Canadian Environmental Protection Act

Priority Substances List
Assessment Report

Cadmium and its Compounds

Government of Canada / Gouvernement du Canada
Environment Canada / Environnement Canada
Health Canada / Santé Canada

Canada

CANADA'S GREEN PLAN

Canadian Environmental Protection Act

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

CADMIUM AND ITS COMPOUNDS

Government of Canada
Environment Canada
Health Canada

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Synopsis

This assessment of cadmium and its compounds focuses on the forms of cadmium that are known to be found in the environment (i.e., several forms of inorganic cadmium).

Cadmium (Cd) is present in the Canadian environment as a result of both natural processes (including forest fires, volcanic emissions and weathering of soil, till, and bedrock) and human activities. Of the natural sources of cadmium to the environment, weathering and erosion of cadmium-bearing rocks represent perhaps the most important source. Approximately 1963 tonnes (t) of refined cadmium are produced, 23 t imported, and 1580 t exported each year in Canada (1992 estimates). Anthropogenic sources of cadmium entry to the Canadian environment include metal production (particularly base metal smelting and refining), stationary fuel combustion (power generation and heating), transportation, solid waste disposal, and sewage sludge application.

Although quantitative releases were not identified for all of these sources, the available data indicate that an estimated 159 t of cadmium are released annually to the Canadian environment as a result of domestic anthropogenic activities. Of this total, 92% is released to air and 8% is released to water. Approximately 340 t of cadmium wastes from the metal smelting and refining industry are deposited into landfills, although the amount of cadmium from this source that is potentially available to the Canadian environment is not known. The most recent estimates identified indicate that base metal smelting and refining operations account for 82% (130 t) of the total releases to air and water.

Cadmium does not break down in the environment, but it may be affected by physical and chemical processes that modify its mobility, bioavailability, and residence time in different environmental media. Atmospheric cadmium compounds (e.g., cadmium oxide) are predominantly in particulate form (fine particulates are more easily solubilized and more bioavailable than larger fractions), have relatively short tropospheric residence times, and are removed from air by wet and dry deposition. The mobility and bioavailability of cadmium in aquatic environments are enhanced under conditions of low pH, low hardness, low suspended matter levels, high redox potential, and low salinity. The movement of cadmium in soil and potential accumulation by biota is enhanced by low pH, low organic matter content, large soil particle size, and high soil moisture.

Mean levels of cadmium in some Canadian lakes in the vicinity of known anthropogenic sources (e.g., base metal smelters) have exceeded the estimated effects threshold for the most sensitive freshwater species *(Daphnia magna).* Mean levels and concentration ranges of cadmium in marine waters and sediments from two locations in Canada (Belledune Harbour, New Brunswick and Vancouver Harbour, British Columbia) have equalled or exceeded the estimated effects thresholds for the most sensitive marine species *(Mysidopsis bahia* and *Rhepoxynius abronius).* Mean levels of cadmium in soils near known sources (e.g., base metal smelters) from four provinces have exceeded the estimated effects threshold for the most sensitive soil. Species *(Aiolopus thalassinus* and *Spinacia olaracea).* Mean cadmium levels in kidney tissue of some Canadian mammalian wildlife and domestic species (e.g., narwhal) have exceeded the estimated

effects threshold for renal dysfunction based on critical concentrations determined in laboratory animals.

Atmospheric inorganic cadmium compounds (oxide, chloride, sulphide, and sulphate) have relatively short tropospheric residence times, low tropospheric concentrations, and do not absorb appreciable amounts of infrared radiation. Thus, inorganic cadmium compounds are not expected to contribute to global climate change. Inorganic cadmium compounds are not expected to react with ozone, and therefore, are not expected to contribute to stratospheric ozone depletion.

Based on estimation of the average daily intake of cadmium (total) from air, drinking water, food, and soil for various age groups in the general population, food is likely the most significant source of human exposure in Canada.

In several studies of workers, exposure to airborne cadmium compounds has been associated with increased mortality from lung cancer, but the increase may have been due, in part, to concurrent exposure to arsenic. However, principally on the basis of results of inhalation studies in animal species, inorganic cadmium compounds have been classified as "probably carcinogenic to humans", i.e., as substances for which there is believed to be some chance of adverse health effects at any level of exposure. For such substances, where data permit, estimated exposure is compared to quantitative estimates of cancer potency, to characterize risk and provide guidance for further action (i.e., analysis of options to reduce exposure). For inorganic cadmium compounds, such a comparison suggests that the priority for analysis of options to reduce exposure would be high.

In addition, renal tubular dysfunction has been observed in human populations exposed to cadmium in the workplace or in the general environment. While these effects were originally reported in populations having relatively high exposure to cadmium, in recent European studies, mild effects on the kidney have been associated with levels of cadmium at or near those to which a portion of the Canadian general population is exposed.

Based on available information, it is concluded that dissolved and soluble* forms of inorganic cadmium are entering the environment in a quantity or concentration or under conditions that are having or may have a harmful effect on the environment. It is concluded that inorganic cadmium compounds are not entering the environment in a quantity or concentration or under conditions that constitute a danger to the environment on which human life depends. Finally, it is concluded that inorganic cadmium compounds are entering the environment in a quantity or concentration or under conditions that may constitute a danger to human life or health in Canada.

***** The term "soluble" includes water-soluble forms of cadmium (e.g., cadmium chloride, cadmium sulphate, cadmium nitrate), as well as more stable forms (e.g., cadmium sulphide, cadmium oxide) that can be transformed and made more soluble under certain conditions of pH (e.g., acidic mine tailings) or redox potential (e.g., buried reducing sediment) in the environment.

1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the Minister of the Environment and the Minister of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined under Section 11 of the Act which states:

> "...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions
>
> (a) having or that may have an immediate or long-term harmful effect on the environment;
>
> (b) constituting or that may constitute a danger to the environment on which human life depends; or
>
> (c) constituting or that may constitute a danger in Canada to human life or health."

Substances that are assessed as "toxic" as defined under Section 11 may be placed on Schedule I of the Act. Consideration can then be given to developing regulations, guidelines, or codes of practice to control any aspect of these substances' life cycle, from the research and development stage, through manufacture, use, storage, transport, and ultimate disposal.

The substance "cadmium and its compounds" is included on the Priority Substances List. The assessment of whether "cadmium and its compounds" are "toxic", as defined under CEPA, was based on the determination of whether they **enter** or are likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota at levels that could cause adverse **effects.**

The assessment of "cadmium and its compounds" as a Priority Substance under Section 11 of CEPA has been limited to inorganic cadmium compounds. [There is no evidence that organocadmium compounds, in which the metal is bound covalently to carbon, occur in nature (WHO, 1992a), and elemental cadmium is rare, and will be oxidized to cadmium oxide in the environment.] The data presented in this report have also been restricted primarily to those cadmium compounds for which it is considered that there is sufficient information on their toxicity to conduct an assessment and that are known to be present in the environment, namely cadmium oxide, cadmium chloride, cadmium sulphate, and cadmium sulphide. (Data on other cadmium compounds have been included in the supporting documentation for "cadmium and its compounds" from both Departments.) Although to the extent possible, the toxicity of these individual cadmium compounds is addressed, the available data do not permit an assessment of exposure to individual cadmium compounds in the general environment. When

additional data on the speciation of cadmium in the environment has been obtained, as is suggested in Section 4.0 of this report, it may be possible to address individual compounds more fully. The term "cadmium" in this report refers to total inorganic cadmium, unless otherwise specified.

Data relevant to the assessment of whether cadmium and its compounds are "toxic" to the environment were identified through searches of commercial and government data bases (1986 to 1990) including: POLLUTION ABSTRACTS, CAB, BIOSIS, AQUAREF, TOXLINE, AQUIRE, ASFA, and Chemical Evaluation Search and Retrieval System (CESARS). Manual searches of pre-1986 to September 1993 issues of 68 scientific journals were also conducted, and provincial and federal agencies were contacted through the Federal-Provincial Advisory Committee on Environment. Data relevant to the assessment of whether cadmium and its compounds are "toxic" to the environment obtained after September 1993 were not considered for inclusion.

For the health-related sections, an extensive background review of the toxicological and epidemiological data was submitted under contract by BIBRA Toxicology International, Carshalton, Surrey, U.K. in March 1992. A literature survey was conducted by the contractor based on existing reviews of the toxicity of cadmium (IARC, 1987a;b; ATSDR, 1987; 1991; CEC, 1989; WHO, 1989; HSE, 1991), supplemented by key papers from the BIBRA toxicity data base and manual searches of primary, secondary, and tertiary hardcopy sources. In addition, to identify more recent toxicological data relevant to the preparation of this assessment, a literature search was conducted in January 1993 in the TOXLINE data base for 1992 only.

To identify data relevant to the estimation of exposure of the general population to cadmium, literature searches for cadmium levels in the environment were conducted in March 1991 on the following data bases: Environmental Bibliography (1989 to 1991 only), ENVIROLINE, POLLUTION ABSTRACTS (1989 to 1991), MICROLOG, Cooperative Documents Project (CODOC), and Environment Canada Departmental Library Catalogue (ELIAS). Searches were also conducted in March of 1992 for information on levels of cadmium in human tissues and fluids, and on the metabolism of cadmium, on the following data bases: DIALOG (to 1966), BIOSIS (to 1969), CODOC, Canada Institute for Scientific and Technical Information (CISTIMON), ELIAS, and Medline (to 1989).

Additional relevant information was obtained from the Drinking Water Surveillance Program of the Ontario Ministry of the Environment, the Brunswick Mining and Smelting Corporation in New Brunswick, Cominco Metals of Trail, British Columbia, Noranda Copper Smelting and Refining at Rouyn-Noranda, Quebec, and the Manitoba Department of Environment.

These sources were supplemented with manual searches of CURRENT CONTENTS throughout 1992 and the first half of 1993. Data identified following the period of peer review of the section related to assessment of effects on human health (i.e., September, 1993) were not considered for inclusion.

As part of the review and approvals process established by Environment Canada for its contributions to assessment reports, environmental sections of this document were reviewed by: Dr. Leah Bendell-Young (University of Ottawa), Dr. Uwe Borgmann (Fisheries & Oceans Canada), Dr. Scott Brown (Fisheries & Oceans Canada), Dr. Matt John (Agriculture Canada), Dr. Jack Klaverkamp (Fisheries & Oceans Canada), Dr. Dianne Malley (Fisheries & Oceans Canada), Dr. Sankar Ray (Fisheries & Oceans Canada), Dr. Rudolph Wagemann (Fisheries & Oceans Canada), and Dr. Norman Yan (Ontario Ministry of the Environment).

The risk assessment and the supporting documentation related to the effects on human health of cadmium and its compounds were externally peer reviewed by Dr. Bob Goyer (Chapel Hill, NC), Dr. David Bayliss (Epidemiologist, United States Environmental Protection Agency, Washington, DC), Dr. William Coker (Geological Survey of Canada; supporting documentation only), BIBRA Toxicology International (risk assessment only), and Mr. Hennie Veldhuizen (Noranda Minerals Inc., Toronto, Ont.; supporting documentation only) and the Mining Association of Canada (supporting documentation only). The Assessment Report and supporting documentation related to the effects on human health were subsequently approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health Canada.

Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether cadmium and its compounds are "toxic" under CEPA have been critically evaluated by the following Health Canada staff (human exposure and effects on human health) and Environment Canada staff (entry, environmental exposure and effects):

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U.A. Schneider	R. Newhook

In this report, a synopsis concerning "cadmium and its compounds" that will appear in the Canada Gazette is presented. Section 2.0 is an extended summary of the technical information that is the basis of the assessment. The assessment of whether cadmium and its compounds are "toxic" is presented in Section 3.0. Supporting documentation that presents the technical information in greater detail has also been prepared.

Copies of this Assessment Report and the unpublished supporting documentation are available upon request from:

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2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production, and Uses

Cadmium (Cd) is a metal of sub-group IIb (which also includes zinc and mercury) of the transition series in the Periodic Table of Elements. The CAS Registry No. for cadmium is 7440-43-9. It is a soft, silver-white, blue-tinged, lustrous metal, with a melting point of 321^0C, and a boiling point of 765^0C (Nriagu, 1980a). Elemental cadmium has an atomic number of 48, an atomic weight of 112.4 g/mol, and a density of 8.65 g/cm^3 at 20^0C (Nriagu, 1980a). In nature, cadmium occurs most commonly in the plus II oxidation state. The principal cadmium-bearing minerals are the zinc sulphides, sphalerite, and wurtzite, in which cadmium occurs as an impurity (NRCC, 1979; Nriagu, 1980a). Greenockite and hawleyite, both cadmium sulphides (CdS), as well as monteponite (CdO) and otavite ($CdCO_3$), are formed by weathering of primary sphalerite (NRCC, 1979).

Metallic cadmium is essentially insoluble in water; however, several of its compounds are freely soluble { such as cadmium chloride ($CdCl_2$), cadmium bromide ($CdBr_2$), cadmium iodide (CdI_2), cadmium nitrate [$Cd(NO_3)_2$], and cadmium sulphate ($CdSO_4$) (Weast, 1986; Budavari *et al.,* 1989)}. The water-insoluble compounds of cadmium, such as cadmium oxide (CdO), cadmium sulphide (CdS), cadmium carbonate ($CdCO_3$), cadmium *ortho*-phosphate [$Cd_3(PO_4)_2$], and cadmium fluoride (CdF_2) (Weast, 1986) may be solubilized under strong oxidizing or acidic conditions (WHO, 1992b). Cadmium and its major atmospheric compounds (CdO, $CdCl_2$, CdS, and $CdSO_4$) do not absorb infrared radiation to any appreciable degree (Sadtler, 1982). These compounds are not expected to be involved in atmospheric ozone reactions (Manahan, 1984; Bunce, 1990).

While a number of different techniques (including polarography, ion chromatography, and mass spectroscopy) are available to measure concentrations of cadmium in solutions such as natural waters and the acid digests of solid materials, the most common methods use atomic absorption spectrometry (AAS) and inductively-coupled plasma emission spectrometry (ICP) (Skoog *et al.,* 1988). Typical detection limits for modern instruments measuring cadmium in solution are 1 µg/L for flame AAS, 0.001 µg/L for graphite furnace AAS, 800 µg/L for flame emission spectrometry, 2 µg/L for ICP (Skoog *et al.*, 1988), and 0.2 µg/L for ICP-MS (Hall, 1992).

Cadmium is produced commercially as a by-product of zinc refining (MacLatchy, 1992) and may also be recovered from recycled cadmium products or industrial scrap. Global production of refined cadmium metal for 1990 was estimated at 21 800 t, which represents an increase of approximately 5% over 1989 (Hoskin, 1991). Canada is the fourth largest producer of refined cadmium in the world with an output of 1963 t in 1992 (Keating, 1993). Base metal smelters and refineries in four provinces account for most of the Canadian production: Quebec (Valleyfield, 455 t); British Columbia (Trail, 570 t); Ontario (Timmins, 640 t), and Manitoba (Flin Flon, 200 t) (EMRC, 1991). The annual production of cadmium in Canada has been relatively stable since 1984, with the mean

level for this period being almost 1570 t annually (Koren, 1992). Zinc concentrate processed by Canadian zinc smelters and refineries typically contains 0.1 to 0.3% cadmium (MacLatchy, 1992). The largest source of cadmium processed in Canada is from zinc concentrates imported from the Red Dog Mine in Alaska, U.S.A. (Koren, 1992).

Between 65% and 89% of Canadian output was exported (primarily cadmium metal) from 1985 to 1990, mainly to the United States, Japan, and France (Koren, 1992). In 1990, this amounted to 1580 t, while 383 t remained in Canada (Koren, 1992). Imports of cadmium into Canada in 1992 were estimated at 39.3 t (23 t and 16.3 t of refined cadmium and cadmium compounds, e.g., cadmium oxide, respectively) (Keating, 1993). It is not known whether these import figures include nickel/cadmium (Ni/Cd) batteries (6.6×10^6 units in 1988), which accounted for imports of 36.7 t (Capowski, 1992). Furthermore, the latter figure may also be underestimated by as much as four times because it may exclude Ni/Cd batteries that are sealed into rechargeable appliances, which represent 80% of the total Ni/Cd battery market (Capowski, 1992). Nickel/ cadmium batteries, however, are not manufactured in Canada (Capowski, 1992).

Globally, cadmium has five main applications: Ni/Cd batteries (approaching 50% of the world's consumption of cadmium), coatings (20%), pigments (18%), stabilizers in plastics and synthetic products (6%), and alloys (6%) (Hoskin, 1991). Small amounts of cadmium compounds are also present in television picture tubes, telephone and trolley wires, automobile radiators, control rods and shields for nuclear reactors, motor oils, and in curing agents for rubber (CCREM, 1987). Domestic industrial consumption in Canada has been increasing steadily in recent years: 18.9 t cadmium in 1987; 20.0 t in 1988; 28.8 t in 1989, and 35.2 t in 1990 (Hoskin, 1991; Koren, 1992). Electroplating accounted for 60 to 77% of the total Canadian consumption between 1987 and 1989, with solder, alloys, chemicals and pigments making up the remainder (Hoskin, 1991).

2.2 Entry into the Environment

The principal natural sources of cadmium entering the atmosphere include windblown transport of soil particles, forest fires, and volcanic emissions (Nriagu, 1989). Enrichment factors to help estimate the relative contributions of natural versus anthropogenic cadmium releases in Canada are not available. Global natural emissions of cadmium to the atmosphere are estimated to be approximately 1300 t annually (Nriagu, 1989). It is estimated that globally, anthropogenic activities add roughly 3 to 10 times more cadmium (3100 to 12 000 t/yr) into the atmosphere than natural sources; 65 to 85% of this originates from the smelting of base metal ores (Yeats and Bewers, 1987; Nriagu and Pacyna, 1988). Fossil fuel combustion accounts for a further 6 to 7% (Nriagu and Pacyna, 1988).

Complete quantitative inventories of cadmium releases from all known or potential anthropogenic sources in Canada are not available. The available data compiled by Environment Canada (Table 1) indicate that an estimated total of 159 t of cadmium are released annually to the Canadian environment. Of this estimate, 147 t are released into the atmosphere (predominantly as particulate cadmium oxide), while 12 tonnes are

Table 1 Estimates of Anthropogenic Cadmium Releases and Disposal in the Canadian Environment

Source/Sector	Estimated Annual Releases of Cadmium (tonnes)				
	Air	Land Disposal	Water	Total	Reference[3]
Metal Production					
Base Metal Smelters and Refineries	120	(340)[1]	10	130	MacLatchy (1992)
Iron and Steel Production	5	NA[2]	1	≥6	Jaques (1987), Hamdy (1991)
Stationery Fuel Combustion					
Power	12	NA	NA	≥12	Jaques (1987)
Commercial, Residential, and Industrial Heating	1	NA	NA	≥1	
Transportation					
Rail	1	NA	NA	≥1	Jaques (1987)
Marine	1	NA	NA	≥1	Jaques (1987)
Road	2	NA	NA	≥2	Jaques (1987)
Tire Wear	<0.1	NA	NA	<0.1	APCD (1976)
Solid Waste Disposal					
Incineration (Refuse And Sewage Sludge)	5	NA	NA	≥5	Jaques (1987)
Tire Disposal	NA	0.1	NA	NA	APCD (1976) and Morgan (1990)
Landfill Refuse	NA	NA	NA	NA	
Agriculture					
Sludge Application	NA	NA	NA	NA	
Phosphate Fertilizer Application	NA	NA	NA	NA	
Other[4]	NA	NA	1	1	Brown, 1992
Total	147.1	(340.1)	12	159.1	

1 Includes 80 tonnes as slag and 260 tonnes as solid waste residue or sludge disposed. The bioavailability of this amount is unknown.

2 NA = no data were identified or available

3 Data of MacLatchy (1992) are for 1988 to 1990; Jaques (1987) are for 1982 (using 1970s emission factors); APCD (1976) are for 1972, and Morgan (1990) are for 1988.

4 Includes data for Ontario only for the following industries: pulp and paper, petroleum refining, chemical manufacturing, metal casting.

released into aquatic environments (as hydrated cadmium ion or in ionic complexes). Approximately 340 t of cadmium slag, sludges, and solid wastes are estimated to be disposed of on land. Although land disposal accounts for most of the total cadmium wastes, the nature of this material and the amount that is bioavailable is unknown. According to the currently available estimates, base metal smelters (primarily lead-zinc) account for the largest percentage [82% (130 t)] of total cadmium released to the Canadian environment.

2.3 Exposure-related Information

2.3.1 *Fate*

In nature, two oxidation states of cadmium (0 and +2) are possible, however, the zero or metallic state is rare (NRCC, 1979). Cadmium does not break down in the environment, but its mobility, bioavailability, and residence times in different environmental media may be affected by physical and chemical processes. Atmospheric cadmium compounds (e.g., cadmium oxide) exist predominantly in a particulate form (fine particulates are more easily solubilized and more bioavailable than larger fractions), have relatively short tropospheric residence times (1 to 4 weeks) and are removed from air by wet and dry deposition. Cadmium mobility and bioavailability in aquatic environments are enhanced by low pH, low hardness, low suspended matter levels, high redox potential, and low salinity. The movement of cadmium in soil and potential accumulation by biota is enhanced by low pH, low organic matter content, large soil particle size, and high soil moisture content.

Cadmium compounds emitted into the air from high temperature sources (>600^{0}C) oxidize rapidly to cadmium oxide (CdO) (Nriagu, 1980b). Virtually all airborne cadmium originating from combustion sources is associated with aerosols and fine particulate in the inhalable range (<10 µm)(ATSDR, 1993). Little information is available on atmospheric transformation processes for cadmium. The common cadmium compounds found in air (e.g., cadmium oxide, cadmium chloride, and cadmium sulphate) are resistant to photolytic degradation (ATSDR, 1993). Cadmium may be dissolved in water vapour and subsequently removed by wet deposition (Fones and Nimmo, 1993). In atmospheric aerosols measured in Ontario, the water-soluble fraction of cadmium is increased in areas with air masses of high acidity (Dvonch *et al.*, 1993). Also, most of the cadmium released into the atmosphere is deposited within four weeks, and generally within 1000 km of the source (Bewers *et al.*, 1987).

