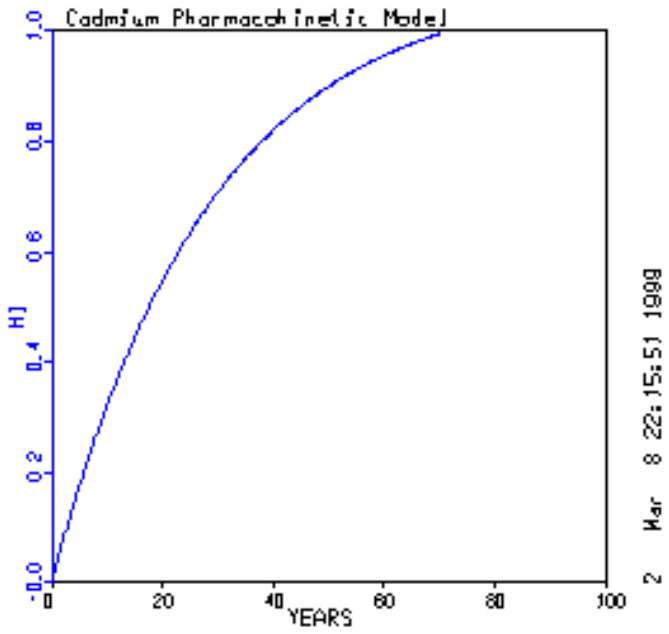


Figure B-2. Simulated time course (from model in Figure B-1) in humans to attainment of critical urinary cadmium excretion rate (CE), 2.7 ug/24 hr in 70 years, at 0.84 ug/kg-day. This value includes a component for dietary intake of 0.14 mg/kg-day. The difference or net allowable concentration of 0.7 ug/kg-day is the RfD at this level of background dietary exposure. The CE is derived from values given by Buchet et al., (1990). The X-axis is in years. The $t_{1/2}$ was 20 years.

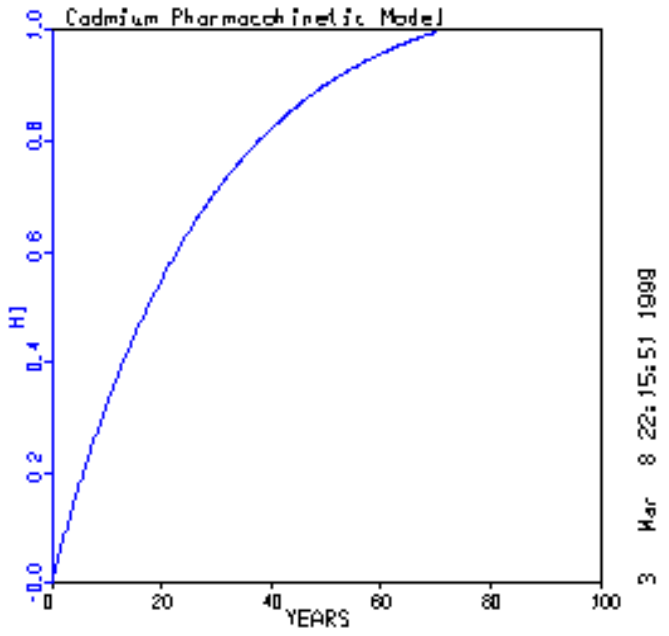
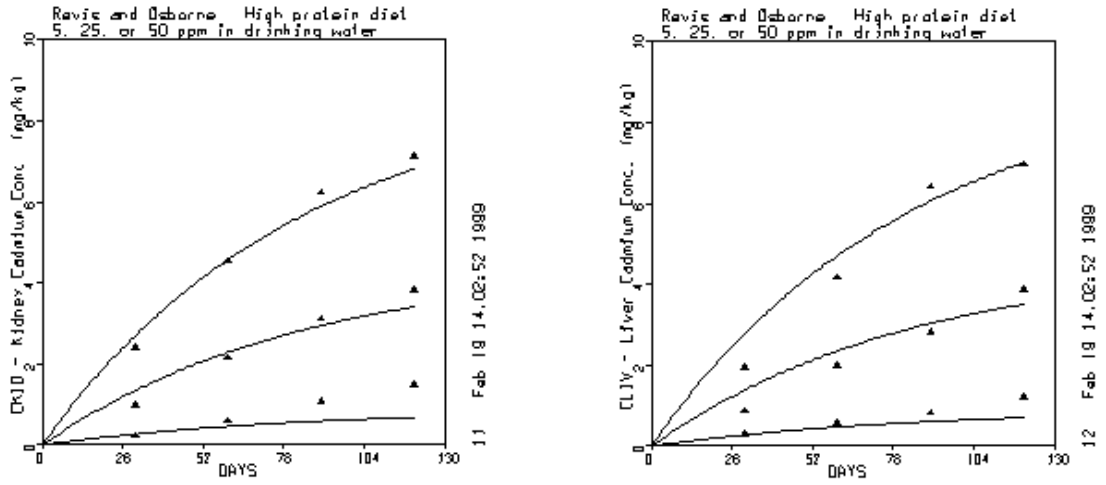
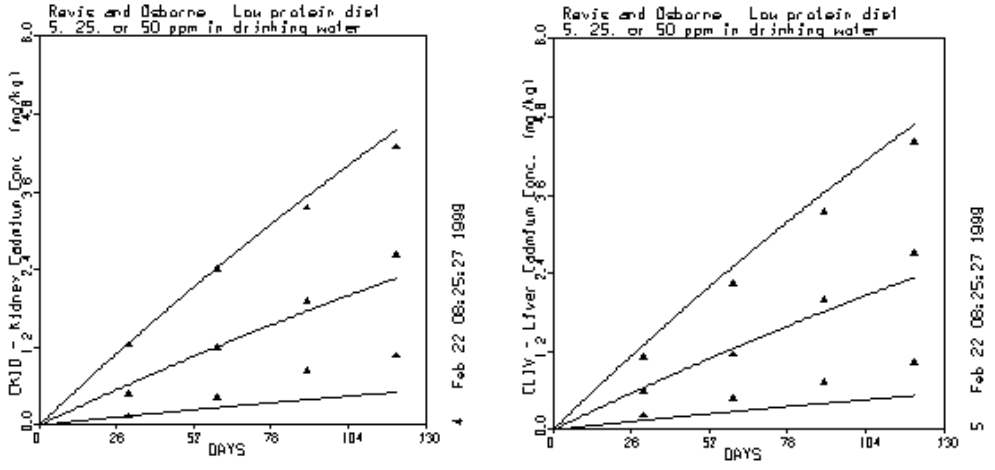