Theoretically, free cadmium ion (Cd^{++}) predominates in dissolved phases (Astruc, 1989), with the free ion considered to be the most bioavailable form of the metal (Rainbow, 1990). In nature, however, certain physical/chemical factors influence the form and fate of cadmium, and ultimately its bioavailability. Concentrations of dissolved cadmium in acidic lakes (pH 5.0 to 6.5) are consistently higher than those in more neutral systems (Steinnes, 1990). Increased acidity inhibits the sorption of cadmium to particles and the formation of precipitates (both of which effectively remove cadmium from the water column)(Stephenson and Mackie, 1988). In Canadian freshwater systems like the

St. Lawrence River and Lake Erie, 60 to 90% of total Cadmium may occur in the "dissolved" phase (i.e., <0.45 µm), although at high concentrations of suspended particulate matter (e.g., >200 mg/L), the particulate phase predominates as a result of particle scavenging (Lum, 1987; Malley *et al.*, 1989). Cadmium precipitated and sorbed to particles is usually carried to bottom sediments (ATSDR, 1993). After particle decomposition, by chemical oxidation of organic detritus, for example, cadmium is redissolved and subsequently recycled into overlying waters. In anaerobic sediment, however, cadmium can be immobilized as cadmium sulphide. As cadmium does not form volatile compounds, water-to-air partitioning does not occur (ATSDR, 1993). Consequently, site-specific factors (e.g., pH, suspended matter levels, redox potential) will determine the fate of cadmium in freshwater environments. However, cadmium tends to be more mobile than other metals and exists predominantly as the dissolved cation in freshwaters (Callahan *et al.*, 1979).

Proportions of dissolved and particulate cadmium in marine waters are primarily influenced by suspended matter content and salinity regime. As salinity increases from estuarine to marine environments, the proportion of soluble cadmium chloride species increases (e.g., CdCl, $CdCl_2$, $CdCl^-_3$)(Bewers *et al.*, 1987). However, cadmium uptake is slower in marine waters (due to competition with calcium) than in freshwater/estuarine environments (Langston, 1990); therefore, increased salinity also confers protection to aquatic species. Most of the particulate cadmium (~95%) entering marine environments from continental runoff is retained in estuaries, whereas 60 to 85% of the dissolved form of cadmium may enter the marine pelagic environment (Bewers *et al.*, 1987; Lum, 1987). A significant proportion of the cadmium entering oceans is eventually deposited in deep ocean sediments. However, there appears to be a consistent pattern of recycling of cadmium in oceans, that closely resembles nutrient-like behaviour (i.e., low concentrations in surface waters relative to deep waters) (Burton and Statham, 1990). Up to 60% of the cadmium can be bound to or incorporated in organic matter, and as such, can be constantly removed from surface waters through settling within biogenic detritus in the euphotic zone or into deeper benthic sediments (Bewers *et al.*, 1987). Through decomposition and oxidation in sediments, much of the cadmium associated with organic matter above the thermocline is released to overlying waters and recirculated to the euphotic zone via upwelling (Bewers *et al.*, 1987).

Soil pH is the principal factor determining the mobility of cadmium in soil (Chanmugathas and Bollag, 1987; Eriksson, 1989; Christensen, 1989; Lodenius and Autio, 1989). Under acidic conditions (pH < 6.0), the mobility of cadmium is enhanced (Tyler and McBride, 1982; Lodenius and Autio, 1989); significant movement of cadmium may occur within soil profiles and into other environmental compartments (e.g., surface and groundwater, sorption by plants and animals) (Bergkvist, 1986; Bergkvist *et al.*, 1989; LaZerte *et al.*, 1989). The mobility of cadmium is restricted by its sorption to organic matter, clays, and hydrous metal oxides (Christensen, 1984; 1989; Eriksson, 1989). Cadmium mobility tends to be greater in sandy soils than in organically-rich soils and cadmium has a greater affinity for organic matter than for clays or oxides (Blume and Brummer, 1991). The transformation of insoluble cadmium (e.g.,

cadmium sulphides) to more soluble forms in soils may be mediated by microbial activity, under both aerobic and anaerobic conditions (Chanmugathas and Bollag, 1987).

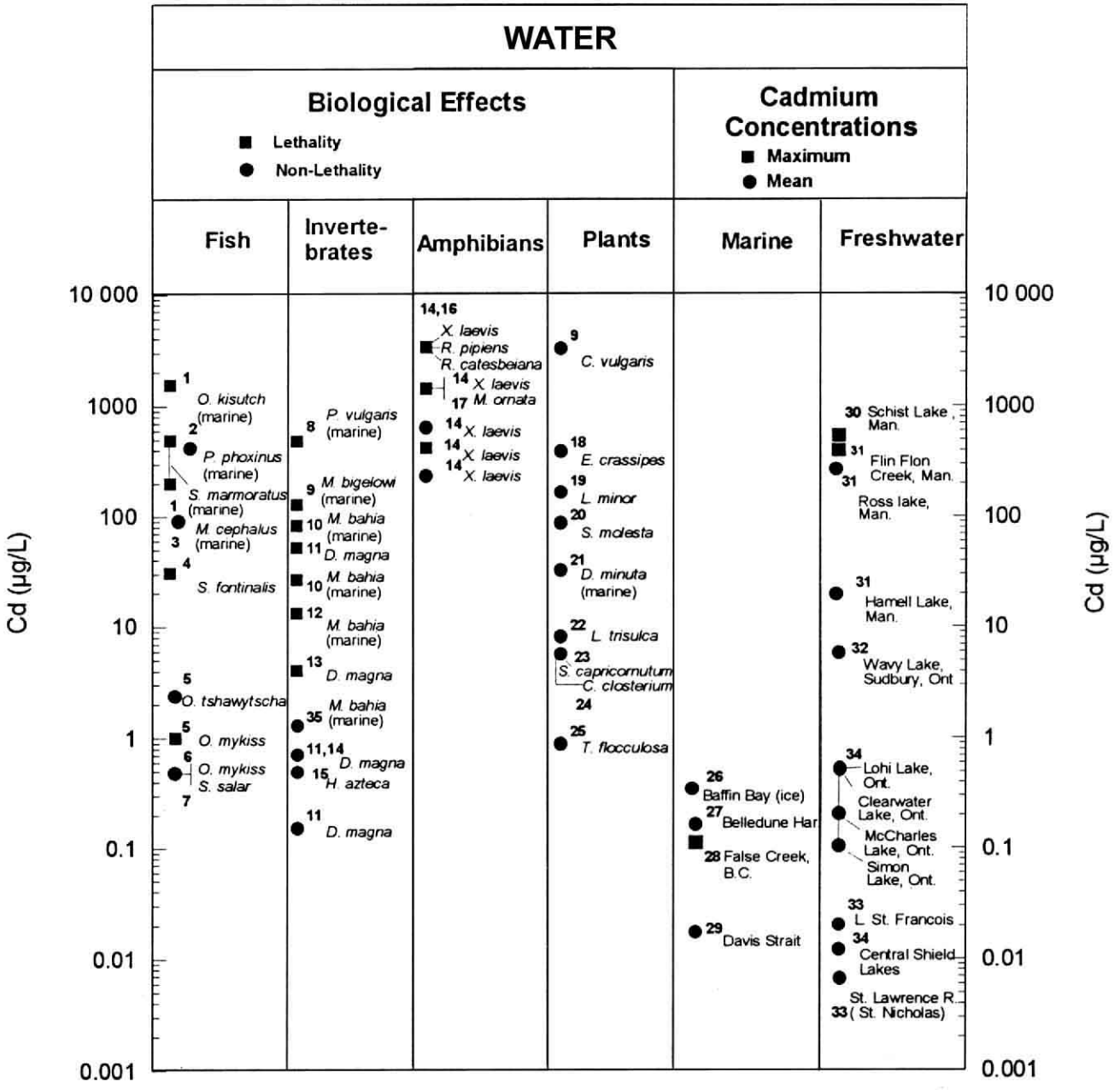
Biota, particularly plants, may play a significant role in biogeochemical cycling of cadmium in certain environments. In nearshore marine systems, macrophytes may contain the largest biological pool of cadmium, with decomposition and growth representing the greatest biological fluxes (Gallagher and Kibby, 1980). Plants may play a similar role in cadmium cycling in some freshwater lakes (Outridge and Noller, 1991). In forest ecosystems, plant biomass may also contain significant amounts of the total cadmium (27% in one instance), although most remains in organic soil horizons (Heinrichs and Mayer, 1980; Van Hook *et al.*, 1977). Although biota may bioaccumulate cadmium, most evidence suggests that little or no biomagnification occurs (Kay, 1985) in either aquatic or terrestrial ecosystems (Guthrie *et al.*, 1979; Wren *et al.*, 1983; van Straalen and van Wensem, 1986; Brams *et al.*, 1989; Levine *et al.*, 1989; Beyer *et al.*, 1990).

2.3.2 *Concentrations*

Cadmium has been detected in most environmental media in Canada including air, freshwater, seawater, soils, sediments, and biota (Figures 1 to 4). In general, there is a lack of data on speciation of cadmium in the environment, although it is known that much of the cadmium found in mammals, birds, fish, and in components of the diet derived from these animals is probably bound to protein molecules such as metallothionein. The cadmium concentrations in the various environmental media were reported as total cadmium, unless otherwise specified.

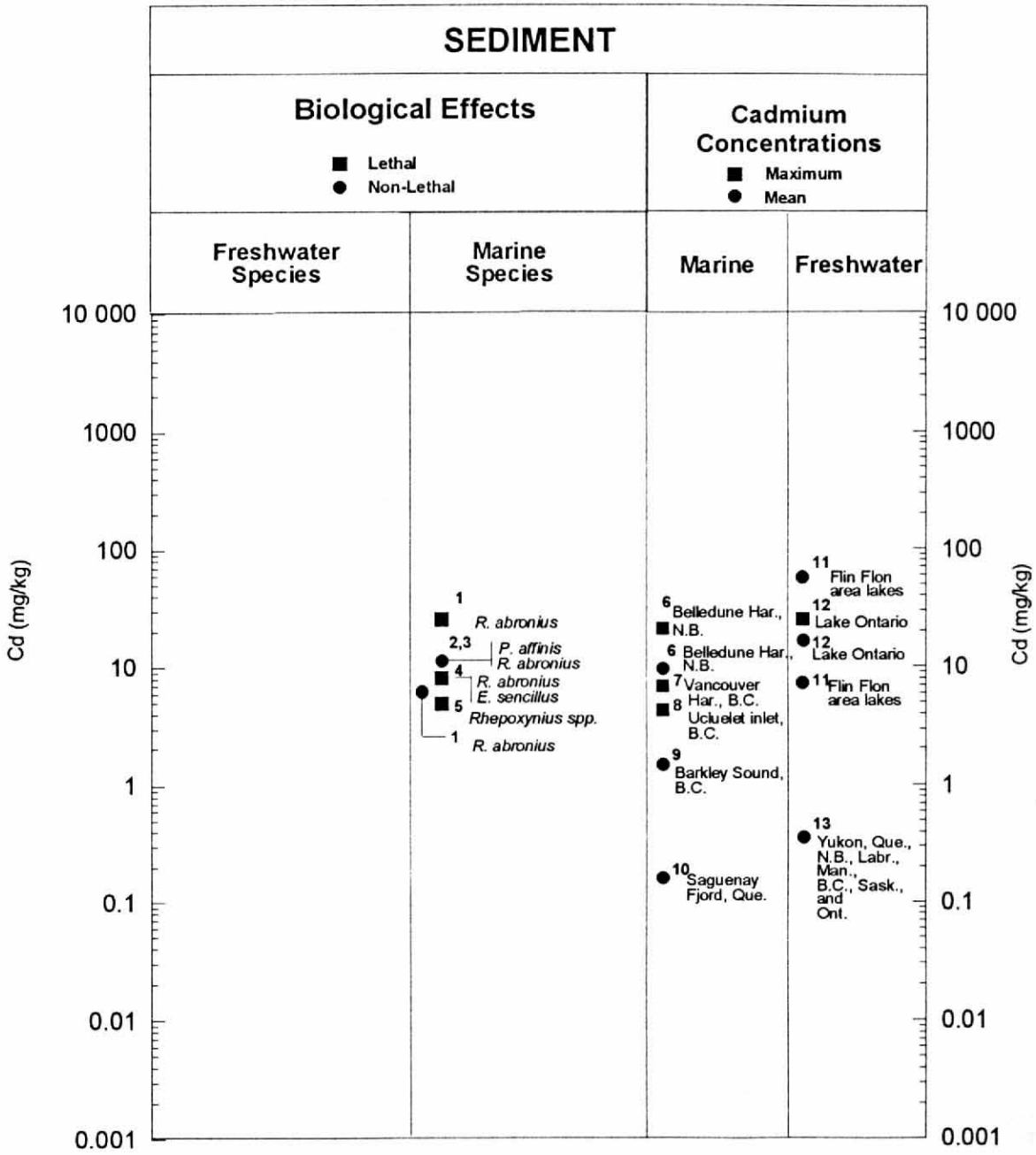
Concentrations of particulate cadmium in ambient air in Canada reflect proximity to industrial and urban areas, and are comparable to values recorded in other parts of the world. The mean concentrations of inhalable (<10 µm aerodynamic diameter) cadmium at 15 sites in 11 cities for the period 1984 to 1989 ranged from 1 ng/m^3 in Winnipeg and Ottawa to 4 ng/m^3 at sites in Windsor and Montreal, with a mean value for all sites of 2 ng/m^3 (EC, 1991). Geometric mean concentrations of cadmium in air from 23 stations in southern, central, and northern Ontario in 1982 were 0.42 ng/m^3 (0.24 to 0.72 ng/m^3), 0.46 ng/m^3 (0.27 to 0.63 ng/m^3), and 0.31 ng/m^3 (0.11 to 0.85 ng/m^3), respectively (Chan *et al.*, 1986). The mean cadmium concentrations from this regional air sampling study ranged from 0.11 ng/m^3 (Pickle Lake, northern Ontario) to 0.85 ng/m^3 (Gowganda, northern Ontario)(Chan *et al.* 1986).

Considerably higher levels of cadmium in ambient air have been observed in the vicinity of certain smelters in Canada. The air in Flin Flon, site of a copper/zinc base metal smelter, sampled for a 24-hour period every six days from December 1988 to March 1991, contained between 5 and 522 ng of Cd/m^3, with a mean value of 46 ng of Cd/m^3 (Bezak, 1991a). The mean annual airborne concentrations of cadmium near other smelters have been similar [20 to 40 ng/m^3 at various sites in the vicinity of a lead/zinc smelter in Trail, British Columbia in 1990 (Kenyon, 1991); 10 to 30 ng/m^3 at three sites in the vicinity of a lead smelter at Belledune, New Brunswick between 1988 and 1990 (Murphy, 1991)) or lower [geometric mean values of 1.0 to 4.3 ng/m^3 at three stations



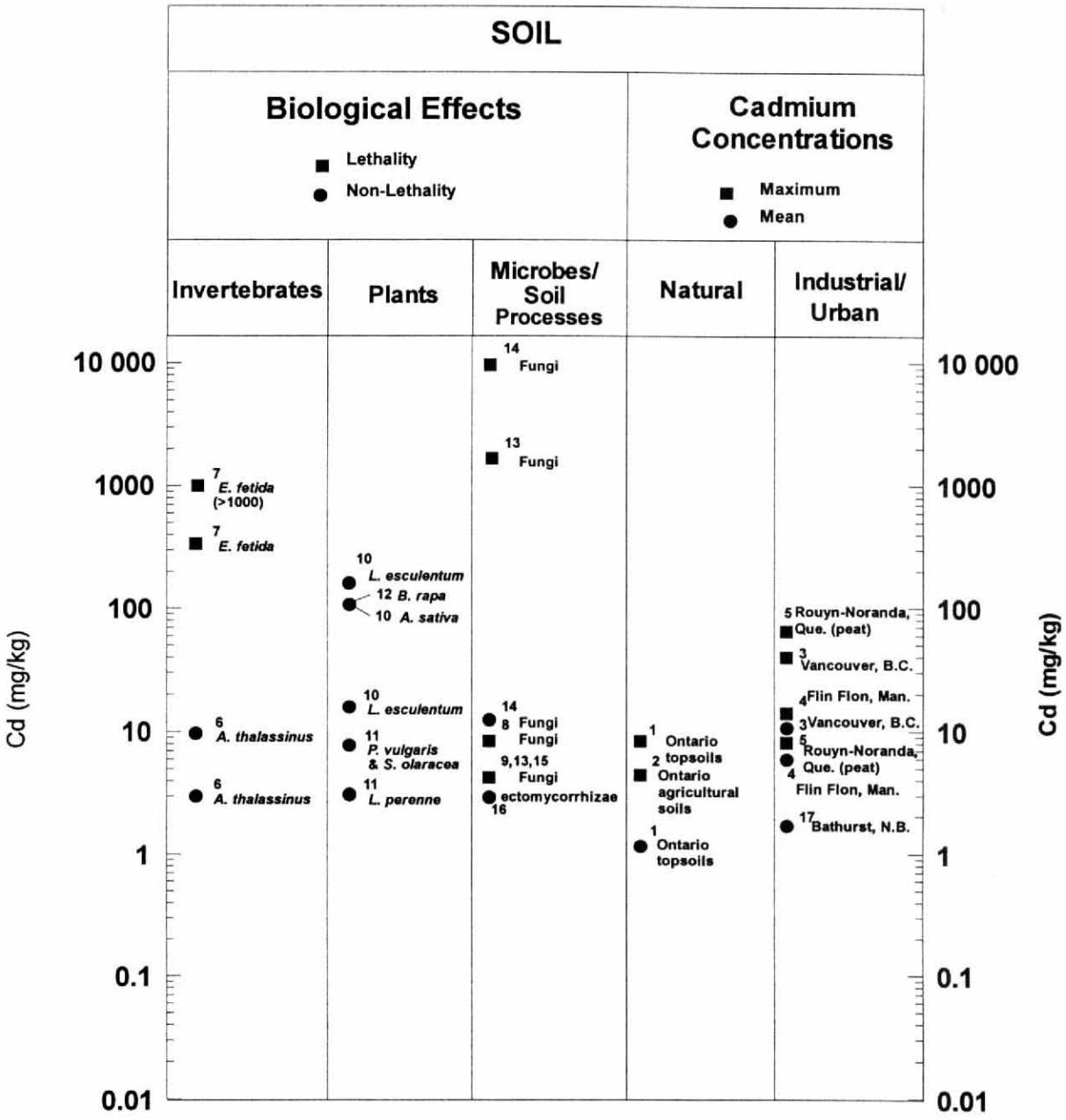
1. Dinnel *et al.*, 1989
2. Bengtsson, 1977
3. Hilmy *et al.*, 1985
4. Finlayson and Verrue, 1982
5. Chapman, 1978
6. Cusimano *et al.*, 1986
7. Rombough and Garside, 1982
8. Eisler, 1971
9. Gentile *et al.*, 1982
10. Voyer and Modica, 1990
11. Biesinger and Christensen, 1972
12. De Lisle and Roberts, 1988
13. Baird *et al.*, 1991
14. Canton and Slooff, 1982
15. Borgmann *et al.*, 1991
16. Zettergren *et al.*, 1991
17. Rao and Madhyastha, 1987
18. Nir *et al.*, 1990
19. Wang, 1986
20. Outridge and Hutchinson, 1991
21. Visviki and Rachlin, 1991
22. Huebert and Shay, 1991
23. Sedlacek *et al.*, 1981
24. Berland *et al.*, 1976
25. Adshead-Simonsen *et al.*, 1981
27. Uthe *et al.*, 1986
26. Campbell and Yeats, 1982
28. Stukas and Erickson, 1984
29. Campbell and Yeats, 1982
30. McFarlane *et al.*, 1979
31. Jackson, 1978
32. Keenan and Alikhan, 1991
33. Lum *et al.*, 1991
34. Stephenson and Mackie, 1988
35. Voyer and McGovern, 1991

Figure 1 **Range of Cadmium (Cd) Concentrations in Canadian Surface Waters and Levels that Induce Adverse Effects on Aquatic Biota**



1. Swartz *et al.*, 1985
2. Sundelin, 1984
3. Mearns *et al.*, 1986
4. Oakden *et al.*, 1984a
5. Oakden *et al.*, 1984b
6. Uthe *et al.*, 1986
7. Goyette and Boyd, 1989
8. Pedersen *et al.*, 1989
9. Harding and Thomas, 1987
10. Pelletier and Canuel, 1988
11. Harrison and Klaverkamp, 1990
12. Mayer and Manning, 1990
13. GSC, 1991

Figure 2 **Range of Cadmium (Cd) Concentrations in Canadian Sediments and Levels that Induce Adverse Effects on Biota**



1. Bewers *et al.*, 1987
2. Webber and Shamess, 1987
3. Golder Assoc., 1989
4. Pip, 1991
5. Dumontet *et al.*, 1990
6. Schmidt *et al.*, 1991
7. van Gestel and van Dis, 1988
8. Naidu and Reddy, 1988
9. Kobus and Kurek, 1990
10. Adema and Henzen, 1989
11. Coppola *et al.*, 1988
12. Gunther and Pestemer, 1990
13. Haanstra and Doelman, 1991
14. Doelman and Haanstra, 1989
15. Reber, 1989
16. Dixon and Buschena, 1988
17. Sergeant and Westlake, 1980

Figure 3 **Range of Cadmium (Cd) Concentrations in Canadian Soils and Levels that Induce Adverse Effects on Biota**

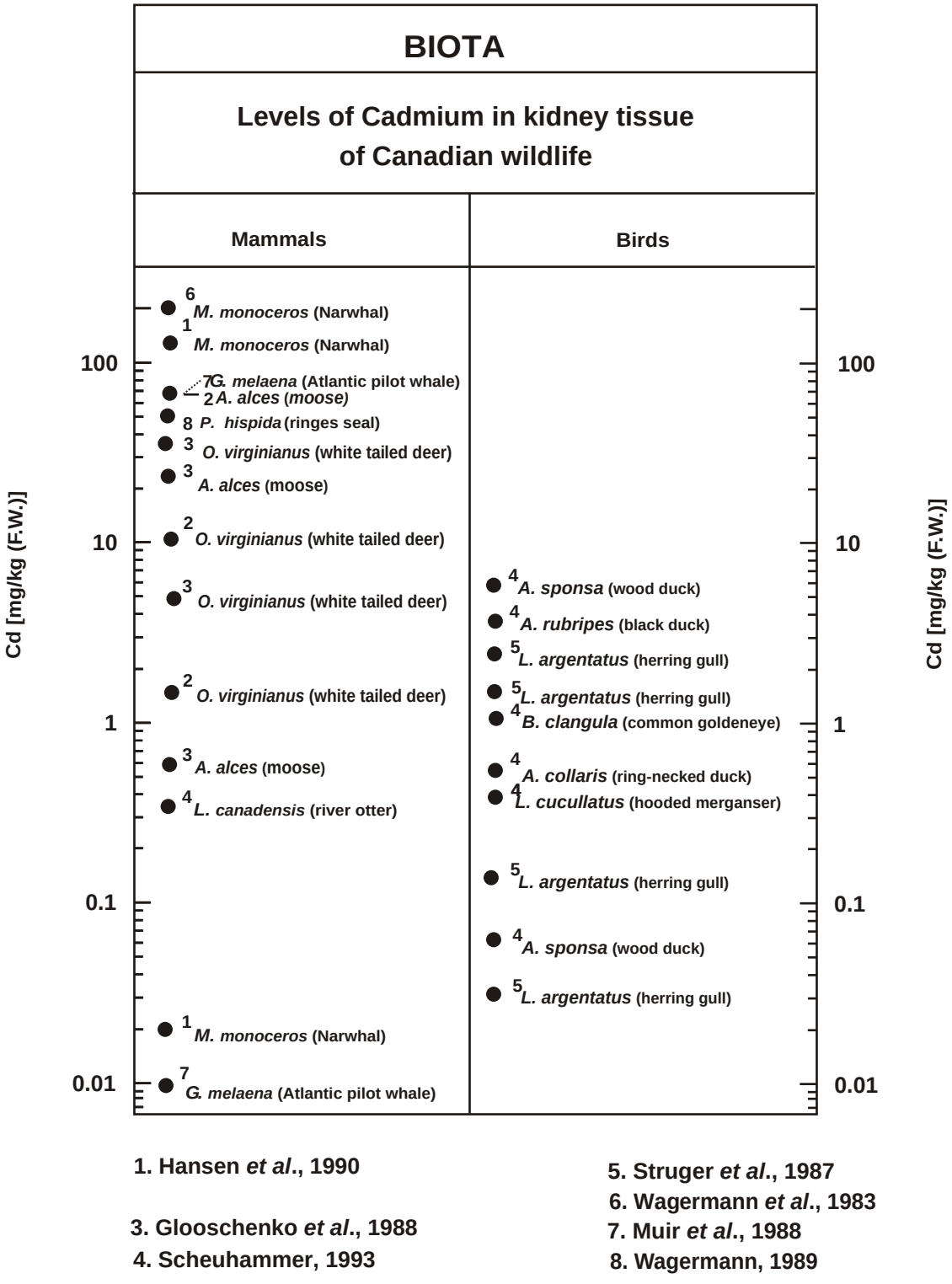


Figure 4 **Range of Cadmium (Cd) Concentrations in Kidney of Canadian Mammalian and Avian Species**

0.8 to 2.5 km downwind of the Home copper smelter at Noranda, Quebec (Moulins, 1991)].

No data were identified on concentrations of cadmium in the indoor air of residential dwellings.

Mean levels of cadmium (1987 to 1991) in surface waters from individual provinces across Canada were obtained from the national water quality data base (NAQUADAT/ENVIRODAT, 1992). The mean values and ranges were: British Columbia, 0.2 µg Cd/L (<0.1 to 8.6 µg Cd/L, n = 2399); Yukon, 0.1 µg Cd/L (<0.1 to 1.3 µg Cd/L, n = 359); Northwest Territories, 0.4 µg Cd/L (<0.1 to 15.4 µg Cd/L, n = 903); Alberta, 0.3 µg Cd/L (<0.1 to 112 µg Cd/L, n = 652); Saskatchewan, 0.1 µg Cd/L (<0.1 to 0.4 µg Cd/L, n = 388); Manitoba, 0.2 µg Cd/L (<0.1 to 2.2 µg Cd/L, n = 481); Quebec, 0.3 µg Cd/L (<0.1 to 10.8 µg Cd/L, n = 750) NAQUADAT/ ENVIRODAT, 1992). The proximity of sampling sites to known or potential sources of Cadmium was not identified in this analysis.

Additional data are also available for more than 70 lakes throughout Ontario (1980 to 1987) and vary widely, depending on the proximity to potential cadmium sources. Mean concentrations of cadmium (n> 100) ranged from 0.011 µg/L for central Shield lakes to 4.78 µg/L for Wavy Lake (near Sudbury) (Stephenson and Mackie, 1988; Lum, 1987; Alikhan *et al.*, 1990; Hinch and Stephenson, 1987; Keenan and Alikhan, 1991). Mean concentrations of dissolved cadmium in Ontario ranged from 0.01 to 0.041 µg/L (n = 100) from Lake Ontario, 29 central Shield lakes, and the St. Lawrence River (Lum, 1987; Lum *et al.*, 1991; Yan *et al.*, 1990). Mean levels of dissolved cadmium in the St. Lawrence River, Quebec (1987; n = 39) ranged from 0.007 µg/L (St. Nicholas, Quebec; n = 10) to 0.018 µg/L (Lake St. François, Quebec; n = 8)(Lum *et al.*, 1991). The mean concentration of cadmium in Wavy Lake (an acidic lake situated 22 km SSE of base metal smelters at Copper Cliff, Ont.) was 4.78 µg/L. Mean levels of cadmium in central Ontario lakes ranged from 0.051 to 0.587 µg/L (lakes situated within 20 km of a base metal smelter complex) and from <0.002 to 0.12 µg/L (lakes situated 70 to 360 km from the smelter complex). Mean levels of dissolved cadmium (1976) in two Manitoba lakes located near a copper/zinc smelter at Flin Flon ranged from 20 µg/L (Hamell Lake; located within watershed separate from smelter tailings pond) to 286 µg/L (Ross Lake; connected to creek that drains tailings pond)(number of samples not reported)(Jacks on, 1978). These data, as well as additional older data, indicate higher levels are usually associated with local industrial/urban activities (Jackson, 1978; McFarlane *et al.*, 1979; Smith, 1987).

Drinking water in Canada generally contains low levels of cadmium, although recent nationwide studies have not been identified. In a 1977 national survey, the concentrations of cadmium in tap-water samples from 71 drinking water supplies across Canada ranged from ≤0.01 to 0.09 µg/L at the various sites, with an overall median concentration of 0.03 µg/L (Méranger *et al.*, 1981a). In limited monitoring of drinking water supplies in the vicinity of smelters, cadmium was detected at a concentration of

1 µg/L (the detection limit) in 4 of 8 spot samples of treated drinking water from Flin Flon, Manitoba, collected between 1983 and 1987 (Bezak, 1991b). Levels of between 5 and 6 µg/L were measured in a small fraction of well water samples collected in 1986 from 15 sites within a 20-km radius of the Belledune, New Brunswick smelting complex compared with none detected in samples from four sites in a reference area (Ecobichon and Hicks, 1986). In routine monitoring of 121 Ontario water supplies under the Drinking Water Surveillance Program in 1992, the mean annual concentration of cadmium in treated water in Sudbury (0.196 µg/L) was among the highest measured (Lachmaniuk, 1993).

Few data were identified on concentrations of cadmium in marine waters in Canada. Mean concentrations of dissolved cadmium off Baffin Island, Northwest Territories (1977 to 1978; n = 68) ranged from 0.029 µg/L in Davis Strait (n = 5) to 0.071 µg/L in Lancaster Sound (n = 4) (Reish *et al.*, 1977; Moore, 1981; Campbell and Yeats, 1982). Mean concentrations in sea ice were reported to be 0.31 µg Cd/L (locations in Baffin Bay, sample size, and ranges not reported)(Campbell and Yeats, 1982). Mean concentrations of dissolved cadmium in the Saguenay Fjord, Quebec (1974; n =47) ranged from 0.044 µg Cd/L (n = 8) to 0.074 µg Cd/L (n = 10) (Yeats, 1988). Mean concentrations of dissolved cadmium in Belledune Harbour, New Brunswick (1984), ranged from 0.09 to 0.17 µg/L (n = 7)(Uthe *et al*, 1986). The higher mean value was observed near a lead smelter outfall. Concentrations of dissolved cadmium in the industrialized False Creek estuary, Vancouver, British Columbia (1983; n = 9) ranged from 0.064 to 0.111 µg/L (mean concentration not given)(Stukas and Erickson, 1984).

In monitoring conducted under the National Geochemical Reconnaissance Survey (1975 to 1991; n = 50 000), the geometric mean concentration of cadmium in stream sediments was 0.35 mg/kg (0.2 to 110 mg/kg) from Yukon, Quebec, New Brunswick, Labrador, and British Columbia, while the corresponding value in lake sediments was 0.38 mg/kg (0.2 to 23.7 mg/kg) from Ontario, Saskatchewan, Northwest Territories, Manitoba, New Brunswick, Labrador, and British Columbia (GSC, 1991).*

As expected, cadmium levels in sediments near industrial and urban areas are generally higher than other areas. For example, the geometric mean concentration of cadmium (1985; n = 33) in sediments from five lakes within 8 km of a copper/zinc smelter located in Flin Flon, Manitoba, was 37.5 mg/kg (15 to 60 mg/kg). In the same study, the geometric mean concentration of cadmium in four lakes located 23 to 43 km from the smelter, was 4.5 mg/kg (<1 to 7 mg/kg)(Harrison and Klaverkamp, 1990). The mean cadmium concentration (1986; n = 6) in a highly industrialized area of Lake Ontario (Hamilton Harbour) was 14.9 mg/kg (6.7 to 20.5 mg/kg)(Mayer and Manning, 1990).

***** All values for concentrations of cadmium in freshwater sediments are reported as dry weight.

Data on cadmium concentrations in marine sediments are limited to coastal Quebec, New Brunswick, and British Columbia, and appear to be higher in industrialized and urban areas. Mean levels of cadmium (1984 to 1986; n = 317; reported on dry weight basis) in marine sediments ranged from 0.15 mg/kg (1986; n = 17) in the Saguenay Fjord, Quebec to 9.2 mg/kg (1984; n = 16) in sediments collected in the vicinity of a lead smelter at Belledune Harbour, New Brunswick (Uthe *et al.*, 1986; Harding and Thomas, 1987; Pelletier and Canuel, 1988; Goyette and Boyd, 1989; Pedersen *et al*, 1989). Sediment samples (1985 to 1986; n = 268) collected in Vancouver Harbour, British Columbia, had concentrations of cadmium that ranged from <0.3 to 7.4 mg/kg (no mean reported) (Goyette and Boyd, 1989).

Data identified on concentrations of cadmium in Canadian soils are limited (all values reported on a dry weight basis). Mean concentrations of cadmium in several studies of rural, urban, and agricultural soils from across Canada (more than 350 sites in total) ranged from 0.56 to 1.1 mg/kg (Bewers *et al.*, 1987). Higher levels have been reported in the vicinity of industrial plants and urban areas, especially near known sources of cadmium. Garden soils collected up to 12.8 km away from a copper/zinc smelter in Flin Flon, Manitoba, contained a mean concentration of cadmium of 5.2 mg/kg (3.2 to 13 mg/kg)(Pip, 1991). Cadmium levels in peat samples collected from 1.0 to 3.7 km away from a copper smelter (Rouyn-Noranda, Quebec) ranged from 54 to 66 mg/kg (mean not reported), while samples collected 25 to 43 km away from the smelter contained between 5.5 to 7.8 mg/kg (Dumontet *et al.*, 1990). The mean concentration of cadmium (n = 5) in soil next to a paint manufacturing plant in Vancouver, British Columbia, was 10.7 mg/kg (0.23 to 37.2 mg/kg)(Golder Assoc. Ltd., 1989). Bisessar (1982) reported that concentrations of cadmium in surface soils in the immediate vicinity of an urban secondary lead smelter in Ontario in 1976 ranged from 151 to 26 mg/kg dry weight at sites 15 to 180 metres from the smelter, respectively, compared with 5 mg/kg at a site 1000 metres from the smelter. Older data (1970 to 1980) also confirm that levels of cadmium in soils are higher in the vicinity of industrial operations and known cadmium sources (John, 1975; Lynch *et al.*, 1980; Sergeant and Westlake, 1980).

Although long-term application of municipal sewage sludge (for which the content of cadmium may be relatively high) to agricultural lands can significantly increase cadmium levels in soils and associated produce (Page *et al.*, 1987), the magnitude of the increase in soils in Canada appears to be small. For example, sewage sludge-treated agricultural soils throughout the Halton region (Ontario) had a median concentration of cadmium (n = 57) of 0.68 mg/kg (0.19 to 4.3 mg/kg), while the corresponding figure for non-treated soils (n = 252) was <0.5 mg/kg (<0.5 to 2.4 mg/kg)(Webber and Shamess, 1987).

Most foodstuffs consumed in Canada contain cadmium. In the most detailed study, of the cadmium content of 105 food types purchased in 1985 in Ottawa and prepared for consumption before being analyzed, the specific food types with the highest concentrations of cadmium were shellfish and potato chips, which consistently contained greater than 100 ng/g fresh weight. Mean concentrations exceeded 20 ng/g in organ

meats, crackers, wheat and bran cereals, plain pasta, celery, lettuce, broccoli, potatoes in a variety of forms, onions, canned tomatoes, and chocolate bars (Dabeka and McKenzie, 1992). In a survey of the cadmium content of 131 infant foods in Canada, concentrations ranged from 0.10 ng/g for cows' milk to 33.6 ng/g for dry infant cereals, with several ng Cd/g in meats and meat dinners, vegetable dishes, and table foods (Dabeka and McKenzie, 1988). In a large survey (282 samples in all) of infant formulas and evaporated milk conducted from 1986 to 1987, the mean concentration of cadmium in evaporated milk was 0.38 ng/g. Mean levels were similar for milk-based formulas (0.35 to 0.85 ng Cd/g, depending on the formulation), but were markedly higher for soy-based formulas (3.39 to 10.83 ng Cd/g, depending on the formulation) (Dabeka, 1989).

In a survey of the lead and cadmium content in 210 human milk samples collected from volunteers across Canada, the concentration of cadmium averaged 0.08 ng/g whole milk, and ranged as high as 4.05 ng/g. Levels of cadmium in breast milk were significantly correlated with smoking by the mother, and by the father if the mother did not smoke (Dabeka *et al.*, 1986).

Levels of cadmium were elevated in some foodstuffs in the vicinity of point sources in Canada, although the available data are quite limited. Home-grown garden produce from the vicinity of the base metal smelter at Flin Flon, Manitoba was sampled in 1989 from 12 sites at locations ranging from 0.29 to 12.8 km northeast to southwest of the smelter. The mean concentrations of cadmium in produce were as follows: tomatoes 154 ng/g (range 108 to 210 ng/g); string beans 229 ng/g (81 to 432 ng/g); apple, raspberry, blueberries, and honeysuckle combined 548 ng/g (390 to 900 ng/g); potato 644 ng/g (437 to 874 ng/g); carrot 367 ng/g (276 to 564 ng/g); beet 252 ng/g; lettuce and chard combined 225 ng/g (222 to 228 ng/g) (Pip, 1991) [these values were reported as dry weight, but have been converted to wet weight based on the water contents reported in NHW (1988)].

Levels in garden produce were similar in spot sampling from a garden site 4.5 km from the smelting and fertilizer complex at Belledune, New Brunswick. Composite samples collected at various times between 1984 and 1988 contained the following concentrations of cadmium: potatoes 160 ng/g wet weight; carrots 193 to 360 ng/g; lettuce 20 to 620 ng/g; beet tops 60 to 520 ng/g; beans 7 to 50 ng/g; cucumbers 50 ng/g; beet stems 160 ng/g; strawberries 20 to 240 ng/g; cabbage 390 ng/g (Lee, 1989). Concentrations were below or near the detection limit of 10 to 50 ng Cd/g in a small survey of eggs, cows' milk, and meats originating from within 22 km of a copper smelter at Noranda, Quebec (Moulins, 1991).

A major source of exposure of the general population to cadmium is tobacco smoking. In recent studies conducted for Health Canada, the average content in five major brands of cigarettes on the Canadian market in 1988 was 2.61 µg Cd/g of tobacco, or roughly 2.0 µg Cd/cigarette (Kaiserman, 1993). Based on these data and assuming a 10% smoke transference, Rickert and Kaiserman (1993) estimated that the mainstream smoke of Canadian cigarettes contained an average of 0.187 µg of cadmium per cigarette.

Mean levels of cadmium in commercially important seaweeds from Atlantic Canada ranged from 0.2 mg/kg (dry weight) in kelp, *Laminaria digitata* (Point Edwards, Nova Scotia) to 9.0 mg/kg in rockweed, *Ascophyllum nodosum* (Belledune Harbour, New Brunswick) with the higher concentrations associated with areas of industrial activity (Sharp *et al.,* 1988). (All values for cadmium levels in biota are in fresh weight, unless otherwise specified).

In a nationwide survey of metals in *Sphagnum fuscum* moss, the mean concentrations of cadmium at 28 of the 37 locations sampled were at or below the detection limit of 0.2 mg/kg (dry weight), while at nine locations in the vicinity of two smelters and an abandoned iron mine in Ontario, the mean levels ranged from 0.2 to 12 mg/kg (Glooschenko, 1989). Moss collected 25 km and 40 km west of a Manitoba copper/zinc smelter contained mean concentrations of cadmium of 2.3 and 1.0 mg/kg (dry weight) respectively, while moss collected 21 km east of a copper smelter in Noranda, Quebec contained 12.0 mg/kg (dry weight), compared with 3 mg/kg (dry weight) 30 km east of the smelter. In other studies, mean concentrations of cadmium in a variety of terrestrial plants within a few kilometres of a copper/zinc smelter in Manitoba ranged from 2.0 to 19.1 mg/kg (Pip, 1991; Stephens, 1992).

Mean concentrations of cadmium (1984 to 1989; n>1300) determined in freshwater invertebrates in Canada ranged from 2.9 mg/kg (dry weight) in whole crayfish *(Cambarus bartoni)* in Wizard Lake, Ontario to 205 mg/kg (dry weight) in the gills of crayfish in Lumsden Lake, Ontario (Hinch and Stephensen, 1987; Hare *et al.,* 1989; Alikhan *et al.,* 1990; Yan *et al.,* 1990; Bendell-Young and Harvey, 1991). Mean concentrations of cadmium (1985 to 1986; n>200) in marine invertebrates in Burrard Inlet, British Columbia, ranged from 0.09 mg/kg in dungeness crab *(Cancer magister)* muscle to 9.5 mg/kg in pink shrimp (*Pandalus borealis*)(Thomas and Goyette, 1989). The digestive glands of American lobsters (*Homarus americanus)* collected at two sites near a lead smelter outfall (Belledune Harbour, New Brunswick) contained geometric mean concentrations of cadmium of 16 mg/kg and 30 mg/kg, respectively (1992; n = 40) (Chou and Uthe, 1993).

Cadmium levels in waterfowl and terrestrial wild birds in Canada are typically <2.0 mg/kg fresh weight (f.w.) in kidney and <0.5 mg/kg (f.w.) in liver tissues (Jury, 1981; Struger *et al.,* 1987; Scheuhammer, 1993). The exception to this pattern is Mallard ducks *(Anas platyrhynchos)* in the Fraser River delta of British Columbia which contain up to 4 mg Cd/kg in kidneys (data converted from dry weight to fresh weight by a factor of 0.25)(Jury, 1981). A study conducted within the Experimental Lakes Area (ELA) (northwestern Ontario) illustrates the influence of pH in Cd transfer from an aquatic ecosystem to tree swallow *(Tachycineta bicolor)* nestlings (St. Louis *et al.,* 1993). For example, mean renal cadmium levels in nestlings from an acidic lake (pH = 5.8) were significantly higher than renal levels from a reference lake [(pH = 6.7) 0.60±0.12 µg/g (f.w.) versus 0.24 ±0.02 µg/g (f.w.)(converted from dry weight)].

Seabirds on the Atlantic coast have much higher levels of cadmium in their tissues than land birds, with maximum concentrations in pelagic species (puffin, *Fractercula*

arctica; Leach's storm petrel, *Oceanodroma leucorhoa,)* ranging from 31.3 to 83.5 mg Cd/kg (f.w.) in kidney (Elliott *et al.,* 1992)(converted from dry weight). Coastal species (herring gull, *Larus argentatus,* double-breasted cormorant, *Phalacrocorax auritus,)* contained substantially less cadmium than the pelagic birds. A similar pattern has recently been observed on the Canadian Pacific coast. Again, pelagic species such as Leach's storm petrel have the highest cadmium levels [25 to 100 mg Cd/kg (f.w.)] (Scheuhammer, 1993).

Many marine mammal populations, particularly in the Canadian Arctic, also have elevated renal and hepatic cadmium levels. Narwhal *(Monodon monoceros)* are especially high in cadmium, with a population in Pond Inlet (Baffin Island, Northwest Territories) having an average of 75 mg Cd/kg (f.w.) in kidney. The explanation for the high cadmium levels in narwhal is unclear, particularly since a co-occurring species (the Baffin Strait population of beluga) which has a diet very similar to narwhal (Evans, 1987), contained less than 10 mg Cd/kg (f.w.) in its kidneys (Hansen *et al.,* 1990). Other species with maximum renal cadmium levels exceeding 50 mg Cd/kg (f.w.) include Atlantic pilot whales *(Globicephala melaena)* off Newfoundland (Muir *et al.,* 1988), harp seal *(Phoca groenlandica)* in the Gulf of St. Lawrence (Wagemann *et al.,* 1988), and ringed seal *(Phoca hispida)* around Baffin Island (Wagemann, 1989).

There is a marked west-to-east increase in Cd levels in polar bear *(Ursus maritimus)* (Braune *et al.,* 1991), ringed seal (MacDonald, 1986), unidentified whales (Beak Consultants Ltd., 1975), and beluga whales *(Delphinaptcrus leucas)* (Wagemann *et al.,* 1990) across the Canadian Arctic. Maximum renal and hepatic Cd concentrations in beluga and polar bear are found in the Baffin Island and Hudson's Bay sub-populations (Wagemann *et al.,* 1990; Braune *et al.,* 1991). Mean renal Cd levels in beluga are twice as high near Pangnirtung and Eskimo Point [up to 106 mg Cd/kg (d.w.)] than near the MacKenzie Delta and Baffin Strait (see also Hansen *et al.,* 1990), and more than an order of magnitude higher than levels in the St. Lawrence estuary sub-population (Wagemann *et al.,* 1990).

In Canada, Cd concentrations in many terrestrial mammals usually reflect their proximity to smelters and other industrial sources. Cervids in parts of Ontario and Quebec in particular, exhibit high levels of cadmium in tissues. Moose, *Alces alces,* and deer, *Odocoileus virginianus,* in Quebec (Crete *et al.,* 1987) and Ontario (Glooschenko *et al.,* 1988), and moose in parts of New Brunswick (Ecobichon *et al.,* 1988), contain the highest average concentrations of cadmium in kidney and liver reported among cervids worldwide, up to 22 and 3.9 mg Cd/kg (f.w.), respectively, in the case of moose. Lower levels, comparable to those in the United States and Scandinavia, occur in moose in Newfoundland (Brazil and Ferguson, 1989) and Manitoba (Wotton and McEachern, 1988; Stephens, 1992), and in deer in Manitoba (Wotton and McEachern, 1988) and New Brunswick (Ecobichon *et al.,* 1988). Caribou *(Rangifer tarandus)* in northern Quebec contain an average of 11.5 mg Cd/kg (f.w.) (converted from dry weight) in their kidneys (Crete *et al.,* 1989), compared to 5.0 mg Cd/kg (f.w.) in Manitoba (Stephens, 1992). Cadmium in moose shows a decreasing gradient away from the smelters located in Abitibi, Quebec. Renal and hepatic concentrations of cadmium in the Gaspé region are

less than half and one-fifth, respectively, from those around Noranda (Crete *et al.,* 1987). Maximum Cd levels in Ontario moose and deer occur on both weakly- and strongly-buffered soils in the Loring-Algonquin area of central Ontario, which receives the highest aerial deposition rates of Cd and sulphates in Ontario (Glooschenko *et al.,* 1988). Mink *(Mustela vison)* and otter *(Lutra canadensis)* around Sudbury, Ontario, have significantly higher levels of cadmium in tissues than populations farther south and north (Wren *et al.,* 1988).