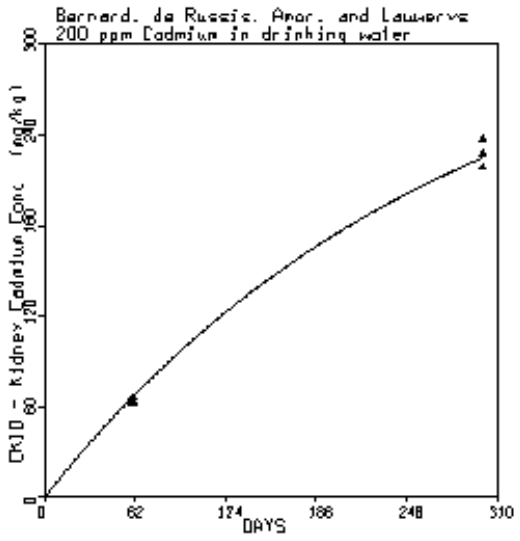
Figure B-3. Simulated time course (from model in Figure B-1) in humans of a continuous air concentration and daily dietary intake of cadmium (0.14 ug/kg-day) to attainment of critical urinary cadmium excretion rate (CE) of 2.7 ug/24 hr in 70 years. At this specific dietary background component, the air concentration necessary to attain the CE was 0.65 ug/m^3, i.e., the RfC at this daily dietary background rate of cadmium intake. The CE is derived from values given by Buchet et al., (1990). The X-axis is years. The $t_{1/2}$ for the urinary excretion rate was 20 years.

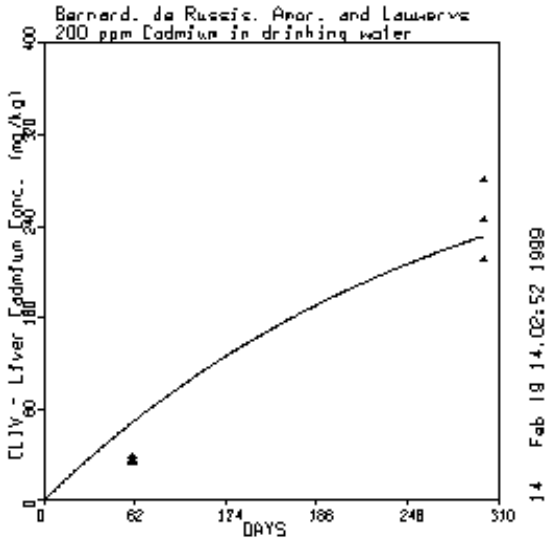


Figures B-4 and B-5. Data and simulations of cadmium levels in kidneys (CKID; B-4) or liver (CLIV; B-5) of male Sprague-Dawley rats fed a high protein diet and drinking water containing 5, 25, or 50 ppm cadmium and cadmium chloride (Revis and Osborne, 1984). Doses are micrograms ingested per kilogram cadmium in kidney and liver. Average weight of rats (180 g) was used in model simulations. (▲) are data points and solid lines are modeled simulations.



Figures B-6 and B-7. Data and simulations of cadmium levels in kidneys (CKID;B-6) or liver (CLIV;B-7) of male Sprague-Dawley rats fed a high protein diet and drinking water containing 5, 25, or 50 ppm cadmium and cadmium chloride (Revis and Osborne, 1984). Doses are micrograms ingested per kilogram cadmium in kidney and liver. Average weight of rats (180 g) was used in model simulations. (▲) are data points and solid lines are modeled simulations.