The highest concentrations of cadmium in the human body accumulate in the kidney (particulary the cortex) and the liver, although the metal can be detected in virtually all tissues in adults from industrialized countries (Elinder, 1985). Levels in the kidney increase with age until roughly age 40 to 60, after which they decline. In several surveys of autopsy samples from members of the Canadian general population, concentrations in kidney cortex at middle age peaked at mean concentrations of between 42 and 66 mg/kg wet weight (LeBaron *et al.,* 1977; Méranger *et al.,* 1981b; Chung *et al.,* 1986). Body burdens of cadmium are higher in smokers; LeBaron *et al.* (1977) reported that the mean concentrations of cadmium in the renal cortex of 31 smokers {69 mg/kg wet weight [estimated as ash values times 0.013 (Elinder, 1985)]} were approximately twice as high as in 30 non-smokers (29 mg/kg wet weight) of similar average age (49.3 and 55.7 years, respectively). The maximum concentration of cadmium in the renal cortex of non-smokers was 84 mg/kg wet weight.

2.4 Effects-related Information

2.4.1 *Experimental Animals and* In Vitro

The effects following dermal exposure to cadmium compounds have not been discussed in this report (although they have been summarized in the health-related supporting documentation for cadmium and its compounds under CEPA); these effects were not considered relevant to environmental exposure to cadmium, as a result of the limited potential for exposure by this route and the small fraction of dermally applied cadmium compounds that is absorbed (Wester *et al,* 1992; ATSDR, 1993).

Acute, Short-term, and Subchronic Toxicity. Reported oral LD_{50} values for cadmium chloride range from 88 to 302 mg/kg (b.w.) in the rat, 63 mg/kg (b.w.) in the guinea pig, and from 5 to 175 mg/kg (b.w.) in the mouse. Oral LD_{50} values in the rat are similar for cadmium oxide [72 to 296 mg/kg (b.w.)] and cadmium sulphate [357 mg/kg (b.w.)], but are much higher for cadmium sulphide, which is insoluble [>5000 mg/kg (b.w.)] (U.S. EPA, 1985a). By the inhalation route, LC_{50}s for 15-min exposures to cadmium oxide were about 29 mg Cd/m^3 and 41 mg Cd/m^3 for rats and mice, respectively. Cadmium oxide was somewhat less acutely toxic to guinea pigs (LC_{50} over 15 min of 200 mg Cd/m^3), rabbits (150 mg Cd/m^3), dogs (230 mg Cd/m^3), and monkeys (880 mg Cd/m^3) (Barrett *et al.,* 1947).

Following oral administration, the most common effects induced by short-term exposure to cadmium chloride are reduced growth, alterations in organ weights or histopathology (particularly of the kidney, testes, liver, and intestine), and effects on the

immune system. For example, in the most comprehensive study identified, there were effects on growth, organ weights, and clinical chemistry in male Sprague-Dawley rats ingesting about 1.1 to 14 mg Cd/[kg (b.w.)·d] for 10 days in the drinking water, or receiving doses of 15 to 65 mg Cd/[kg (b.w.)·d] by gavage; organ weights were also affected in females (Borzelleca *et al.,* 1989). Exposure of various strains of mice to between 1 and 10 mg Cd/[kg (b.w.)·d] as cadmium chloride for three to four weeks has been associated with decreased humoral immune function (Blakley, 1985; Blakley and Tomar, 1986; Borgman *et al.,* 1986; Chowdhury *et al.,* 1987) or increased lymphoproliferative responses to mitogens by spleen cells (Malavé and de Ruffino, 1984). No studies were identified of the effects of short-term exposure to cadmium oxide, cadmium sulphate, or cadmium sulphide following administration by the oral route.

Short-term inhalation exposures to between 50 µg/m^3 of cadmium chloride and 270 µg Cd/m^3 of cadmium chloride, cadmium oxide, or cadmium sulphide primarily caused inflammatory and (at higher concentrations) degenerative effects on the lung, although the range of other effects examined was limited (Prigge, 1978a; Glaser *et al.,* 1986; Paulini *et al.,* 1990; Manca *et al.,* 1991). In comparative studies, the potency of cadmium compounds varied in the order cadmium oxide > cadmium chloride > cadmium sulphide (Glaser *et al.,* 1986; Paulini *et al.,* 1990).

In subchronic studies, oral exposure of Wistar rats to 0.04 to 0.4 mg Cd/(kg (b.w.)·d] as cadmium chloride in the diet for 40 days reduced the activities of several liver enzymes and oxidative phosphorylation in liver mitochondria (Sporn *et al.,* 1970). With higher oral doses, a range of adverse effects has been reported, most commonly anemia, damage to and biochemical changes in organs including the kidney, liver, heart, and intestine, and changes related to the impairment of bone mineralization. In one of the most comprehensive studies, a dose of 0.6 mg Cd/[kg (b.w.)·d] in Sprague-Dawley rats of both sexes caused decreases in growth, thymus weight, and serum albumin, as well as increases in the relative weights of the lungs and heart, and in serum creatinine. In females exposed to 6 mg Cd/[kg (b.w.)·d] there were, additionally, decreased liver and ovary weights and increased adrenal weights, hematological effects including decreased hemoglobin and hematocrit values, and damage to the liver, kidneys, adrenal glands, and intestinal mucosa (Sutou *et al.,* 1980a). In immunotoxicity studies in various strains of mice, exposure to doses of cadmium chloride of between 0.6 and 10 mg Cd/[kg (b.w.)·d] in drinking water for 9 to 13 weeks most often produced alterations in lymphoproliferative responses of splenocytes to various mitogens, a measure of cell-mediated immunity (Koller *et al.,* 1979; Malavé and de Ruffino, 1984; Thomas *et al.,* 1985), whereas host resistance and delayed-type hypersensitivity (DTH) were not adversely affected by doses of 31 to 60 mg Cd/[kg (b.w.)·d] of cadmium chloride or cadmium sulphate (Thomas *et al.,* 1985; Exon *et al.,* 1986; Ohsawa *et al.,* 1988). No studies were identified on the effects of subchronic exposure to cadmium oxide and cadmium sulphide following administration by the oral route.

Inflammatory and proliferative changes in the lungs were induced in Fischer 344 rats and in rabbits inhaling 0.3 to 0.4 mg Cd/m^3 of cadmium chloride for

6 hours/day, 5 days/week, for 4 to 9 weeks (Johansson *et al.,* 1984; Kutzman *et al,* 1986), and in rats and mice following inhalation of 25 to 50 g Cd/m^3 of cadmium oxide for 63 to 100 days (Prigge, 1978b; Mast *et al.,* 1991). Continuous exposure of female Wistar rats to 25 to 50 µg Cd/m^3 of cadmium oxide for 100 days also caused reduced growth, increases in hemoglobin and hematocrit levels, and slight histopathological alterations in the kidney (Prigge, 1978b). Subchronic studies on the effects of inhalation of cadmium sulphate and cadmium sulphide were not identified.

Carcinogenicity/Chronic Toxicity. In a recent study in male Wistar rats exposed for 77 weeks to between 25 and 200 ppm cadmium chloride in the diet {approximately 1.25 to 10 mg Cd/[kg (b.w.)·d]}, the incidence of proliferative lesions in the ventral prostate was significantly increased at 50 ppm cadmium in both zinc-adequate and zinc-deficient rats. In addition, the incidence of leukemia was increased in rats consuming diets containing concentrations of 50 to 100 ppm cadmium in zinc-adequate diets and at 200 ppm in zinc-deficient diets. In rats on zinc-adequate diets containing 200 ppm cadmium, there was a significantly increased incidence of benign interstitial cell tumours of the testes (Waalkes and Rehm, 1992). In contrast, cadmium chloride was not carcinogenic by the oral route in a more comprehensive carcinogenicity study, in which the same strain of rats was exposed to some concentrations that were similar. There were no increases in tumour incidence upon administration of up to 50 ppm cadmium (as cadmium chloride) in diet {about 2.5 mg Cd/[kg (b.w.)·d]} to Wistar rats of both sexes for 2 years in a wide range of tissues that were examined histopathologically, even though growth was reduced in males at the highest concentration (Loser, 1980). There were also no cadmium-induced neoplasms in rats (unspecified strain) exposed to cadmium in the diet over four generations, although the doses administered were extremely low {maximum of 6.9 µg/[kg (b.w.)·d]}, and both the report of results and the range of tissues examined in this study were limited (Wills *et al,* 1981). Bomhard *et al* (1987) reported that in male Wistar rats administered cadmium chloride by gavage [1 x 50 mg Cd/kg (b.w.) or 10 x 5 mg Cd/kg (b.w.) weekly], the incidence of testicular tumours or tumours at other sites was not increased; however, the sensitivity of the bioassay was probably low due to the inadequate period of exposure. Blakley (1986) reported that in female Swiss mice exposed to 10 ppm or more of cadmium as cadmium chloride in drinking water {about 2 mg Cd/[kg (b.w.)·d]}, mortality from lymphocytic leukemia of thymic origin was significantly increased, but this result was attributed to a cadmium-induced increase in susceptibility to the virus that induces this neoplasm.

In the earliest study of adequate design in which rodents were exposed to cadmium compounds by inhalation, there were significant dose-related increases in the incidence of primary lung tumours (including adenocarcinomas, epidermoid carcinomas, mucoepidermoid carcinomas, and combined epidermoid carcinomas and adenocarcinomas, most of which were multiple) in male Wistar rats exposed to 13.4 to 50.8 µg Cd/m^3 cadmium chloride aerosols (23 hours/day for 18 months)(Takenaka *et al,* 1983; Oldiges *et al.,* 1984). In a subsequent study, there were compound-related increases in malignant lung tumours in Wistar rats of both sexes following long-term exposure (22 hours/day for 18 months) to 30 µg Cd/m^3 as cadmium chloride aerosol (Oldiges *et al,* 1989; Glaser *et al.,* 1990). In this study, there were also significant

increases in lung cancers in rats following exposures of lesser duration (40 hours/week for 6 months) to 90 µg Cd/m^3 as cadmium chloride aerosol.

In contrast to the results of studies in rats, there was no significant increase in lung tumours following exposure to cadmium chloride in female NMRI mice exposed to 30 to 90 µg Cd/m^3 for 19 hours/day, 5 days/week, for 42 to 69 weeks, and observed for 82 to 89 weeks, or in Syrian golden hamsters of both sexes exposed to 30 to 90 µg Cd/m^3 for 19 hours/day, 5 days/week, for 60 to 65 weeks, and observed for between 76 weeks (females) and 102 to 113 weeks (males). However, there was compound-related mortality in mice at both concentrations which may have limited the sensitivity of the bioassay. In this study, exposure to cadmium chloride caused dose-dependent histopathological alterations, including proliferative and hyperplastic lesions, in the respiratory tract of mice and hamsters (Aufderheide *et al,* 1989; Heinrich *et al,* 1989; Rittinghausen *et al,* 1990). The incidence of lung tumours was not markedly increased in female Wistar rats by direct (intratracheal) instillation of 1 to 9 µg Cd/week of cadmium chloride for 15 to 20 weeks, although no statistical analysis was presented (Pott *et al,* 1987). While only the lungs were examined in most of these studies, Takenaka *et al.* (1983); Oldiges *et al.* (1984) reported no evidence of carcinogenic activity at other sites in rats following long-term inhalation of cadmium chloride.

In studies in which animals were exposed to cadmium chloride by routes less relevant to environmental exposure, the compound induced injection-site sarcomas and interstitial Leydig cell tumours of the testes in rats (and the latter also in mice) following subcutaneous injection of several mg Cd/kg (b.w.) (Gunn *et al,* 1963; 1964; Knorre, 1970a;b; 1971; Lucis *et al.*, 1972, all cited in IARC, 1976; Reddy *et al,* 1973; Poirier *et al.,* 1983; Waalkes *et al.,* 1988; 1989; 1991a). Intramuscular or subcutaneous injection of 5.5 mg Cd/kg (b.w.) cadmium chloride induced prostatic tumours in rats (Waalkes *et al.*, 1989).

There is little indication that cadmium chloride acts as a promoter of cancer, although only a few relevant studies were identified (Kurokawa *et al.,* 1989; Waalkes *et al.,* 1991b).

No studies were identified in which cadmium oxide was administered to experimental animals by the oral route.

Primary lung tumours (adenomas, adenocarcinomas, squamous cell tumours, and combined forms) were induced by cadmium oxide in Wistar rats of both sexes, following long-term (22 hours/day for up to 18 months) inhalation of 30 to 90 µg Cd/m^3 as cadmium oxide dust (although the incidence was lower at 90 µg Cd/m^3, as a consequence of early compound-related mortality). Exposure to 30 µg Cd/m^3 cadmium oxide fumes induced adenomas and adenocarcinomas of the lung in an additional investigation with a similar protocol. In this study, there were also significant increases in both primary lung tumours and lung nodules in rats following exposure of lesser duration (40 hours/week for 6 months) to 90 µg Cd/m^3 as cadmium oxide dust (Oldiges *et al.,* 1989; Glaser *et al.,* 1990). There were small, but statistically significant, increases in the incidence of lung

tumours (not further described) in female NMRI mice exposed to cadmium oxide fume (30 µg Cd/m^3, 19 hours/day, 5 days/week for 50 weeks, or 90 µg Cd/m^3, 40 hours/week for 64 weeks) and cadmium oxide dust (10 µg Cd/m^3, 19 hours/day, 5 days/week for 64 weeks) (Heinrich *et al.*, 1989). However, the incidence of lung tumours was not increased in Syrian golden hamsters inhaling cadmium oxide fume (10 to 30 µg Cd/m^3, 19 hours/day, 5 days/week for 50 to 55 weeks, or 90 µg Cd/m^3, 8 hours/day, 5 days/week for 64 weeks) or cadmium oxide dust (10 to 270 µg Cd/m^3, 19 hours/day, 5 days/week, for 13 to 64 weeks). In this study, exposure to cadmium oxide dust and fumes caused dose-dependent histopathological alterations, including proliferative and hyperplastic lesions in the respiratory tract (Aufderheide *et al.*, 1989; Heinrich *et al.*, 1989; Rittinghausen *et al.*, 1990). The incidence of lung tumours was not markedly increased in female Wistar rats by direct (intratracheal) instillation of 1 to 9 µg Cd/week of cadmium oxide for 15 to 20 weeks, although no statistical analysis was presented (Pott *et al.*, 1987). In male Fischer 344 rats receiving 25 µg of cadmium oxide by intratracheal instillation between one and three times over the lifetime, there was no evidence of carcinogenicity in a range of organs, including the lungs or prostate, although there was a non-significant increase in the incidence of fibroadenomas of the mammary glands (Sanders and Mahaffey, 1984). Female rats developed injection-site tumours following subcutaneous injection of 25 mg cadmium oxide (Kazantzis and Hanbury, 1966, cited in IARC, 1976).

There was no effect on the incidence of tumours in male CB hooded rats ingesting relatively low doses of cadmium {up to 0.4 mg Cd/[kg (b.w.)·wk], or about 0.06 mg Cd/[kg (b.w.)·d]} as cadmium sulphate by stomach tube for 2 years, a dose which did not affect survival, growth, or histopathology of a limited range of tissues (Levy and Clack, 1975). There were also no effects on survival, growth, organ weight, the gross appearance of a wide range of organs, the microscopic appearance of a number of the major organs, or on the incidence of tumours in groups of 50 male Swiss mice receiving up to 1.8 mg Cd/[kg (b.w.)·wk] {about 0.3 mg Cd/[kg (b.w.)·d] as cadmium sulphate for 18 months by stomach tube. However, histopathological examination was limited to tissues that appeared abnormal on macroscopic examination and to major organs of randomly selected subsets of 20 each of the control and high-dose mice (none from the intermediate-dose groups) (Levy *et al.*, 1975).

There were compound-related increases in lung tumours (adenomas, adenocarcinomas, squamous cell tumours, and combined forms) in Wistar rats of both sexes following exposure to 90 µg Cd/m^3 cadmium sulphate aerosol for 22 hours/day, 7 days/week, for 14 months (males) to 18 months (females) (Oldiges *et al*, 1989; Glaser *et al*, 1990). However, there was no significant increase in lung tumours in female NMRI mice following exposure to 30 to 90 µg Cd/m^3 cadmium sulphate for 19 hours/day, 5 days/week, for 42 to 69 weeks, and followed for 95 to 96 weeks, or in Syrian golden hamsters of both sexes exposed to 30 to 90 µg Cd/m^3 for 19 hours/day, 5 days/week, for 61 to 65 weeks, and followed for 76 to 77 weeks (females) to 103 to 113 weeks (males). However, there was compound-related mortality in mice at both concentrations, which may have limited the sensitivity of the bioassay. In this study,

exposure to cadmium sulphate caused dose-dependent histopathological alterations, including proliferative and hyperplastic lesions, in the respiratory tract of mice and hamsters (Aufderheide *et al,* 1989; Heinrich *et al,* 1989; Rittinghausen *et al.,* 1990).

In studies in which animals were exposed to cadmium sulphate by routes less relevant to environmental exposure, the compound induced interstitial Leydig cell tumours of the testes in rats following subcutaneous injection of 2 mg Cd/kg (b.w.) weekly for 19 weeks, but not in similarly exposed mice (Roe *et al.,* 1964, cited in IARC, 1976).

No studies were identified in which cadmium sulphide was administered to experimental animals by the oral route.

Inhalation of cadmium sulphide aerosols (90 to 2430 µg Cd/m^3, 22 hours/day for 3 to 18 months) induced adenomas, adenocarcinomas, and squamous cell tumours in the lungs of Wistar rats of both sexes. In this study, there were also significant increases in both primary lung tumours and lung nodules in rats following exposures of lesser duration (40 hours/week for 6 months) to 270 µg Cd/m^3 as cadmium sulphide aerosol (Oldiges *et al.,* 1989; Glaser *et al,* 1990). [It should be noted that exposure to cadmium sulphide in these studies would have included cadmium sulphate as a photolytic product (König *et al.,* 1992)]. Lung tumours were observed in female Wistar rats following intratracheal instillation of 63 to 1000 µg Cd/week of cadmium sulphide for 10 weeks, although no statistical analysis was presented (Pott *et al,* 1987). Rats injected subcutaneously (25 mg) or intramuscularly (50 mg) with cadmium sulphide developed injection-site sarcomas (Kazantzis and Hanbury, 1966, cited in IARC, 1976).

In contrast to the results of studies in rats, there was no significant increase in lung tumours following exposure to cadmium sulphide in female NMRI mice exposed to 90 to 1000 µg Cd/m^3 for 19 hours/day, S days/week, for 26 to 64 weeks, and followed for 71 to 101 weeks, or in Syrian golden hamsters of both sexes exposed to 90 to 1000 µg Cd/m^3 for 19 hours/day, 5 days/week, for 26 to 64 weeks, and followed for between 61 to 87 weeks (females) and 60 to 111 weeks (males). In this study, exposure to cadmium sulphide caused dose-dependent histopathological alterations, including proliferative and hyperplastic lesions, in the respiratory tract of mice and hamsters (Aufderheide *et al.,* 1989; Heinrich *et al.,* 1989; Rittinghausen *et al.,* 1990).

A range of non-neoplastic effects has been observed at oral doses of cadmium chloride below those that were carcinogenic in the study by Waalkes and Rehm (1992). Exposure of rats to 0.03 mg Cd/[kg (b.w.)·d] for 11 months via the drinking water produced biochemical changes in the liver (Sporn *et al.,* 1970). A pair of monkeys ingesting 0.09 mg Cd/[kg (b.w.) ·d] in diet for 1 year had slight histopathological alterations in the kidney (Nomiyama *et al,* 1979). Long-term exposure to daily doses of about 0.2 to 0.6 mg Cd/kg (b.w.), via the diet or drinking water has produced kidney damage in rats and dogs (Anwar *et at.,* 1961; Takashima *et al.,* 1980); increased systolic blood pressure in rats (Schroeder and Vinton, 1962); lung emphysema in rats (Petering *et al.,* 1979); anemia and reduced weight gain in mice (Watanabe *et al,* 1986; Valois and

Webster, 1989); and effects on bone, including abnormalities and increased bone resorption in rats, mice, and dogs (Takashima *et al.*, 1980; Watanabe *et al.*, 1986; Sacco-Gibson *et al.*, 1992). No studies of the non-neoplastic effects of chronic exposure to cadmium oxide, cadmium sulphate, or cadmium sulphide following administration by the oral route were identified.

Mutagenicity and Related Endpoints. Cadmium chloride has been genotoxic in a number of experiments *in vivo*, most often inducing chromosome aberrations in the bone marrow or germ cells of exposed animals. In *in vivo* germ cell assays, the compound induced increases in the frequency of abnormal sperm heads in mice with single or short-term intraperitoneal exposure to doses as low as 0.6 to 4 mg/[kg (13.w.) •d] (Pomerantseva *et al.*, 1980; Mukherjee *et al*, 1988a; Han *et al.*, 1992), and aneuploidy in oocytes, blastocytes, or spermatocytes from mice or hamsters following single subcutaneous injection of 1 to 6 mg/kg (b.w.) (Shimada *et al.*, 1976; Watanabe *et al*, 1979; Watanabe and Endo, 1982; Selypes *et al.*, 1992). Chromosomal aberrations were induced in bone marrow cells of mice following short-term exposure to 3.5 mg/[kg(b.w.)•d] or more of cadmium chloride by gavage (Mukherjee *et al*, 1988b). A single intraperitoneal injection of cadmium chloride increased the frequency of chromosomal aberrations, sister chromatid exchanges, and micronuclei in bone marrow cells of mice at doses of 0.42 to 0.84 mg/kg (b.w.) (Mukherjee *et al.*, 1988a; Han *et al.*, 1992).

In vitro investigations have shown that cadmium chloride is genotoxic to mammalian cells (including those of humans) in numerous studies, causing DNA single strand breaks, mutations, chromosomal damage, or cell transformation. A weak mutagenic response has also been observed in some studies of bacteria exposed to cadmium chloride; this compound has also induced DNA damage in bacteria (U.S. EPA, 1985b; Rossman *et al.*, 1992).

In the sole study with cadmium oxide identified, this compound did not induce point mutations in *Salmonella typhimurium* in a preincubation-plate incorporation assay at concentrations as high as 3333 µg per plate, with or without metabolic activation (Mortelmans *et al*, 1986).

The genotoxicity of cadmium sulphate has not been investigated *in vivo*, and has been examined in only a limited number of *in vitro* studies. There was a dose-related, but not statistically significant, increase in SCE frequency in human lymphocytes to 1.6 to 6.2 µ*M* cadmium sulphate for 72 hours (Bassendowska-Karska and Zawadzka-Kos, 1987). Oberly *et al* (1982) reported that 0.10 to 0.20 µg/mL of cadmium sulphate induced a dose-related increase in forward mutations in mouse L5178Y TK^+/TK^- cells. Chinese hamster Hy fibroblast cells exposed to 100 µ*M* cadmium sulphate for 1 hour had an increased frequency of chromosome aberrations between 12 and 30 hours after exposure ceased (Röhr and Bauchinger, 1976). Sina *et al.* (1983) reported that 0.03 to 3 µ*M* cadmium sulphate for 3 hours caused DNA damage in rat hepatocytes *in vitro*. In *Saccharomyces cerevisiae*, unspecified concentrations of cadmium sulphate induced deletions, but not recombinations (Schietsl, 1989), while

100 µ*M* cadmium sulphate did not induce reverse mutation or gene conversion (Singh, 1983). Damage to DNA was induced by 0.05 mL of 0.005 *M* cadmium sulphate in a differential cytotoxicity assay in *Bacillus subtilis* (Kanematsu *et al.*, 1980). Up to 0.3 µ*M* cadmium sulphate did not cause point mutations in *Salmonella typhimurium* (Marzin and Phi, 1985) or DNA damage in *Escherischia coli* in amounts up to 1 µ*M* (Olivier and Marzin, 1987), although no detailed data were reported for either study.

In vitro exposure of human lymphocytes to 0.062 µg/mL of cadmium sulphide induced increased chromosome aberrations, including chromatid and isochromatid breaks, translocations, and dicentrics (Shiraishi *et al.*, 1972). Exposure of Chinese hamster ovary cells to 10 µg/mL of cadmium sulphide for 24 hours caused DNA single strand breaks (Robison *et al.*, 1982). Morphological cell transformation was induced in Syrian hamster ovary cells exposed to 1 or 5 µg/mL of crystalline cadmium sulphide in a clonal assay (Costa *et al.*, 1982).

Reproductive and Developmental Toxicity. The results of one study, which was reported only in a rather limited fashion, indicated that as little as 6.9 µg Cd/[kg (b.w.)·d] in the diet for four generations decreased fertility in rats {when compared with a control diet providing 4.4 µg Cd/[kg (b.w.)·d]} (Wills *et al.*, 1981). However, in other studies, fertility has only been affected, if at all, at much higher doses. Thus, gestational or subchronic exposure to between 1.5 and 10 mg Cd/[kg (b.w.)·d] did not affect fertility of male or female rats in several studies (Kotsonis and Klaassen, 1978; Sutou *et al.*, 1980b; Zenick et *al.*, 1982). Fertility (and pup survival) was decreased, but maternal survival was unaffected in female CF1 mice ingesting 6.5 mg Cd/[kg (b.w.)·d] as cadmium chloride in the diet for six consecutive rounds of gestation and lactation; at 0.7 mg Cd/[kg (b.w.)·d], litter size was reduced (Whelton *et al.*, 1988).

Fetotoxicity has commonly resulted in rats and mice from maternal doses, by the oral route, of about 0.5 to 4.7 mg Cd/[kg (b.w.)·d] or more as cadmium chloride, administered either during pregnancy alone or during pregnancy and premating, or postnatally. Effects observed, in some instances at doses that were not maternally toxic, included reduced fetal or pup weights, slower pup growth, delayed ossification, and increased resorptions (Choudhury *et al.*, 1978; Cooper *et al.*, 1978; Webster, 1978; Laskey *et al.*, 1980; Sutou *et al.*, 1980b; Baranski *et al.*, 1982; Baranski, 1985; 1986; 1987; Magri *et al.*, 1986; Webster, 1988; Sorell and Graziano, 1990). Skeletal malformations have been observed in offspring of female rats exposed to cadmium chloride during pregnancy, but only at higher, maternally toxic, doses *i.e.*, 10 to 40 mg Cd/[kg (b.w.)·d] (Sutou *et al*, 1980b; Machemer and Lorke, 1981; Baranski *et al.*, 1982; Baranski, 1985).

Locomotor activity was decreased and coordination poorer in offspring of female Wistar rats following oral administration of as little as 0.04 mg Cd/[kg (b.w.)·d] before and throughout pregnancy (Baranski *et al.*, 1983). In other studies, however, neurobehavioural development was affected only at higher maternal doses, *i.e.*, between 1.0 and 3.6 mg Cd/[kg (b.w.)·d] (Choudhury *et al.*, 1978; Cooper *et al.*, 1978; Baranski, 2.0 1986). Changes in pup biochemistry (e.g., in tissue levels of calcium, copper, and iron)

were also observed following exposure of Sprague-Dawley rat dams to 0.25 to 10 mg Cd/[kg (b.w.)·d] cadmium chloride, either before and during pregnancy, or during pregnancy only (Choudhury *et al.,* 1978; Cooper *et al.*, 1978). These neurochemical and biochemical effects were associated with doses that were not maternally toxic.

No studies were identified on reproductive and developmental effects of exposure to cadmium oxide, cadmium sulphate, or cadmium sulphide following administration by the oral route.

In Wistar rats exposed to cadmium chloride by inhalation, exposure to 0.2 mg Cd/m^3 continuously during pregnancy resulted in decreased fetal hemoglobin levels and maternal toxicity, with fetal weights reduced at 0.6 mg Cd/m^3 (Prigge, 1978b). There were no effects on male or female fertility, or on the numbers of live embryos, fetal deaths, resorptions, or corpora lutea in F344 rats exposed to up to 2 mg Cd/m^3 (6 hours/day, 5 days/week) for 62 days, a concentration that was lethal (Kutzman *et al.*, 1986).

Retarded ossification and changes in neurobehavioural development occurred in the offspring of female Wistar rats exposed to 0.02 mg Cd/m^3 cadmium oxide by inhalation for 5 hours/day, 5 days/week for 5 months, as well as during mating and pregnancy. Pup survival was reduced at 0.16 mg Cd/m^3; however, maternal weight was unaffected (Baranski, 1984; 1985). Daily exposure to 0.88 to 1 mg Cd/m^3 (5 to 6 hours/day, 5 days/week) as cadmium oxide for 13 to 20 weeks lengthened the estrus cycle in female rats of various strains and reduced spermatid concentration in males, but maternal toxicity was observed at such concentrations (Baranski and Sitarek, 1987; Mast *et al.*, 1991).

No studies were identified on reproductive and developmental effects following inhalation of cadmium sulphate or cadmium sulphide.

2.4.2 *Humans*

Studies of Occupationally Exposed Populations. There are numerous case reports of skin and eye irritation from cadmium compounds, and of acute poisoning in humans following either inhalation of high (unspecified) concentrations of cadmium, fumes of cadmium oxide, or cadmium sulphate, or ingestion of about 25 to 1500 mg Cd/kg (b.w.) of cadmium chloride or cadmium iodide (U.S. EPA, 1985a; WHO, 1992a; ATSDR, 1993).

There have been numerous investigations of the nephrotoxic effects of cadmium in exposed workers (reviewed in Kjellström, 1985a). The earliest sign of kidney damage is an increase in tubular proteinuria, characterized by the urinary excretion of a number of low-molecular-weight proteins including ß2-microglobulin, retinol-binding protein, and N-acetylglucosaminidase. These proteins are normally filtered through the glomerulus and reabsorbed in the proximal tubule; therefore, their excretion in the urine indicates damage to the proximal tubules. The tubular proteinuria may be followed by other signs of kidney dysfunction, such as glomerular proteinuria (urinary excretion of high-

molecular-weight proteins, e.g., albumin, possibly due to glomerular damage), increased urinary excretion of glucose, amino acids, calcium, phosphorus, and uric acid, and a reduced concentrating ability of the kidneys.

Secondary effects resulting from the disturbance in the calcium and phosphorus balance include hypercalciuria (Adams *et al.,* 1969; Kazantzis *et al.,* 1963; Kazantzis, 1979; Scott *et al.,* 1978; 1980), reduced blood phosphate levels (Kazantzis, 1979; Scott *et al.,* 1978; Thun *et al.,* 1989), kidney stone formation (Adams *et al.,* 1969; Axelsson, 1963; Elinder *et al.,* 1985a; Kazantzis, 1979; Scott *et al.,* 1978; Thun *et al.,* 1989), and osteoporosis and osteomalacia (Adams *et al.,* 1969; Blainey *et al.,* 1980; Gervais and Delpech, 1963; Kazantzis, 1979; Kjellström, 1985b; Nicaud *et al.,* 1942).

The prevalence of such renal dysfunction has been quantitatively related to the degree of exposure to airborne cadmium in the workplace in a number of investigations. The threshold for tubular proteinuria, based on a number of urinary markers of renal dysfunction, has been reported by various investigators to be 800 yr.µg/m^3 (Thun *et at.,* 1989), 691 yr.µg/m^3 (Järup *et al.,* 1988), 1100 yr.µg/m^3 (Mason *et al.,* 1988), and between 459 and 1137 yr.µg/m^3 (Falck *et al.,* 1983). However, it is difficult to reliably establish such thresholds, due to such factors as uncertainties in the estimates of exposure and variations in the sensitivity of individual workers.

As cumulative exposure to cadmium is difficult to assess reliably, a number of investigators have attempted to assess the critical concentrations in the kidney or liver tissues above which kidney dysfunction (proteinuria) might occur. In the two most comprehensive investigations (Ellis *et al.,* 1981, of 61 workers; Roels *et al.,* 1981a, of 264 workers), cadmium levels were measured in the liver and the left kidney of cadmium-exposed workers by neutron activation analysis, and urinary protein levels were determined as indicators of kidney function. By analyzing the cadmium levels in the renal cortex associated with both normal and abnormal kidney function (based on urinary levels of ß$_2$-microglobulin and total protein), Roels *et al.* (1983) estimated the 'critical level' in the renal cortex to range from around 215 ppm (µg/g) wet weight (the lowest cortex concentration at which proteinuria was observed) to 385 µg/g (the 95th percentile of the levels in cadmium workers without renal dysfunction). The corresponding range from the study by Ellis *et al.* (1981) is from 217 µg/g [the 10th percentile of the concentration in renal cortex at the inflection point in the ratio of cadmium levels in liver and kidney (Foulkes, 1986)] to 345 µg/g [the 95th percentile of the levels in cadmium workers without renal dysfunction, assuming a ratio of 1.25 between cortex and whole kidney concentrations (Kjellström *et al.,* 1984), instead of the value of 1.5 assumed by Ellis *et al.,* 1981]. In both these studies, there was a considerable overlap in the concentrations of cadmium in the kidney between healthy workers and those with renal dysfunction, and no data on exposure levels. The lower end of these ranges is similar to an earlier estimate of 200 ppm (200 µg/g) by Friberg *et al.* (1974), which was based on histopathological alterations or proteinuria, and determinations of renal concentrations of cadmium, in autopsies/biopsies of 30 people occupationally or environmentally exposed to cadmium (cited in Bernard and Lauwerys, 1984; Kjellström *et al.,* 1984). Based on the data from these studies, Kjellström *et al.*

(1984) estimated that 10% of the population would have renal tubular dysfunction at a concentration of cadmium in renal cortex of between 180 and 220 ppm (µg/g).

The critical concentration of cadmium in the liver has been estimated on the basis of cumulative frequency distributions for both normal and abnormal kidney function; levels of 30 to 60 ppm (µg/g) and above (Roels *et al*., 1981a) or 59 to 72 ppm (µg/g) and above (Ellis *et al.*, 1981) were associated with renal dysfunction. These figures are in the same range as the critical level reported by Mason *et al.* (1988), who applied a two-phase linear regression model with liver cadmium as the independent variable; the inflection points for various urinary and blood measures of renal dysfunction ranged from 20 to 55 ppm (µg/g) of cadmium in the liver.

Roels *et al*. (1981a) determined that urinary cadmium levels were significantly correlated with the body burden of cadmium, while blood cadmium levels were not. The body burden estimated for the critical cadmium levels in the kidney and the liver (160 to 170 mg cadmium) corresponded to a urinary cadmium level of 10 µg/g of creatinine. The investigators concluded that the probability of developing cadmium-induced renal dysfunction appeared to be very low if the urinary cadmium level of the workers did not regularly exceed the critical level of 10 µg Cd/g of creatinine. While the results of some other studies support this value of 10 µg Cd/g of creatinine as the urinary threshold for kidney dysfunction (Jakubowski *et al.*, 1987; Shaikh *et al.*, 1987), there are several reports of increased urinary excretion of a variety of proteins indicative of renal dysfunction in workers with concentrations of cadmium in urine in the range of 2 to 10 µg/g of creatinine (Elinder *et at.*, 1985a; Verschoor *et al.*, 1987; Mason *et al.*, 1988; Chia *et al*, 1989; Kawada *et al*., 1989; 1990; Mueller *et al.*, 1989; 1992; Bernard *et al.*, 1990; Roels *et al.*, 1993).

Increased excretion of protein in the urine often continues even after exposure to cadmium has ceased, indicating that cadmium-induced proteinuria is not readily reversible (Tsuchiya, 1976; Kazantzis, 1979; Piscator, 1984; Elinder *et al*, 1985b; Mason *et al*, 1988; Thun *et al*, 1989; Roels *et at.*, 1989; Järup *et al.*, 1993). Nonetheless, end-stage renal disease is not a common cause of death among cadmium workers; although in some investigations, an excess of deaths from 'kidney disease' or from 'nephritis/nephrosis' has been reported (Armstrong and Kazantzis, 1985; Elinder *et al.*, 1985c; Kjellström *et al.*, 1979), these results are based on only small numbers of cases, and have not been confirmed in other, larger, studies.

A small number of historical cohort studies have been conducted among workers employed in cadmium smelters, cadmium-nickel battery factories, cadmium-copper alloy smelters, and other cadmium-related industries, to assess the possible association between carcinogenicity and long-term occupational exposure to cadmium dust or fumes. There is some evidence from these studies of increased mortality due to lung cancer and prostate cancer, following prolonged inhalation exposure to cadmium. However, interpretation of the results is difficult because of potential confounding by exposure to other heavy metals (e.g., arsenic, lead, zinc, and/or nickel), to other airborne chemicals,

and of smoking. In addition, the number of cases was small in most of the studies, and there were few data on the levels of cadmium to which the workers were exposed.

In a small historical cohort study of 606 workers involved in production work at a cadmium smelter in the United States for at least 6 months between 1940 and 1969 (98% traced, 162 deaths), and who were first employed in 1926 or later (before this date, the facility was an arsenic smelter) there was a significant excess of lung cancer deaths for non-Hispanics [21 observed versus 9.95 expected; standardized mortality ratio (SMR) = 211; $p < 0.01$], (Stayner *et al,* 1990; 1992a;b; this is a 6-year update of a report by Thun *et al,* 1985). A significant relationship was reported for non-Hispanics between deaths due to lung cancer and estimated exposure to cadmium [= 584 mg Cd/m^3 of air-days, 1 observed, SMR =29; 585 to 1460 mg Cd/m^3, 7 observed, SMR =265, $p < 0.05$; 1461 to 2920 mg Cd/m^3, 6 observed, SMR = 217, not significant (ns) $\geq$2921 mg Cd/m^3, 7 observed, SMR = 290, $p < 0.05$) and for latency period (<10 years, 0 observed; 10 to 19 years, 2 observed, SMR = 142 ns $\geq$20 years, 19 observed, SMR = 233, $p < 0.01$) (this is the only cohort for which there are quantitative data on exposure for individual members). Approximately 70 to 80% of the cohort had median urinary levels of cadmium greater than 20 µg/L, indicating that the population was heavily exposed (Thun *et al.,* 1985). Confounding by exposure to arsenic was addressed to some extent by the exclusion of workers employed before the plant was converted from an arsenic smelter. Stayner *et al.* (1990; 1992a;b) also speculated that cumulative exposure to arsenic was similar throughout the cohort, which would reduce confounding in the analyses for period of latency and level of exposure to cadmium. In the earlier follow-up, Thun *et al* (1985) estimated that exposure to arsenic could account for only 0.77 deaths from lung cancer, on the basis of a risk assessment model developed by the Occupational Safety and Health Administration (OSHA), and assuming that 20% of the person-years of exposure were spent in high-exposure jobs, that airborne concentrations measured in 1950 or later were representative of those between 1926 and 1950, and that respirators were worn according to regulation and reduced exposure by 75%. As far as smoking was concerned, Stayner *et al.* (1990; 1992a;b) noted that the internal comparisons used in the analysis reduced the likelihood of confounding by smoking. Thun *et al* (1985) also noted that the prevalence of current or former smokers in the cohort (77.5%, based on data for approximately 70% of the cohort members) was similar to that of the general population (72.9%), and argued that even if the proportion of heavy smokers in the workforce was double that in the United States white male general population, this would only account for a 1.25-fold increase in deaths from lung cancer, compared with the two-to three-fold increase observed in this study (for post-1926 workers employed for 2 years or more). Stayner *et al.* (1990; 1992a;b) concluded that the excess of lung cancer deaths associated with cadmium exposure was unlikely to be accounted for by smoking or by exposure to arsenic.

This conclusion has been disputed by Lamm (1987), Lamm *et al.* (1992), and Kazantzis (1990; 1991), because of uncertainties with respect to respiratory protection [ventilation controls and a mandatory respirator program were only introduced in the 1940s (Thun *et al.*, 1985)] and the extent of exposure to arsenic after 1926 [feedstock contents of arsenic between 1926 and 1950 were roughly three times higher than after

this period (Lamm *et al.*, 1992), and airborne concentrations would probably have been similarly elevated]. The possibility of a synergistic effect from combined cigarette smoking and arsenic exposure in the induction of lung cancer, demonstrated in some studies of arsenic-exposed workers (Pershagen *et al*, 1981; Järup and Pershagen, 1991), was also not taken into account. It has been suggested that with the potential confounding due to smoking and arsenic exposure, the excess lung cancer mortality reported by Thun *et al.* (1985) can no longer be attributed to exposure to cadmium (Kazantzis, 1990). In a nested case-control study, Lamm *et al.* (1992) reported that the mean cumulative exposures to cadmium of 25 incident lung cancer cases (9.24 mg Cd-year/m^3) did not differ from that of 75 controls matched by date and age at hire (9.29 mg Cd-year/m^3). Cases were eight times more likely to have been smokers than were controls. Lung cancer risk and feed-stock concentrations of arsenic followed similar temporal patterns, i.e., before 1926> 1926 to 1939> 1940 to 1969, and it was suggested that differences in lung cancer risk reflected differences in exposure to arsenic, rather than cadmium.

Stayner *et al.* (1993) have criticized the study by Lamm *et al.* (1992) on the basis of overmatching (date of hire, age when hired, and period of potential exposure were all correlates of cumulative cadmium exposure) and failure to account for the matching in their case-control analysis, both factors which would potentially reduce the ability to detect differences in exposure between cases and controls. Stayner *et al.* (1993) also performed a nested case-control analysis, for which only a brief account has been published, in which an unspecified number of cases was matched to approximately 50 controls per case, based on survival to the same age. A significant linear trend with cumulative exposure to cadmium was observed in both the overall analysis and for only those workers employed during or after 1940 (when arsenic exposure was relatively low). It was argued that the analyses by Lamm *et al.* (1992) did not support the conclusion that lung cancer risk was attributable to arsenic exposure in this cohort, although Stayner *et al.* (1993) considered that it was “impossible to fully discount the potential influence of arsenic exposure”.

In a series of investigations of a much larger cohort of 6958 cadmium-exposed workers in 17 major plants in the United Kingdom (98.7% traced, 1902 deaths), Kazantzis and his colleagues (1988) reported evidence of increased lung cancer mortality (mainly among those employed before 1940, when exposure to cadmium and other compounds would have been particularly high) (Armstrong and Kazantzis, 1983; Kazantzis *et al.,* 1988). In the most recent follow-up, 277 deaths from lung cancer were observed [SMR = 115, 95% confidence interval (CI) = 101 to 129], and there was a non-significant increase in the SMRs with increasing intensity of exposure ('ever high', 'ever medium', or 'always low'). Although no quantitative data on cadmium exposure were provided, Armstrong and Kazantzis (1982, cited in U.S. EPA, 1985b) reported that only 3% of this cohort had exposures considered likely to give rise to concentrations of over 20 µg/L of cadmium in urine compared to 70 to 80% in the cohort reported by Thun *et al.* (1985). No data were provided on smoking history of the workers or on concomitant exposure to other chemicals. However, the results of a subsequent case-control study (of 174 cases employed at a zinc-lead-cadmium smelter representing

64% of the workers in the total cohort), which took account of past exposure to cadmium, lead, zinc, arsenic, sulphur dioxide, and total dust, indicated that the increased risk of lung cancer with increasing duration of employment was not significantly associated with cumulative exposure to cadmium, but was instead associated with estimates of cumulative exposure to arsenic and lead (Ades and Kazantzis, 1988). Kazantzis *et al* (1988) also reported excesses of deaths from bronchitis (178 observed, SMR = 132, 95% CI = 113 to 151), particularly in the 'ever high' exposure group (13 observed, SMR = 382, 95% CI =203 to 654). Significant excesses of deaths from emphysema and stomach cancer were limited primarily to the least exposed workers.

In historical cohort studies of workers from other plants in the United Kingdom, Sorahan (1987) reported that mortality due to cancer of the lung and bronchus among 3025 workers (97.4% traced, 836 deaths) employed for at least one month in a cadmium-nickel battery factory was significantly increased (110 observed, SMR = 130, $p < 0.01$). Mortality from lung cancer appeared to be associated with duration of employment in high or moderate exposure jobs in early workers (first employed, 1923 to 1946). There was no information on the levels of cadmium to which the workers were exposed, on concomitant exposure to other chemicals, or on smoking. Holden (1980) conducted an historical cohort study of 347 men (95.1% traced) exposed to cadmium for at least one year in a cadmium-copper alloy factory in the United Kingdom, and 624 'vicinity workers' (96.3% traced) working in the same building, who were exposed to much lower levels of cadmium than the cadmium workers (means of 6 µg Cd/m^3 and 70 µg Cd/m^3, respectively). There was a significant excess of deaths from respiratory cancer and prostate cancer among the 'vicinity workers', but not among the cadmium workers; the 'vicinity workers' were also exposed to unspecified levels of arsenic, nickel, and silver, and there were no data on smoking histories for any of the workers.