Figures B-8 and B-9. Data and model simulations of cadmium concentrations in the kidneys (CKID;B-8) or liver (CLIV;B-9) of female Sprague-Dawley rats given 200 ppm of cadmium as cadmium chloride in drinking water. Weights given in the study (175 grams) were used in the model simulations. Plots are concentration as mg/kg wet kidney weight versus time in days. Doses are micrograms ingested per kilogram cadmium in kidney and liver (Bernard et al., 1990). (▲) are data points and solid lines are modeled simulations.

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Appendix B-1
Toxicokinetic Model Code

```
PROGRAM: CADMIUM3.CSL -- Cadmium model
'October 3, 1996'

INITIAL

'Tissue Volumes (fraction of body weight)'
  CONSTANT      BW = 0.175    $'Body weight (kg)'
  CONSTANT   VKidC = 0.007   $'Kidney'
  CONSTANT   VLivC = 0.034   $'Liver'

'Fractional Coefficients'
  CONSTANT    fKid = 0.15    $'Fraction of cadmium in kidney'
  CONSTANT    fLiv = 0.75    $'Fraction of cadmium in liver'
  CONSTANT fUptake = 0.001   $'Fraction of dose absorbed'

'Partition Coefficients'
  CONSTANT     Pkt = 50      $'Kidney/Testes partition'
  CONSTANT     Plt = 50      $'Liver/Testes partition'

'Rate Constants (/hr)'
  CONSTANT  kUrine = 2.0e-4  $'Rate from central compartment to urine'

'Dosing Parameters'
  CONSTANT    Dose = 0.0     $'Oral dose (mg/kg/day)'

'Simulation Control Parameters'
  CONSTANT    TMax = 24.0    $'Time to terminate dosing (hrs)'
  CONSTANT   TStop = 24.0    $'Time to terminate simulation (hrs)'

CINTERVAL     CINT = 24.0

'Allometric Scaling of Tissue Volumes (kg)'
      VKid = VKidC * BW
      VLiv = VLivC * BW
    VOther = BW - (VKid + VLiv)

'Set Initial Values'
   fExcret = 1 - fUptake          $'Fraction of dose excreted in feces'
    fOther = 1 - (fKid + fLiv)    $'Fraction of cadmium in other tissues'

END               $'End of Initial Block'


DYNAMIC           $'Execution Block'

  ALGORITHM IALG = 2         $'Gear algorithm'


DISCRETE DoseOn    $'Start dosing'
```

```
  INTERVAL DoseInt = 100000.0          $'Interval to repeat dosing'
  SCHEDULE DoseOff .AT. T + TMax
  kDose = (Dose * BW) / 24.0           $'Convert mg/kg/day to mg/hr'
END

DISCRETE DoseOff   $'Turn off dosing'
  kDose = 0.0
END


DERIVATIVE         $'Definition of model derivative equations'

      Days = T/24.0

'Cadmium in Body Compartment'
    RABody = (fUptake * kDose) - (kUrine * ABody)
     ABody = INTEG(RABody,0.0)

'Cadmium in Feces'
   RAFeces = fExcret * kDose
    AFeces = INTEG(RAFeces,0.0)

'Cadmium in Kidney'
      AKid = fKid * ABody
      CKid = AKid / VKid

'Cadmium in Liver'
      ALiv = fLiv * ABody
      CLiv = ALiv / VLiv

'Cadmium in Testes'
    CTestK = CKid/Pkt
    CTestL = CLiv/Plt

'Cadmium in Other Tissues'
    AOther = fOther * ABody
    COther = AOther / VOther

'Cadmium in Urine'
   RAUrine = (kUrine * ABody)
    AUrine = INTEG(RAUrine,0.0)

'Fraction of Dose Excreted in Urine'
  IF (T.GT.0.0) FracEx = AUrine / TotDose

'Total Dose Given'
   TotDose = INTEG(kDose,0.0)

TERMT(T.GT.Tstop)
```

```
END             $ 'End of Derivative Block'
END             $ 'End of Dynamic Block'
END             $ 'End of Program'
```

Appendix D
Cancer Risk Output

The doses shown in the attached output differs from the oral human equivalent doses presented in the main document because the modeling was conducted on the animal doses, and dose conversions were conducted *after* the cancer modeling was completed. It does not matter whether dose conversions are conducted before or after the risk modeling, because all conversions are linear. To calculate the human equivalent dose from the oral animal doses provided in the output, multiply by $(0.35/70)^{1/4}$, or 0.266.

The $q1^*$ can be calculated from the output for testicular tumors by dividing the risk of 0.1E-5 by the lower bound on dose for that risk (in this case, 0.145E-4 mg/kg/day), for the animal $q1^*$. The animal $q1^*$ is then divided by the scaling factor of 0.266 for the human $q1^*$.

The exposure concentrations used for modeling of the lung cancer risk using the Takenaka et al. (1983) data were the duration adjusted human equivalent concentrations, calculated using the RDDR program (U.S. EPA, 1994). Adjustment was also made for differences in particle distributions between the cadmium particles in the animal study and cadmium particles in ambient air, as described in the main document. No further adjustments were made.

(The actual model output are available from the Chemical Manager, Gary L. Foureman 919-541-1183.)