In a small cohort (n = 269) of cadmium-nickel battery production workers with more than five years exposure to cadmium in Sweden (percentage traced not reported, 43 deaths), there were non-significant increases, based on very small numbers of observed cases, in mortality from lung cancer [2 observed, 1.35 expected, relative risk (RR) = 1.48] and prostate cancer (2 observed, 1.2 expected, RR = 1.67), although there was a significant excess of deaths due to nasopharyngeal cancer (2 observed, 0.2 expected, RR = 10, $p < 0.05$) (Kjellström *et al.*, 1979). Elinder *et al.* (1985c) also conducted a small historical cohort study of 545 men (96.3% traced, 133 deaths) exposed to cadmium for at least one year in a Swedish cadmium-nickel battery factory. There was no excess of mortality from cancers of several sites including the lung (8 observed, SMR = 133) and prostate (4 observed, SMR = 108), although mortality from lung, bladder, and prostate cancer increased (not significant) in proportion to the latency period. There was a significant excess of deaths from nephritis/nephrosis in workers with at least 5 years of exposure and at least 10 or 20 years of follow-up. In both of these studies, no data were provided on smoking, and workers were concurrently exposed to nickel hydroxide dust at higher levels than those for cadmium oxide dust (Kjellström *et al.*, 1979).

Limited available data from analytical epidemiological studies indicate that there may be a weak association between occupational exposure to cadmium and cancer of the prostate gland. Kipling and Waterhouse (1967) reported a significant excess of cancer of the prostate (4 observed, 0.58 expected, $p = 0.003$) in a small study of 248 workers from the United Kingdom exposed to cadmium oxide for one year or more. The association was not confirmed, however, in two subsequent historical studies on much larger extended cohorts that both included the original cohort of Kipling and Waterhouse (Sorahan and Waterhouse, 1983; Kazantzis *et al.*, 1988). In a case-control study of 39 workers (from three different cohorts) who died from prostate cancer, there was a slightly increased risk from exposure to cadmium, but this was not statistically significant (Armstrong and Kazantzis, 1985). In small historical cohort studies in Sweden, there was suggestive evidence of an association between exposure to cadmium and prostate cancer, but the values were not statistically significant (Elinder *et al*, 1985c; Kjellström *et al.*, 1979). A significant excess of mortality from prostate cancer was initially reported in a cohort of cadmium smelter workers in the United States (Lemen *et al.*, 1976), but there was no significant increase in the most recent update, after an additional five years of follow-up, in which three deaths were observed versus 1.41 expected, SMR = 213, 95% CI = 44 to 622 (Thun *et al.*, 1985). Results of a population-based case-control study (358 men with cancer of the prostate, 679 controls from Utah) indicated that occupational exposure to cadmium was associated with a non-significant increased risk for cancer of the prostate (Elghany *et al.*, 1990).

The weight of available data indicates that there is an association between occupational exposure to cadmium and adverse effects on lung function. Impairment of lung function was reported in cadmium-exposed workers in a number of case-control studies (Lauwerys *et al.*, 1974; 1979; Smith *et al.*, 1976; Sakurai *et al.*, 1982; Davison *et al.*, 1988), although this effect was not observed in other small case-control (Edling *et al.*, 1986) and cross-sectional (Lauwerys *et al.*, 1974) studies. In those studies in which lung function was affected, the reductions were greatest in workers having the heaviest cumulative exposure or the longest duration of exposure. Unfortunately it is not possible, from the various studies, to reliably establish concentrations associated with adverse effects on the lungs, because over the years, the workers were exposed to gradually diminishing airborne levels of cadmium. Holden (1980) and Kazantzis *et al* (1988) reported increased mortality from non-malignant respiratory disease in historical cohort studies of cadmium-exposed workers. However, no data were provided in either study on history of smoking, and the latter study did not include information on exposure to other chemicals.

In most cross-sectional studies of hypertension associated with occupational exposure to cadmium, there has been little evidence of an association, when potential confounders were taken into account (Engvall and Perk, 1985; de Kort *et al.*, 1987; Mason *et al.*, 1988; Neri *et al.*, 1988). Thun *et al.* (1989) reported that systolic blood pressure was increased in 45 workers from a cadmium smelter compared with 32 hospital workers of similar age, after controlling for a series of confounders. In historical cohort studies of cadmium-exposed workers, the death rate from cardiovascular disease was lower than national rates (Elinder *et al.*, 1985c; Thun *et al*, 1985; Kazantzis *et al.*, 1988).

There is no convincing evidence of reproductive and developmental effects associated with exposure to cadmium in the workplace (Tsvetkova, 1970; Huel *et al,* 1981; Mason, 1990; Lindbohm *et al.,* 1991; Gennart *et al.,* 1992), although such effects have not been adequately investigated in humans.

In cytogenetic studies of workers exposed to unspecified cadmium compounds in the workplace, the frequencies of chromosome aberrations in peripheral blood lymphocytes were not significantly increased in some studies (Bui *et al.,* 1975; O'Riordan *et al,* 1978; Fleig *et al.,* 1983). In other studies, in which results were positive, there was confounding exposure to lead (Deknudt *et al.,* 1973; Deknudt and Leonard, 1975; Bauchinger *et al.,* 1976).

Studies of Environmentally Exposed Populations. Numerous epidemiological studies have been conducted in Japan to investigate the role of cadmium in the etiology of 'itai-itai' ('ouch-ouch') disease, a disease that was endemic among post-menopausal women in certain cadmium-polluted areas of Japan after the Second World War (Kjellström, 1985b;c). The characteristic symptoms of the disease are osteomalacia, osteoporosis, and kidney dysfunction; cases were observed in a number of areas that had heavy metal pollution from nearby mines or refineries. High concentrations of both cadmium and zinc were detected in soil. However, while the concentrations of zinc in the locally-produced rice, and urinary excretion of zinc and lead by inhabitants were similar in the polluted and control areas, the concentrations of cadmium in rice and excretion of cadmium were higher in the polluted areas (Yamagata and Shigematsu, 1970; Kjellström, 1985c).

Rough estimates of exposure in these areas have been made on the basis of limited data on measured concentrations of cadmium in locally-produced rice and other foods. Based upon two different measures of kidney dysfunction, one group of investigators concluded that the total cadmium intake resulting in $ß_2$-microglobulinuria or metallothioneinuria was approximately 2000 mg (Nogawa *et al.,* 1989; Kido *et al.,* 1991a). This is equivalent to 110 µg/day over a 50-year period, or 78 µg/day over a 70-year period { i.e., 1 to 2 µg/[kg (b.w.)·d] } for an entire lifetime. A higher estimate (1000 to 2000 µg/day) has been made based on the estimated peak concentrations of cadmium in the livers of patients with 'itai-itai' disease, and estimated intakes and levels of cadmium in the livers of inhabitants in regions of Japan where levels of cadmium in the general environment are lower (Kjellström, 1985b). In view of the difficulties of accurately determining the level of intake of cadmium (because of variations in the concentration of cadmium in rice and in rice consumption), urinary cadmium levels in the inhabitants of cadmium-polluted areas have been used as a measure of the systemic dose associated with renal dysfunction. The threshold urinary cadmium concentration associated with $ß_2$-microglobulinuria or metallothionuria in Japanese populations has been estimated to be between 3.2 and 5.2 µg/g of creatinine (Nogawa *et al.,* 1979; Ishizaki *et al.,* 1989; Kido *et al.,* 1991b). Kawada *et al* (1992) observed an association between urinary levels of cadmium and N-acetylglucosaminidase in 400 inhabitants living in cadmium-polluted areas of Japan for whom the mean concentration of cadmium in urine was 2 µg/g of creatinine.

Renal tubular dysfunction has also been observed in studies from other parts of the world in populations exposed to cadmium in the general environment. In the most comprehensive study, a total of 1699 individuals was surveyed in two urban and two rural districts in Belgium (Lauwerys *et al.*, 1990; Buchet *et al.*, 1990). Levels of cadmium in environmental media were considered to be high in one urban area (Liège: 4 to 39 ppm in the soil, 95th percentile for airborne cadmium, 0.165 µg/m^3, 50th percentile 0.018 µg/m^3) and in one rural area (Noorderkempen: 0.5 to 24 ppm in the soil, 95th percentile in the air, 0.04 µg/m^3, 50th percentile <0.010 µg/m^3). Levels were lower in the other urban area (Charleroi: 0.5 to 1 ppm in the soil, 95th percentile in the air <0.03 µg/m^3) and the other rural area (Hechtel-Eksel: <1 ppm in the soil, 95th percentile in the air <0.01 µg/m^3). After standardization for confounding factors such as age, sex, smoking status, and diabetes, there were significant associations between the amount of cadmium excreted in the urine over 24 hours and the urinary levels of ß2-microglobulin, retinol-binding protein, N-acetylglucosaminidase, amino acids, and calcium. The level of excretion of these five indicators was considered to indicate mild renal dysfunction at urinary cadmium excretion of > 2 µg/day, which the investigators estimated to be equivalent to a mean renal cortical concentration of 50 ppm (assuming an oral absorption rate of 5%, a daily excretion rate of 0.005% of the body burden, and one-third of the body burden being present in the kidneys). This figure of 50 ppm is much lower than the critical renal concentration estimated for cadmium-exposed workers; Buchet *et al.* (1990) suggested that this difference reflected a 'healthy-worker effect'.

Evidence of renal dysfunction has also been reported in a study of a population exposed to increased environmental levels of cadmium in a region of the Netherlands having a history of zinc smelting [mean renal cortex concentration in autopsies of 42 residents 34 mg/kg wet weight], as compared with residents of two reference areas [mean in autopsies of 57 residents 27 mg/kg (wet weight)] (Kreis, 1992). Urinary excretion of total protein, 132-microglobulin, albumin, and amino acids was also correlated with excretion of cadmium in urine in a study of elderly women who were long-term residents from regions of Belgium in which environmental levels of cadmium differed (Roels *et al*, 1981b). However, there was no association between urinary levels of cadmium and the prevalence of kidney dysfunction in a similarly-sized, population-based study of elderly women from three German cities exposed to environmental concentrations similar to those in the Belgian study (Ewers *et al.*, 1985).

There is evidence that environmental exposure may result in a progressive worsening of cadmium-induced renal dysfunction, even after exposure has ceased (Kido *et al.*, 1988;1990). As was noted for occupationally-exposed cohorts, end-stage renal disease does not appear to be a common cause of death in populations exposed to cadmium in the general environment, although there have been reports of increased mortality from nephritis/nephrosis/renal insufficiency in some studies from Belgium or Japan (Lauwerys and De Wals, 1981; Shigematsu *et al*, 1982; Nakagawa *et al.*, 1987).

The bone deformities reported in many Japanese patients with 'itai-itai' disease were usually a late manifestation of severe chronic cadmium poisoning, secondary to renal tubular dysfunction, although dietary deficiencies (particularly of vitamin D and

calcium) and lack of sunlight may also have contributed to observed effects. The kidney dysfunction in populations living in cadmium-polluted areas of Japan results in disturbances in the calcium and phosphorus balance, and is also believed to have an adverse effect on vitamin D metabolism leading to impaired calcium absorption from the intestine and reduced bone mineralization (Friberg *et al.,* 1985). Subsequent bone degeneration was noted almost exclusively in women, particularly post-menopausal women who had had many children (and who would therefore be more susceptible to such a mineral imbalance) (Kjellström, 1985c). There is also evidence from Belgium and the Netherlands that calcium metabolism in the population at large is disrupted by exposure to cadmium (Staessen *et al.,* 1991a; Kreis, 1992). For example, Staessen *et al.* (1991a) observed positive associations between the levels of cadmium and calcium in the urine and between urinary cadmium levels and serum alkaline phosphatase activity in both sexes after adjusting for confounding factors such as age and body mass, in a random sample of inhabitants from four districts of Belgium in which cadmium levels in the environment differed [further details are discussed in relation to renal effects (Buchet *et al.,* 1990; Lauwerys *et al.,* 1990)]. There was an inverse correlation between urinary cadmium levels and total serum calcium levels for men, although no such association was evident for women.

The results of studies conducted to assess the possible influence of environmental exposure to cadmium on blood pressure or on the prevalence of hypertension have been mixed. While a positive association has been reported in some studies (Tulley and Lehmann, 1982; Vivoli *et al.,* 1989; Laudanski *et al.,* 1991; Kreis, 1992), in other studies there has either been no association (Shigematsu *et al.,* 1979; Beevers *et al.,* 1980; Ewers *et al.,* 1985; Geiger *et al.,* 1989; Lazebnik *et al.,* 1989; Shiwen *et al.,* 1990; Whittemore *et al.,* 1991), or an inverse relation between levels of cadmium and blood pressure/hypertension (Cummins *et al.,* 1980; Kagamimori *et al.,* 1986; Staessen *et al.,* 1984; 1991b; Iwata *et al.,* 1991). Similarly, there has been no consistent evidence in the limited number of available studies of an association between exposure to cadmium in the general environment and increased mortality due to hypertension or cardiovascular disease; an excess of deaths from cerebrovascular disease in a study of 501 residents of Shipham, United Kingdom (a village with high levels of cadmium in soil) was not confirmed in two Japanese studies of much larger populations (Shigematsu *et al,* 1982; Nakagawa *et al.,* 1987).

Associations have been reported between environmental exposure to cadmium (using hair cadmium content as an index of exposure) and various measures of neuropsychological development in children, including verbal I.Q. (Thatcher *et al.,* 1982), motor, and perceptual abilities (Bonithon-Kopp *et al.,* 1986), degree of aggressive and disruptive behaviour in the classroom (Marlowe *et al.,* 1985) or diagnosis of mental retardation (Hui *et al.,* 1990). However, in view of the possible confounding effects of exposure to lead and the lack of quantitative data on exposure to cadmium, it is not possible to assess the effects of cadmium on neuropsychological development on the basis of these studies.

The reproductive and developmental toxicity of cadmium in environmentally exposed populations has not been extensively investigated. Associations between exposure to cadmium and reductions in sperm quality (Chia *et al,* 1992) or birth weight, or numbers of births or full-term deliveries (Laudanski *et al.,* 1991; Fréry *et al.,* 1993) observed in some studies have not been confirmed in others (Saaranen *et al.,* 1989; Loiacono *et al.,* 1992).

In the majority of limited studies in populations exposed to cadmium in the environment, there has been no consistent evidence of an increased risk of cancer in general (Inskip *et al.,* 1982; Shigematsu *et al.,* 1982; Nakagawa *et al.,* 1987), or of specific types of cancer, including cancer of the kidney and urinary tract (Lauwerys and De Wals, 1981), bladder (Inskip *et al.,* 1982), stomach or liver (Shigematsu *et al.,* 1982), breast, lung or gastrointestinal tract (Inskip *et al.,* 1982), or prostate (Bako *et al.,* 1982; Inskip *et al,* 1982; Shigematsu *et al,* 1982). However, the limitations of the studies (mostly ecological) conducted to date preclude assessment of the carcinogenicity of cadmium in populations exposed in the general environment.

The frequency of chromosome aberrations was increased in two of three studies of itai-itai patients (Bui *et al,* 1975; Shiraishi and Yosida, 1972; Shiraishi, 1975), and in one study of residents of a cadmium-polluted region of China (Tang *et al.,* 1990); however, information on exposure to cadmium was inadequate in these studies, all of which involved small numbers of subjects.

2.4.3 *Ecotoxicology*

The following section focuses on studies of non-mammalian and wildlife species considered to be particularly sensitive to cadmium. Only those studies in which proper controls were used and abiotic parameters were reported (e.g., pH, hardness, or salinity, which may influence toxicity) are considered in this assessment report. Cadmium chloride was the form of cadmium used most often in aquatic and terrestrial toxicity bioassays; cadmium sulphate and cadmium nitrate were used occasionally. Regardless of the original cadmium compound used in laboratory exposures, the "free ion" is considered to be the most bioavailable and toxic chemical species (Rainbow, 1990).

Aquatic Ecosystems. Figure 1 summarizes data from toxicity studies in which the lowest effect levels have been observed. In general, cadmium is more toxic to aquatic species at low pH (5 to 7), low salinity (<15‰) and in soft water (<100 mg/L calcium carbonate) (Wong, 1987; Sprague, 1987; Langston, 1990; Voyer and McGovern, 1991). However, some species have shown no pronounced differences in toxicity over various ranges in the above-noted physical/chemical parameters (Canton and Slooff, 1982).

Data on lethality, and the effects of cadmium compounds on reproduction and growth were examined for 28 species of freshwater invertebrates representing six broad taxonomic groups. Crustaceans were the most Cd-sensitive group of invertebrates, while aquatic insect larvae were the most tolerant. The lowest-observed-effect-level in a chronic toxicity study was 0.17 µg Cd/L ($CdCl_2$) resulting in a 16% decrease in reproductive output for *Daphnia magna* during a 21-day static renewal test at 18°C in

soft water (median water hardness 48.5 mg/L as $CaCO_3$) (Biesinger and Christensen, 1972). This laboratory-derived chronic threshold is strongly supported by recent field work in experimentally-contaminated lakes in northwestern Ontario. Lawrence and Holoka (1991) reported that the abundance of two Cladoceran species *(Daphnia galeata mendotae* and *Holopedium gibberum)* was reduced by 39% and 28%, respectively, following a 14-day exposure to 0.2 µg Cd/L ($CdCl_2$) using *in situ* flowthrough containers. In a whole lake-contamination experiment, exposure to cadmium chloride concentrations at and below 0.08 µg Cd/L had no observed effects on the composition or abundance of most zooplankton species (Malley and Chang, 1991). Cadmium is lethal to freshwater invertebrates *(Daphnia* sp.) following short-term exposures (48 hours) to cadmium chloride concentrations as low as 3.6 µg Cd/L (Baird *et al.,* 1991).

Toxicity data were compiled for 37 species of marine invertebrates, representing eight broad taxa. As was the case for freshwater invertebrates, crustaceans were the most sensitive species. The lowest-observed-effect-level (LOEL) of 1.2 µg Cd/L (cadmium compound not specified) was reported for the mysid, *Mysidopsis bahia;* this concentration reduced survival by 33% and reproductive success by 26% in a 28-day flowthrough test (salinity = 20.1‰) (Voyer and McGovern, 1991).

Data were reviewed on the acute and chronic toxicity of cadmium compounds to 22 species of freshwater fish, representing eight families. The salmonids appeared to be the most sensitive group as a whole. The lowest-observed-effect-concentration for freshwater fish was reported from a 46-day study, in which a 12% reduction in the growth of Atlantic salmon (*Salmo salar)* alevins resulted from exposure to 0.47 µg Cd/L ($CdCl_2$) in soft water (pH = 7.3) (Rombough and Garside, 1982). Acutely lethal concentrations of cadmium to rainbow trout *(Oncorhyncus mykiss)* have been reported at similar concentrations (0.5 to 1.0 µg Cd/L) of cadmium chloride over 96 hours (Chapman, 1978; Cusimano *et al.,* 1986).

Data on the toxicity of cadmium were identified for 10 marine fish species, representing seven families. The lowest-effect-level reported for estuarine/marine fish species was a median lethal concentration (LC_{50}) of 420 µg Cd/L (cadmium compound not specified) in the Cyprinid minnow *(Phoxinus phoxinus)* derived from a 70-day flowthrough test (salinity = 6.7 ‰) (Bengtsson, 1977).

Only two studies were identified in which the effect of cadmium exposure on amphibians was examined (Canton and Slooff, 1982; Rao and Madhyastha, 1987). The lowest-observed-effect-concentration (LOEC) was 220 µg Cd/L ($CdCl_2$), for 25% impairment of larval development in clawed toad tadpoles *(Xenopus laevis),* in a 100-day flowthrough test (hard water)(Canton and Slooff, 1982).

Data on the toxicity of cadmium (observed as growth impairment, photosynthetic reduction, and morphological changes) to vascular and non-vascular freshwater plants were compiled for 74 species. The diatom algae, *Tabellaria flocculosa,* is the most sensitive freshwater plant tested; Adshead-Simonsen *et al.* (1981) reported

morphological cell changes in this species following a 14-day static renewal exposure to cadmium ($CdNO_3$) at 1 µg Cd/L.

Data on the toxicity of cadmium to marine plants were identified for 14 algal species from five families (Berland, 1976; Berland *et al.* 1977; Visviki and Rachlin, 1991). The LOEC was 25 µg Cd/L ($CdCl_2$) which impaired the growth of cultures of the diatom *(Skeletonema costatum)* by 80% over 8 days (pH = 7.8; salinity = 35 ‰) (Berland *et al.*, 1977).

Figure 2 summarizes the data from critical studies of concentrations of cadmium in sediments at which adverse effects on aquatic biota have been observed. No acceptable freshwater spiked-sediment studies were identified. However, in a field study of 422 sediment sites in the Ontario Great Lakes region, 5% of the known sensitive species of benthic invertebrates were absent from sediments having cadmium concentrations of >0.6 mg Cd/kg dry weight (d.w.) (Jaagumagi, 1990). Additionally, 95% of known invertebrate species were absent from sediments with cadmium concentrations of = 9.5 mg Cd/kg (d.w.).

Dose-response data on the toxicity of cadmium to marine benthic invertebrates were identified for five species, representing two families. Acute and chronic toxicity thresholds (for lethality and behavioural effects) occurred at concentrations of cadmium in sediment ranging from 5.8 to 40 mg Cd/kg (d.w.) for the amphipod *(Rhepoxynius abronius)* and the polychaete worm *(Nereis virens)*, respectively (Oakden *et al.*, 1984a;b; Sundelin 1984; Swartz *et al.*, 1985; Kemp *et al.*, 1986; Mearns *et al*, 1986; Olla *et al.*, 1988; Robinson *et al*, 1988). Statistically significant mortality (40%) and avoidance behaviour (44%) were observed for *Rhepoxynius* spp. following a 72-hour exposure to cadmium chloride at concentrations as low as 5.8 mg Cd/kg (d.w.) in a flowthrough bioassay (Oakden *et al*, 1984b).

Terrestrial Ecosystems. Figure 3 summarizes data from those studies of soil biota in which the lowest effect concentrations have been observed. Only two studies were identified in which the effect of cadmium on terrestrial invertebrates was examined (van Gestel and van Dis, 1988; Schmidt *et al.*, 1991). The LOEL for exposure to cadmium ($CdCl_2$) in soil was 2 mg $CdCl_2$/kg (d.w.), a concentration which caused a significant reduction (15%) in egg hatching of the grasshopper *(Aiolopus thalassinus)*. Also, the growth rate of adults was significantly impaired (8.5 to 12.5%) over a two generation soil test at the same cadmium concentration (Schmidt *et al.*, 1991).

Four studies were identified in which the effects of exposure to cadmium in soil on populations of free-living bacteria and fungi, and parasitic microbes were studied (Dixon and Buschena, 1988; Naidu and Reddy, 1988; Dixon, 1988; Kobus and Kurek, 1990). The LOEC for soil microbes was similar to that for invertebrates. In this study, levels of cadmium in soil (cadmium chloride) of 2.0 mg Cd/kg (d.w.) and 5.0 mg Cd/kg (d.w.) inhibited colonization of ectomycorrhizae on white pine *(Picea glauca)* roots by 62% and 87 %, respectively (Dixon and Buschena, 1988).

Eight studies were identified on the effects of cadmium on soil metabolic processes [e.g., nitrogen fixation and carbon dioxide (CO_2) production] (Naidu and Reddy, 1988; Coppola *et al,* 1988; Reber, 1989; Doelman and Haanstra, 1989; Kobus and Kurek, 1990; Wilke, 1991; Haanstra and Doelman, 1991). Impairment of soil microbial community function occurred at cadmium concentrations in soil (cadmium compound not specified) as low as 2.9 mg Cd/kg (d.w.), a level that caused a 60% reduction in nitrification (soil pH = 6.4; clay content =7.7%) over 60 days (Kobus and Kurek, 1990).

Data on the toxicity of cadmium to terrestrial plants were identified for 17 species from six families. The cadmium levels in soil that elicited adverse effects on these species ranged from 4.0 to 171 mg Cd/kg (d.w.) (Kelly *et al,* 1979; Coppola *et al,* 1988; Dixon, 1988; Adema and Henzen, 1989). Spinach was identified as the most sensitive species; the lowest-observed- effect-concentration of 4.0 mg Cd/kg ($CdSO_4$) caused a 30% reduction in yield during a 90-day study (soil pH = 6.6; clay content = 69%) (Coppola *et al.,* 1988).

Previous reviews of cadmium toxicity in vertebrate animals have used either dietary cadmium concentrations, renal tissue cadmium concentrations, or dietary cadmium intake, as indicators of cadmium exposure that could be related to toxicity (e.g., Friberg *et al.,* 1974; Scheuhammer, 1987; U.S. EPA, 1988). The present review has been limited to studies in which cadmium exposure was measured directly, i.e., renal cadmium concentrations. Use of this approach avoids the possible confounding effects of dietary changes and reduced food intake (e.g., Weigel *et al.,* 1987) inherent in dietary concentration data.

Altered kidney morphology or function are considered to be the most widely accepted endpoints of toxicity in both wild birds and mammals. Based on the limited data identified, a renal concentration of 100 mg of Cd/kg fresh weight (f.w.) is the best estimate of threshold toxicity in wild birds. Wood ducks *(Aix sponsa)* fed cadmium in their diet for 3 months showed widespread renal pathological changes at an average renal concentration of 132 mg of Cd/kg, but not at 62 mg of Cd/kg (Mayack *et al.,* 1981). Captive mallard ducks exposed to cadmium in their diet exhibited moderate to severe tubular degeneration over a renal cadmium concentration range of 88 to 134 mg of Cd/kg (White *et al.,* 1978). Nicholson and Osborn (1983) detected necrosis of renal proximal tubule cells in free-living seabirds from Britain and experimentally in Starlings *(Sturnus vulgaris)* at kidney concentrations of 10 to 70 mg of Cd/kg (f.w.) (converted from dry weight). However, Elliott *et al.* (1992) examined several species of seabirds collected on the Atlantic Coast of Canada and found no renal lesions in birds with up to 83 mg of Cd/kg (f.w.) in the kidney. Since the results of Nicholson and Osborn (1983) are significantly below accepted effect levels and these levels have not been reproduced elsewhere, they will not be included in this report.

Mammals may be more susceptible to cadmium than birds, based on the concentrations in kidney at which histopathological changes have been observed. The lowest renal concentration associated with tissue damage in a mammal was 13 to 20 mg of Cd/kg (f.w.) in mice exhibiting mild to moderate degeneration of tubular epithelial

cells (Exon *et al.* 1986). Elinder *et al.* (1981) found that horses in Sweden, which had spent between 4 and 20+ years in the fields, showed a marked increase in moderate to severe kidney morphological disorders (tubular dilation, interstitial infiltration, and glomerular changes) at a renal cadmium level of 75 mg/kg, even after accounting for the effect of age. Notably, cadmium concentration and the prevalence of lesions were significantly correlated down to about 25 mg of Cd/kg, suggesting the presence of susceptible individuals within the population. In dogs exposed to cadmium chloride in their diet for four years, atrophied and inflamed tubules and other morphological alterations in kidney were observed at renal levels of cadmium of 33 to 52 mg/kg (Anwar *et al*, 1961). Corroborating this study, threshold changes in renal ultrastructure in rats occurred at 30 mg Cd/kg (Chmielnicka *et al*, 1989), and in hepatic enzyme activity in mice at 56 mg Cd/kg (Chaney *et al.*, 1978). The weight of evidence therefore suggests that 30 mg of Cd/kg (f.w.) may be an appropriate indicator of a threshold concentration associated with renal effects in susceptible mammalian receptors.

3.0 Assessment of "Toxic" Under CEPA

3.1 CEPA 11(a) Environment

Cadmium (Cd) is present in the Canadian environment as a result of both natural processes (including forest fires, volcanic emissions, and weathering of soil, till, and bedrock) and human activities. Of the natural sources of cadmium to the Canadian environment, weathering and erosion of cadmium-bearing rocks represent perhaps the most important source. Approximately 1963, 23, and 1580 t of refined cadmium are produced, imported, and exported, respectively in Canada per year (1992 estimates). Anthropogenic sources of cadmium entry to the Canadian environment include metal production (particularly base metal smelting and refining), stationary fuel combustion (power generation and heating), transportation, solid waste disposal, and sewage sludge application.

Although quantitative releases were not identified for all of these sources, the available data indicate that an estimated 159 t of cadmium are released annually to the Canadian environment as a result of domestic anthropogenic activities. Of this total, 92% is released to air and 8% is released to water. Approximately 340 t of cadmium wastes from the metal smelting and refining industry are deposited into landfills, although the amount of cadmium from this source potentially available to the Canadian environment is not known. The most recent estimates identified indicate that base metal smelting and refining operations account for 82% (130 t) of the total releases to air and water.

Cadmium does not break down in the environment, but it may be affected by physical and chemical processes that change its mobility, bioavailability, and residence time in different environmental media. Atmospheric cadmium compounds (e.g., cadmium oxide) exist predominantly in a particulate form (fine particulate matter being more easily solubilized and bioavailable), have relatively short tropospheric residence times, and are removed from air by wet and dry deposition. Cadmium mobility and bioavailability in aquatic environments is enhanced under conditions of low pH, low hardness, low levels of suspended matter, high redox potential, and low salinity. The movement of cadmium in soil and potential accumulation by biota is enhanced by low pH, low organic matter content, large soil particle size, and high soil moisture.

This assessment focuses on the environmental compartments having the highest concentrations of cadmium in Canada and the biota considered to be most sensitive to cadmium exposure. Based on the toxicity data reviewed, effect thresholds for pelagic organisms were compared to measured (or estimated) concentrations of dissolved (i.e., the most bioavailable) cadmium in fresh and marine waters. For soils and sediments, effect thresholds were compared to total concentrations of cadmium. Because of the complex nature of these matrices, the bioavailibility of cadmium is highly variable (difficult to determine). In the case of soils, however, it was assumed that if the cadmium was likely to have been added in an acid-soluble form (e.g., CaO) and the pH of the contaminated soils was acidic, a significant fraction of the cadmium detected could be bioavailable. In addition, if mean total concentrations of cadmium in soil or sediment

greatly exceeded estimated biological effects thresholds, it was considered likely that the bioavailable fractions exceeded effects thresholds.

Cadmium toxicity has been extensively investigated in aquatic plant, invertebrate, and vertebrate taxa. For freshwaters, planktonic and benthic invertebrates appear to be the most sensitive biota, with laboratory-derived LOECs (reproductive impairment) reported as low as 0.17 µg Cd/L (48.5 mg $CaCO_3$/L) for the zooplankton, *Daphnia magna.* This laboratory threshold is strongly supported by recent *in situ* field experiments in Ontario demonstrating growth inhibition in two Cladocerans *(Daphnia galeata mendotae* and *Holopedium gibberum)* at 0.2 µg Cd/L. The effects threshold of 0.17 µg Cd/L for freshwaters is exceeded by total mean concentrations recently reported in waters from four lakes in the vicinity of known sources (e.g., base metal smelters) in Ontario. Older data collected in the vicinity of known sources in Manitoba also exceed this threshold (see Figure 3). Limited data on amounts of cadmium in filtered (<0.45 µm) as opposed to unfiltered samples of lake water suggest that most of the cadmium in Canadian lake waters is present in the dissolved phase (Lum, 1987; Malley *et al*, 1989).

Invertebrates are also considered to be among the most sensitive biota tested in marine water. The lowest-observed-effect-concentration identified was 1.2 µg Cd/L, based on reduced survival and reproduction of the zooplankton, *Mysidopsis bahia.* Dividing the LOEC by a factor of 10 to account for differences in species sensitivity and to extrapolate laboratory findings to the field yields an estimated effects threshold of 0.12 µg Cd/L. Although monitoring data for marine waters in Canada are limited, this threshold is exceeded by a mean dissolved cadmium concentration in Belledune Harbour, New Brunswick, and is within the range of dissolved cadmium concentrations observed in False Creek estuary (Vancouver Harbour), British Columbia (see Figure 1).

Only limited data were identified to determine the effects of cadmium in sediments on freshwater biota. No spiked-sediment bioassays were identified. However, in a co-occurrence screening survey of benthic invertebrate communities and sediment chemistry in selected Ontario lakes, community structure changes (absence of 5% of the species) occurred in sediments with cadmium concentrations > 0.6 mg/kg (d.w.). Major community structure changes (absence of 95% of the species) were observed in sediments with concentrations of cadmium > 9.5 mg/kg (d.w.). Given that experimentally-derived dose-response data on freshwater benthic biota were not identified, the significance of the estimated thresholds derived using the screening level approach cannot be fully evaluated and compared against identified sediment concentration data.

A range of acute and chronic sediment bioassay data were identified for marine benthic biota. The most sensitive effects reported were mortality (40%) and behavioural effects (44%) for the amphipod *Rhepoxynius abronius* at 5.6 mg/kg (d.w.) following a 72-hour exposure period. Concentrations associated with lethality following acute exposure and with various sublethal effects following chronic exposure range from 6.5 to 11.5 mg/kg (d.w.) for *R. abronius* and two other infaunal amphipods, *Eohaustorius*

sencillus and *Pontoporeia affinis.* Dividing the lowest-observed- effect-level by a factor of 10 to account for differences in species sensitivity and to extrapolate laboratory findings to the field yields an estimated effects threshold of 0.56 mg/kg (d.w.). Although monitoring data for marine sediments in Canada are limited to three regions (Quebec, New Brunswick, and British Columbia), this estimated effects threshold is exceeded (by at least a factor of 10) by the mean concentrations of cadmium reported from Belledune Harbour, New Brunswick, and the range of concentrations from Vancouver Harbour, British Columbia (see Figure 2).

The sensitivity of flora and fauna in soil to cadmium is well established. A wide range of laboratory and field effects studies with soil invertebrates, micro-organisms, metabolic processes, and vascular plants consistently support an effects threshold in soil of 2.0 mg/kg (d.w.) (total cadmium). Effects associated with this threshold range from physiological impairment in individual organisms (e.g., growth, reproduction) to impacts on soil community structure (e.g., altered microbial populations) and function (e.g., nitrogen fixation, CO_2 evolution). This effects threshold is exceeded by mean soil concentrations recently reported from various sites and regions in the vicinity of known or suspected sources (e.g., base metal smelters, and other industrial operations) in Manitoba, Ontario, Quebec, and British Columbia (see Figure 3).

Critical tissue concentrations of cadmium of 30 mg Cd/kg (f.w.) in mammalian kidney and 100 mg Cd/kg (f.w.) in avian kidney were used to identify wildlife populations at potential risk from cadmium toxicity. In long-term studies with dogs (4 years), horses (4 to 20+ years), and rats (18 months), renal tissue damage was observed at cadmium tissue levels of 33, 75, and 120 mg Cd/kg (f.w.), respectively. Due to a lack of information on renal histopathology in wildlife having elevated kidney cadmium levels, risk to those species was assessed using the data collected on domesticated animals exposed to cadmium under controlled conditions. Therefore, based on an estimated effects threshold concentration of 30 mg Cd/kg (f.w.) in mammalian renal tissue, moose from Ontario and Quebec as well as white-tailed deer from Ontario are considered to be at risk from cadmium toxicity (Figure 4). In addition, several species of marine mammals collected in the Canadian Arctic and Atlantic coasts (narwhal, pilot whale, ringed seal, and harp seal) had renal cadmium levels which exceeded the estimated effects threshold concentration. Leach's storm petrels collected on the Canadian Pacific coast were found to have kidney cadmium levels equal to 100 mg Cd/kg (f.w.), the calculated effects threshold for avian kidney.

Based on available information, it has been concluded that dissolved and soluble* forms of inorganic cadmium are entering the environment in a quantity or concentration or under conditions that are having or may have a harmful effect on the environment.

* The term "soluble" includes water-soluble forms of cadmium (e.g., cadmium chloride, cadmium sulphate, cadmium nitrate), as well as more stable forms (e.g., cadmium sulphide, cadmium oxide) that can he transformed and made more soluble under certain conditions of pH (e.g., acidic mine tailings) or redox potential (e.g., buried reducing sediment) in the environment.

3.2 CEPA 11(b) Environment on Which Human Life Depends

Inorganic cadmium compounds occur primarily in particulate form in the atmosphere. These compounds have relatively short residence times (1 to 4 weeks), low average concentrations (0.40 ng/m^3), and do not absorb infrared radiation. Thus, inorganic cadmium compounds are not expected to contribute to global climate change. Also, these compounds are not expected to react with ozone, and therefore, are not likely to be involved in stratospheric ozone depletion.

Therefore, based on available information, it has been concluded that inorganic cadmium compounds are not entering the environment in a quantity or concentration or under conditions that constitute a danger to the environment on which human life depends.

3.3 CEPA 11(c) Human Health

3.3.1 *Exposure*

Estimates of the average daily intake of cadmium (on a per body weight basis) for the general population in Canada are presented in Table 2. Due to the lack of identified data on the speciation of cadmium in various environmental media, it was not possible to estimate the exposure of the general population to individual cadmium compounds. Therefore, the values presented refer to total cadmium. Based on these estimates, the principal route of intake for all age groups is from ingestion of food. Intakes of cadmium by the general population via air are estimated to be roughly two to three orders of magnitude lower, although cadmium compounds are more readily absorbed by inhalation (up to 50%) than by ingestion (approximately 5%) (Nordberg *et al.,* 1985). The estimated intakes in drinking water and soil are also relatively small, compared to those in food.

Cigarette smoking also contributes substantially to total exposure to cadmium by smokers; the estimated intake from this source ranges from 0.053 and 0.066 µg/[kg (b.w.)·d] for persons smoking 20 cigarettes daily. The contribution of smoking to total exposure to cadmium is confirmed by the elevated body burdens of cadmium in smokers (Section 2.3). Exposure to cadmium in other household products has not been estimated. Exposure to cadmium in foods contaminated by glazed ceramic containers is considered to be minimal, and available data are insufficient to estimate the magnitude of exposures from hobbies *(e.g.,* metal working, pottery) that involve working with materials that contain cadmium compounds.

People residing in the vicinity of point sources may be exposed to higher levels of cadmium, in air, water, soil, and food, than the general population. The data on levels in the vicinity of point sources in Canada are primarily those for smelters. Based on the most complete dataset identified, the estimated intakes in air and drinking water by people in the vicinity of some smelters in Canada are between one and two orders of

Table 2 Estimated Intakes of Cadmium for Various Age Classes of the General Population of Canada

	Estimated Cadmium Intake {µg/[kg(b.w.)·d]}				
	Age				
Medium	0 to 6 mo[a]	7 mo to 4 yr[b]	5 to 11 yr[c]	12 to 19 yr[d]	20 to 70 yr[e]
Air[f]	0.00029 to 0.0011	0.00039 to 0.0015	0.00044 to 0.0018	0.00037 to 0.0015	0.00033 to 0.0013
Drinking water[g]	0 to 0.0026	≤0.00015 to 0.0014	≤0.00011 to 0.0010	≤0.000088 to 0.00079	≤0.000057 to 0.00051
Food[h]	0.27 to 0.62	0.64	0.51	0.29	0.21
Soil[i]	0.0028 to 0.0057	0.0022 to 0.0044	0.00073 to 0.0015	0.00020 to 0.00040	0.00016 to 0.00033
Cigarette smokers[j]	-	-	-	0.066	0.053

a Assumed to weigh 7 kg, breathe 2 m^3 of air, drink 0 (breast fed) or 0.2 (not breast fed) L of water per day, and ingest 35 mg of soil daily (EHD, 1992).

b Assumed to weigh 13 kg, breathe 5 m^3 of air, drink 0.2 L of water per day, and ingest 50 mg of soil daily (EHD, 1992).

c Assumed to weigh 27 kg, breathe 12 m^3 of air, drink 0.3 L of water per day, and ingest 35 mg of soil daily (EHD, 1992).

d Assumed to weigh 57 kg, breathe 21 m^3 of air, drink 0.5 L of water per day, and ingest 20 mg of soil daily (EHD, 1992).

e Assumed to weigh 70 kg, breathe 23 m^3 of air, drink 0.4 L of water per day, and ingest 20 mg of soil daily (EHD, 1992).

f Based on the range of mean concentrations of inhalable (< 10 µm diameter) cadmium reported for 1984 to 1989 in 24-h samples of ambient air at 15 sites in 11 cities across Canada (1 to 4 ng/m^3, or 0.001 to 0.004 µg/m^3) (EC, 1991), and assuming the same concentrations for indoor air.

g Based on the range of concentrations of cadmium in water supplies (≅ 10 to 90 ng/L, or =0.01 to 0.09 µg/L) in a 1977 national survey of tap water samples from 71 drinking water supplies across Canada (Méranger *et al,* 1981a); the results of more recent monitoring from various regions of Canada, including the maritime provinces between 1985 and 1988 (EC, 1989) and Ontario in 1992 (Lachmaniuk, 1993), have been similar. Because exclusively breast-fed infants do not require supplementary liquids (NHW, 1983), the lower end of the range for the 0 to 6 month age class assumes no drinking water consumption.

h For infants (0 to 6 months), based on range of mean intakes estimated by Dabeka (1989), 0.27 to 0.62 µg/[kg(b.w.)·d] for infants exclusively fed on breast milk and on soy-based formula, respectively; for other age classes, intakes were estimated based on the concentrations of cadmium determined in the Total Diet Program (Dabeka and McKenzie, 1992), assuming that foods were consumed in the amounts determined in the Nutrition Canada Survey (EHD, 1992).

i Based on range of mean concentrations of cadmium in limited surveys from Ontario and British Columbia (0.56 to 1.14 mg/kg dry weight, or 0.000 56 to 0.001 14 µg/mg dry weight) compiled by Bewers *et al* (1987).

j Based on cadmium content of mainstream cigarette smoke (0.187 µg/cigarette) estimated by Rickert and Kaiserman (1993), and a smoking rate of 20 cigarettes per day [the approximate average for Canadians aged 15 and older as of 1990 (Kaiserman, 1993)].

Table 3 Estimated Intakes of Cadmium for Populations in the Vicinity of Some Point Sources in Canada

	Estimated Cadmium Intake {µg/[kg(b.w.)·d]}				
	Age				
Medium	0 to 6 mo[a]	7 mo to 4 yr[b]	5 to 11 yr[c]	12 to 19 yr[d]	20 to 70 yr[e]
Air[f]	0.013	0.018	0.020	0.017	0.015
Drinking water[g]	0 to 0.11	0.031 to 0.062	0.017 to 0.033	0.011 to 0.023	0.011 to 0.021
Food[h]	0.27 to 0.62	0.64	0.51	0.29	0.21
Soil[i]	0.026	0.020	0.0067	0.0018	0.0015
Cigarette smokers[j]	-	-	-	0.066	0.053

a Assumed to weigh 7 kg, breathe 2 m^3 of air, drink 0 (breast-fed) or 0.75 L (not breast-fed) of water per day, and ingest 35 mg of soil daily (EHD, 1992).

b Assumed to weigh 13 kg, breathe 5 m^3 of air, drink 0.8 L of water per day, and ingest 50 mg of soil daily (EHD, 1992).

c Assumed to weigh 27 kg, breathe 12 m^3 of air, drink 0.9 L of water per day, and ingest 35 mg of soil daily (EHD, 1992).

d Assumed to weigh 57 kg, breathe 21 m^3 of air, drink 1.3 L of water per day, and ingest 20 mg of soil daily (EHD, 1992).

e Assumed to weigh 70 kg, breathe 23 m^3 of air, drink 1.5 L of water per day, and ingest 20 mg of soil daily (EHD, 1992).

f Based on mean concentrations of cadmium reported between December 1988 and March 1991 in 24-h samples of ambient air in Flin Flon, Manitoba (46 ng/m^3, or 0.046 µg/m^3), site of a base metal smelter (Bezak, 1991 a), and assuming the same concentrations for indoor air.

g Based on the potential range of cadmium concentrations (0.5 to 1 µg/L) in treated drinking water in Flin Flon, Manitoba, between 1983 and 1987 (4/8 samples contained 1 µg cadmium/L) (Bezak, 1991b), assuming 0 and 1 µg/L (the detection limit) for samples with no detectable cadmium; concentrations of cadmium were also elevated (0.2 µg/L) in samples collected from Sudbury in 1992 (Lachmaniuk, 1993). Cadmium has not been detected in several other surveys in the vicinity of smelters in Canada, but these are limited by high limits of detection. Because exclusively breast-fed infants do not require supplementary liquids (NHW, 1983), the lower end of the range for the 0 to 6 month age class assumes no drinking water consumption.

h For infants (0 to 6 months), based on range of mean intakes estimated by Dabeka (1989), 0.27 to 0.62 µg/[kg (b.w.) · d] for infants fed exclusively on breast milk and on soy-based formula, respectively; for other age classes, intakes were estimated based on the concentrations of cadmium determined in the Total Diet Program (Dabeka and McKenzie, 1992), assuming that foods were consumed in the amounts determined in the Nutrition Canada Survey (EHD, 1992). Available data were considered inadequate to derive reliable estimates of exposure for populations consuming foods originating in the vicinity of smelters in Canada.

i Based on mean concentration of cadmium at 12 sites in the vicinity of the smelter at Flin Flon, Manitoba (5.2 mg/kg dry weight, or 0.005 2 µg/mg dry weight) (Pip, 1991).

j Based on cadmium content of mainstream cigarette smoke (0.187 µg/cigarette) estimated by Rickert and Kaiserman (1993), and a smoking rate of 20 cigarettes per day [the approximate average for Canadians aged 15 and older as of 1990 (Kaiserman, 1993)].

magnitude higher than those for the general population (Table 3). Intakes via soil are also estimated to be substantially increased in the vicinity of point sources, although not to the same extent as for air and drinking water, i.e., several times the intake for the general population. It is also possible that the intake of cadmium is elevated in populations consuming substantial quantities of food originating in the vicinity of point sources such as smelters. However, the available data are inadequate to reliably estimate the increased contribution to the daily intake of cadmium from the consumption of such foods, since analyses have only been performed on a very limited range of foods, and there are no data on the consumption by Canadians of produce originating from the vicinity of such point sources.

3.3.2 *Effects*

One of the critical endpoints for assessment of whether cadmium and its compounds are "toxic" under Paragraph 11(c) of CEPA is considered to be carcinogenicity. Most of the relevant information for this endpoint relates to inhalation exposure. Therefore, the weight of evidence for carcinogenicity of inhaled cadmium compounds has been assessed based on the criteria developed for this endpoint for "Determination of "Toxic" under Paragraph 11(c) of the *Canadian Environmental Protection Act"* (EHD, 1992).

The carcinogenicity of cadmium compounds has been investigated in only a small number of occupationally exposed populations. Interpretation of the results of these studies is difficult for several reasons. In all cases, exposure to cadmium compounds in the workplace was accompanied by exposure to compounds of other heavy metals (most often lead, zinc, and/or nickel, some of which are associated with cancer of the same sites as for cadmium, particularly the lung), and potential confounding by smoking was adequately assessed in only one study. In addition, the observed number of deaths due to lung cancer was small in most studies, and there was only limited information on the levels of cadmium to which the workers were exposed.

There is evidence of increased mortality due to lung cancer following prolonged inhalation of cadmium compounds (mainly cadmium oxide dust and fumes, as well as cadmium sulphide) in the workplace. In an historical cohort study of 606 production workers at a cadmium smelter in the United States (Stayner *et al.,* 1990; 1992a;b), there was a significant excess of deaths from lung cancer among non-Hispanics hired after 1926, when the facility was converted from an arsenic smelter. Mortality from lung cancer increased significantly with increasing cumulative exposure to cadmium; urinary concentrations of cadmium, measured in almost half of the cohort, indicated that these workers were heavily exposed. This is the only available study in which smoking was considered. The prevalence of current or former smokers in the cohort was similar to that in the general population, and the observed excess was greater than what would be expected from variations in smoking alone. However, exposure to arsenic occurred even after the facility was no longer an arsenic smelter, and it was not possible to completely eliminate the possibility of confounding exposure to arsenic [a fact that Stayner *et al.*

(1993) acknowledged], particularly considering that there were only between two and seven lung cancer cases in each cumulative exposure class.

In the largest cohort of nearly 7000 workers who were exposed to unspecified cadmium compounds (Armstrong and Kazantzis, 1983; Kazantzis *et al.*, 1988), there again was excess mortality from lung cancer with increasing intensity of exposure, but the increase could not be accounted for by cumulative exposure to cadmium. Rather, based on a nested case-control study, it was associated with the estimated cumulative exposure to arsenic or lead (Ades and Kazantzis, 1988). It should be noted that this cohort was not as heavily exposed as the one studied by Stayner *et al.* (1990; 1992a;b). The smoking history of the workers was not taken into account in these studies.

The results of other studies of the possible association between occupational exposure to cadmium and lung cancer are mixed (Kjellström *et al.*, 1979; Holden, 1980; Elinder *et al.*, 1985c; Sorahan, 1987). However, these investigations contribute little to the weight of evidence for carcinogenicity due principally to their small sizes and/or lack of account for potentially confounding exposures.

There is some evidence of a weak association between exposure to cadmium compounds and prostatic cancer. Although some excesses have been observed (Kipling and Waterhouse, 1967; Lemen *et al.*, 1976; Elghany *et al.*, 1990; Holden, 1980; Bako *et al.*, 1982; Shigematsu *et al*, 1982), they have not been confirmed in subsequent follow-up (Sorahan and Waterhouse, 1983; Thun *et al.*, 1985) or in the studies of strongest design (Kazantzis *et al.*, 1988).

Increases in other cancers have not been consistently observed in historical cohort studies of cadmium-exposed workers or in limited studies in Japanese, Belgian, and U.K. populations exposed to cadmium in the environment.

Cytogenetic studies of humans exposed to cadmium compounds in the workplace or in the general environment have yielded inconsistent results, and the positive studies have often been confounded by concomitant exposure to other metals which may themselves cause cytogenetic changes (Shiraishi and Yosida, 1972; Deknudt *et al.*, 1973; Bui *et al.*, 1975; Deknudt and Leonard, 1975; Shiraishi, 1975; Bauchinger *et al.*, 1976; O'Riordan *et al.*, 1978; Fleig *et al.*, 1983; Nogawa *et al.*, 1986; Tang *et al.*, 1990).

Toxicological studies in animal species considered most relevant for assessing the weight of evidence of carcinogenicity are those in which animals were exposed by routes similar to those by which humans are exposed in the general environment. Results of investigations in which compounds have been injected directly are considered as supporting data only.

In studies with experimental animals, the carcinogenicity of cadmium chloride has been investigated most extensively. In the earliest study of adequate design in which rodents were exposed to cadmium compounds by inhalation, there were significant dose-related increases in the incidence of lung cancers in male rats exposed chronically to cadmium chloride aerosols at concentrations of 13.4 to 50.8 µg Cd/m^3 (Takenaka *et*

al, 1983; Oldiges *et al.*, 1984). In a subsequent study, there were compound-related increases in malignant lung tumours in rats of both sexes following long-term exposure to 30 µg Cd/m^3 as cadmium chloride. In this study, there were also significant increases in lung cancers in rats following exposures of shorter duration (40 hours/week for 6 months) to 90 µg Cd/m^3 as cadmium chloride aerosol (Oldiges *et al.*, 1989; Glaser *et al.*, 1990). In contrast to the results of studies in rats, lung tumour incidence was not increased in female mice or in hamsters of both sexes exposed chronically to 30 or 90 µg Cd/m^3 as cadmium chloride aerosol (Heinrich *et al.*, 1989). However, there was compound-related mortality in mice at both concentrations which may have limited the sensitivity of the bioassay. The evidence that ingestion of cadmium chloride is carcinogenic to experimental animals is limited, based on the two available studies of adequate design. In the most comprehensive study, there was no significant increase in the incidence of benign or malignant tumours in rats of both sexes exposed for two years to as much as 50 ppm of Cd {approximately 2.5 mg Cd/[kg (b.w.) · d]} as cadmium chloride in the diet (Loser, 1980). However, in a somewhat smaller study where the maximum concentrations to which animals were exposed were greater, male rats exposed to 25 to 200 ppm of Cd {approximately 1.25 to 10 mg Cd/[kg (b.w.) · d]} as cadmium chloride in their diet for 77 weeks exhibited significant increases in the incidences of leukemia at 50 to 100 ppm of Cd in zinc-adequate diets and 200 ppm of Cd in zinc-deficient diets. There were also significant increases in benign interstitial cell tumours of the testes at 200 ppm in a zinc-adequate diet, and of proliferative lesions of the ventral prostate at 50 ppm of Cd in both diets (Waalkes and Rehm, 1992). In addition, in studies involving routes less relevant to environmental exposure, subcutaneous injection of cadmium chloride has produced local sarcomas in rats (also following intramuscular or prostatic injection), testicular tumours in rats and mice, and (in single studies) pancreatic islet-cell and prostatic tumours (IARC, 1976; 1987a; Waalkes *et al,* 1989).

The genotoxicity of cadmium chloride has been extensively studied. *In vivo* studies of this compound have shown it to be genotoxic following ingestion or injection (Shimada *et al,* 1976; Watanabe *et al.,* 1979; Pomerantseva *et al.,* 1980; Watanabe and Endo, 1982; Mukherjee *et al.*, 1988a;b; Han *et al.,* 1992). Cadmium chloride has had some genotoxic activity in extensive testing *in vitro,* most consistently manifested as cytogenetic alterations or DNA damage in mammalian cells (including human) (U.S. EPA, 1985b).

The carcinogenicity of cadmium oxide has been investigated in a number of studies. There were compound-related increases in malignant lung tumours in rats of both sexes following long-term inhalation of 30 to 90 µg of Cd/m^3 as cadmium oxide dust, and 30 µg/m^3 as cadmium oxide fumes. In this study, there were also significant increases in lung cancers in rats following exposures of shorter duration (40 hours/week for 6 months) to 90 µg of Cd/m^3 as cadmium oxide dust (Oldiges *et al.,* 1989; Glaser *et al.,* 1990). Lung tumours were also induced in female mice following long-term exposure to 10 µg of Cd/m^3 as cadmium oxide dust or to 30 µg of Cd/m^3 as cadmium oxide fumes [also with intermittent exposure (40 hours/week) to 90 µg of Cd/m^3 as the

oxide fume], although lung tumour incidence was not increased in hamsters of both sexes exposed chronically to 30 or 90 µg of Cd/m^3 (Heinrich *et al,* 1989). Subcutaneous injection of cadmium oxide induced local sarcomas in rats in one study (Kazantzis and Hanbury, 1966, cited in IARC, 1976).

In the sole investigation that was identified of the genotoxicity of cadmium oxide, the compound did not induce point mutations in *Salmonella typhimurium* (Mortelmans *et al,* 1986).

The carcinogenicity of cadmium sulphate has been investigated in only a few studies. There were compound-related increases in malignant lung tumours in rats of both sexes following long-term inhalation of 90 µg of Cd/m^3 as cadmium sulphate aerosol (Oldiges *et al,* 1989; Glaser *et al,* 1990). In contrast, lung tumour incidence was not increased in female mice or in hamsters of both sexes exposed chronically to 30 or 90 µg of Cd/m^3 as cadmium sulphate aerosol (Heinrich *et al.,* 1989), although compound-related mortality in mice at both concentrations may have limited the sensitivity of the bioassay. Cadmium sulphate had no effect on the incidence of tumours in rats and mice following long-term exposure by stomach tube (Levy and Clack, 1975; Levy *et al,* 1975), but the sensitivity of these experiments was inadequate due to the low doses administered {up to about 0.06 mg of Cd/[kg (b.w.) · d] in rats and 0.3 mg/[kg (b.w.) · d] in mice, doses that did not affect the range of parameters examined}, and the limited range of tissues examined microscopically. Subcutaneous injection of cadmium sulphate induced testicular tumours in rats, but not in mice (Roe *et al,* 1964, cited in IARC, 1976).

The genotoxicity of cadmium sulphate has not been studied *in vivo,* but results have been positive in some *in vitro* studies with this compound (Röhr and Bauchinger, 1976; Kanematsu *et al,* 1980; Oberly *et al,* 1982; Sina *et al,* 1983).

The carcinogenicity of cadmium sulphide has been examined in only a few studies. There were compound-related increases in malignant lung tumours in rats of both sexes following long-term inhalation of between 90 and 810 µg of Cd/m^3 as cadmium sulphide aerosol. In this study, there were also significant increases in primary lung tumours in rats following exposures of shorter duration (40 hours/week for 6 months to 270 µg of Cd/m^3, or 22 hours/day for 3 to 4 months to 2430 µg of Cd/m^3) to cadmium sulphide aerosol (Oldiges *et al.,* 1989; Glaser *et al,* 1990). However, lung tumour incidence was not increased in female mice or in hamsters of both sexes exposed chronically to 90 to 1000 µg of Cd/m^3 as cadmium sulphide aerosol (Heinrich *et al,* 1989). [It should be noted that exposure to cadmium sulphide in all of these studies would have included cadmium sulphate as a photo-oxidative product (König *et al,* 1992)]. Lung tumours also developed following repeated direct (intratracheal) administration of cadmium sulphide to the lungs of rats (Pott *et al,* 1987). Subcutaneous or intramuscular injection of cadmium sulphide induced injection-site sarcomas in rats (Kazantzis and Hanbury, 1966, cited in IARC, 1976).

Cadmium sulphide has been genotoxic in mammalian cells *in vitro* (Shiraishi *et al.,* 1972; Costa *et al.,* 1982; Robison *et al.,* 1982).

Principally on the basis of results from inhalation studies in animal species and supporting data on genotoxicity, inorganic cadmium compounds* have been classified in Group II ("probably carcinogenic to humans") of the classification scheme for carcinogenicity developed for the determination of "toxic" under Paragraph 11(c) of CEPA (EHD, 1992). For substances classified in Group II, where data permit, the estimated total daily intake or concentrations in relevant environmental media are compared to quantitative estimates of carcinogenic potency [the concentration or dose that induces a 5% increase in the incidence of or mortality due to relevant tumours ($TD_{0.05}$)], and expressed as an exposure/carcinogenic potency index (EPI), to characterize risk and provide guidance for further action (i.e., analysis of options to reduce exposure) (EHD, 1992).

The available epidemiological studies of populations exposed to cadmium compounds in the workplace are not considered suitable for estimating a $TD_{0.05}$, due to the lack of adequate account of confounding by other substances.** Since there is sufficient evidence of carcinogenicity of cadmium compounds (namely, cadmium chloride, cadmium oxide, cadmium sulphate, and cadmium sulphide) to animals following exposure by inhalation, but not by the oral route, the estimate of carcinogenic potency has been derived on the basis of data from a long-term bioassay in which animals were exposed to cadmium compounds by inhalation. The estimate of carcinogenic potency has been derived from the data on lung cancers induced in rats by chronic exposure to cadmium chloride aerosols (Takenaka *et al.,* 1983; Oldiges *et al.,* 1984); these data are considered to provide the most reliable estimate of the $TD_{0.05}$, as a consequence of the clear dose-response observed in this experiment for total lung tumour incidence (0 µg of Cd/m^3, 0/38; 13.4 µg Cd/m^3, 6/39; 25.7 µg Cd/m^3, 20/38; 50.8 µg Cd/m^3, 25/35).

The estimated $TD_{0.05}$ for cadmium chloride was calculated by first fitting the multistage model to the lung tumour incidences observed by Takenaka *et al.* (1983; Oldiges *et al.,* 1984), which yields a $TD_{0.05}$ for the rat of 2.9 µg of Cd/m^3. This value was subsequently amortized to be constant over the lifetime of the rat (the exposure was 23 hours/day for 72 weeks), adjusted for the longer than standard lifetime duration of the experiment (130 weeks), and converted to an equivalent concentration in humans using standard values for the breathing volumes and body weights of rats and humans. The

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***** These four compounds have not been classified individually since available data indicate that it is most likely the cadmium ion itself that is carcinogenic. For example, exposure to zinc compounds reduced the carcinogenicity of inhaled cadmium oxide to rats (Oldiges *et al,* 1989; Glaser *et al.,* 1990), and of cadmium chloride injected subcutaneously in rats and mice (IARC, 1976; Waalkes *et al.,* 1989).

** It should be noted that a $TD_{0.05}$ derived on the basis of the data on lung cancer mortality in the cohort of cadmium smelter workers reported by Stayner *et al* (1990; 1992a;b) - the only population for which there are quantitative data relating exposure to cadmium compounds and mortality from cancer-would be within the same range as those based on the studies in animals.

resultant $TD_{0.05}$ estimated for humans is 5.1 µg of Cd/m^3. [It should be noted that $TD_{0.05}$ values derived from the lung tumour incidences observed in rats inhaling cadmium chloride, cadmium oxide dust, cadmium sulphate, and cadmium sulphide* (Oldiges *et al.*, 1989; Glaser *et al.*, 1990) are similar, ranging from 2.7 to 12.7 µg/m^3. A $TD_{0.05}$ was not calculated based on the results for cadmium oxide fume, since the general population is unlikely to be exposed to this form.]

The exposure/carcinogenic potency indices (EPI) have been calculated on the basis of the calculated $TD_{0.05}$, and the concentration of cadmium in ambient air to which the general population of Canada and populations in the vicinity of point sources of industrial emissions (i.e., certain smelters) are exposed. [No data were identified on the speciation of cadmium present in ambient air in Canada. Hence, the $TD_{0.05}$ can be compared only to concentrations of total cadmium in air. This approach is justified on the basis that particulate cadmium chloride, cadmium oxide, and cadmium sulphate are generally the principal compounds of cadmium in ambient air (ATSDR, 1993), and the carcinogenic potencies of these compounds are similar.] The mean concentration of inhalable (<10 µm aerodynamic diameter) cadmium at monitoring stations across Canada between 1984 and 1989 ranged from 1 ng/m^3 in Winnipeg and Ottawa to 4 ng/m^3 at sites in Windsor and Montreal (EC, 1991). Based on these data, EPIs for the general population in Canada range from 2.0×10^{-4} to 7.8×10^{-4} (0.001 µg/m^3 ÷ 5.11 µg/m^3 to 0.004 µg/m^3 ÷ 5.11 µg/m^3). The mean concentration of cadmium in Flin Flon, Manitoba (where a base metal smelter is located) between December 1988 and March 1991, was 46 ng/m^3 (Bezak, 1991a); levels were similar in the vicinity of smelters in British Columbia and New Brunswick. The EPI for populations in the vicinity of point sources (i.e., certain smelters) in Canada is 9.0×10^{-3} (0.046 µg/m^3 ÷ 5.11 µg/m^3). Based on these EPIs for the general population and those in the vicinity of point sources, which are in turn based solely on considerations of potential health effects, the priority for further action (i.e., analysis of options to reduce exposure) is considered to be high.

A range of non-neoplastic effects has also been observed in humans and animals exposed to cadmium compounds. The critical non-neoplastic effect of exposure to cadmium in occupationally and environmentally exposed human populations is renal tubular dysfunction, characterized initially by an increased excretion of low molecular weight proteins in the urine. (Osteoporosis and osteomalacia, which are the only other effects clearly demonstrated following environmental exposure to cadmium, occur at higher exposures than those affecting kidney function.)

The results of studies in animals chronically exposed to cadmium chloride, cadmium oxide, cadmium sulphate, or cadmium sulphide by the oral route (the principal route of exposure for the general population) generally support those from the epidemiological studies of environmentally exposed humans. Thus, in a number of animal species, damage to the kidney is one of the effects observed at the lowest levels, although blood pressure, skeletal morphology or mineralization, and metabolism of

* $TD_{0.05}$ values for cadmium sulphide were calculated based on the tumour incidences from only the two lowest concentrations, because of high compound-related mortality at the higher concentrations.

calcium were also affected at similar doses in some studies. (Effects on fertility and neurobehavioural development have been reported at much lower doses in isolated studies, but these results require confirmation.)*

Indeed, several lines of evidence indicate that members of the general population in Canada are exposed to cadmium compounds in amounts that are at or near those that have been associated with mild effects on the kidney. Concentrations of cadmium in ambient air and soil in the vicinity of some point sources of industrial emissions (i.e., certain smelters) in Canada are similar to those in regions of Belgium where zinc smelters have operated, where there was a statistically significant association between exposure to cadmium (as indicated by urinary levels of cadmium) and proteinuria (Buchet *et al.*, 1990; Lauwerys *et al.*, 1990; Sartor *et al.*, 1992), or alterations in metabolism of calcium (Staessen *et al.*, 1991 a), after controlling for a number of confounding factors. [For example, mean concentrations near Canadian smelters range from 10 to 46 ng of Cd/m^3 in ambient air, and 5.2 to 19 mg of Cd/kg (d.w.) in soil, compared with a 50th percentile in ambient air of < 10 to 18 ng of Cd/m^3, and a mean in soil of 7.4 to 21 mg of Cd/kg (d.w.) for the more contaminated regions studied in Belgium.) The threshold for proteinuria in the population in this study occurred at an estimated mean renal cortical concentration of cadmium of 50 ppm (mg/kg) (w.w.)** (Buchet *et al.*, 1990), a level that is exceeded in some non-smoking members of the Canadian general population (LeBaron *et al.*, 1977). Cadmium-associated proteinuria was also observed in a Dutch study of a population in a region with a history of non-ferrous metal smelting; significant differences in urinary excretion of several proteins, as well as of calcium and sodium, were noted between an exposed population and a control population in which the mean measured concentrations of cadmium in renal cortex [34 and 27 ppm (w.w.), respectively] were similar to those of the Canadian general population (Kreis, 1992). The observed variation in the concentrations of cadmium in renal cortex with age in the general population is also consistent with the estimate of 50 ppm (mg/kg) for the threshold concentration for tubular proteinuria. Thus, in surveys of autopsy samples, the level of cadmium in the renal cortex of Canadians from the general population peaks at middle age at a mean concentration of approximately 50 ppm [from 42 to 66 mg/kg (w.w.) in various studies (LeBaron *et al.*, 1977; Méranger *et al.*, 1981b; Chung *et al.*, 1986)], after which the concentration declines, possibly as a consequence of renal tubular dysfunction.

On the basis of available data, inorganic cadmium compounds have been classified as "probably carcinogenic to humans" by the inhalation route (i.e., as substances for which there is considered to be some probability of harm for one of the critical effects at

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* In the limited number of studies in which other cadmium compounds were administered to laboratory mammals (these have been summarized in the health-related supporting documentation for "cadmium and its compounds"), the effects observed were similar to those following exposure to cadmium chloride, cadmium oxide, cadmium sulphate, or cadmium sulphide.

** It should be noted, however, that this estimate of the critical concentration in the renal cortex is uncertain, as there is a considerable range in the reported values for the pharmacokinetic parameters on which it is based.

any level of exposure). Moreover, available data indicate that portions of the Canadian population may be exposed to levels of cadmium near those that induce mild renal effects.

It has been concluded, therefore, that inorganic cadmium compounds are entering the environment in a quantity or concentration or under conditions that may constitute a danger in Canada to human health or life.

This approach is consistent with the objective that exposure to non-threshold toxicants should be reduced wherever possible and obviates the need to establish an arbitrary *"de minimis"* level of risk for the determination of harm under the Act.

3.4 Conclusion

Based on available information, it has been concluded that dissolved and soluble forms of inorganic cadmium are entering the environment in a quantity or concentration or under conditions that are having or may have a harmful effect on the environment. It has been concluded that inorganic cadmium compounds are not entering the environment in a quantity or concentration or under conditions that constitute a danger to the environment on which human life depends. Finally, it has been concluded that inorganic cadmium compounds are entering the environment in a quantity or concentration or under conditions that may constitute a danger to human life or health in Canada.

4.0 Recommendations for Research and Evaluation

In assessing the entry, exposure, and effects of cadmium and its compounds on the environment and human health in Canada, data gaps have been identified, although these data are not considered to be critical to the determination of "toxic" under CEPA. It is recommended that additional information be collected on:

1. updating and completing the inventory of cadmium releases from anthropogenic sources in Canada (e.g., incineration facilities, sewage sludge application to soils, and chemical manufacturing), and natural sources;

2. species of cadmium present in the Canadian environment and their bioavailability in different environmental media;

3. levels of cadmium in Arctic marine mammals, pelagic seabirds, and cervids, including the sources of exposure that contribute to the high tissue cadmium burdens in some species; (histopathological examinations of the above species exposed to elevated levels of cadmium should be carried out to further identify populations that may be at risk from cadmium toxicity);

4. dietary cadmium intake by wild mammals (particularly cervids) and birds (particularly seabirds), to complement the oral-dose toxicological studies recommended below;

5. species and concentrations of cadmium in foodstuffs originating from the vicinity of point sources in Canada, and on the amounts of such produce that are consumed by Canadians;

6. effects of cadmium in freshwater sediments on benthic biota;

7. the toxicity of cadmium compounds to wild birds and mammals by the oral route of exposure;

8. the carcinogenicity of cadmium compounds in animal species in well conducted and documented bioassays; and

9. the genotoxicity of cadmium oxide in a variety of test systems, particularly *in vivo.*

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