Canadian Environmental Protection Act

Priority Substances List
Assessment Report

Hexachlorobenzene

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

HEXACHLOROBENZENE

Government of Canada
Health and Welfare Canada
Environment Canada

Also available in French under
the title: *Loi canadienne
sur la protection de l'environnement
Liste des substances d'intérêt prioritaire
Rapport d'évaluation Hexachlorobenzène*

CANADIAN CATALOGUING IN PUBLICATION DATA

Main entry under title:

Hexachlorobenzene
(Priority substances list assessment report)
At head of title: Canadian Environmental Protection Act.
Issued also in French under title: Hexachlorobenzène.
Includes bibliographical references.
ISBN 0-662-20291-0
DSS cat. no. En40-215/7E

1. Hexachlorobenzene. 2. Hexachlorobenzene – Toxicity testing.
3. Hexachlorobenzene – Environmental aspects. I. Canada.
Environment Canada. II. Canada. Health and Welfare
Canada. III. Series.

TD196.C5H5 1993 363.73'84 C93-099427-2

Canada	Groupe
Communication	Communication
Group	Canada
Publishing	Édition

Available in Canada through
your local bookseller
or by mail from
Canada Communication Group -- Publishing
Ottawa, Canada K1A 0S9
Cat. No. En40-215/7E
ISBN 0-662-20291-0

Printed on
Recycled Paper

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Overview of Findings

Between 1948 and 1972, hexachlorobenzene (HCB) was used as a seed dressing for several crops to prevent fungal disease. HCB has not been used commercially in Canada since 1972, although it is released to the Canadian environment in small quantities as a by-product from the manufacture and use of chlorinated solvents and pesticides, through long-range transport and deposition, and "in emissions" from incinerators and other industrial processes. HCB is a persistent substance that has been distributed to all regions of Canada, primarily through long-range transport and deposition. As a result, HCB has frequently been detected in the various media to which humans and other organisms in Canada may be exposed, particularly in sediments and fatty tissues, where it tends to accumulate.

The highest concentrations of HCB have been observed near point sources in the Great Lakes and connecting channels. Current levels in air, water and forage fish from this area have the potential to cause harmful effects to fish-eating mammals, such as mink. The available data on current levels further indicate that HCB has the potential to cause reproductive impairment to predatory bird species across Canada, including the endangered peregrine falcon.

HCB is removed from the troposphere by photolysis and deposition to soil and water. These processes, combined with the low levels of HCB currently in the troposphere, indicate that HCB is not likely to trap significant quantities of thermal radiation from the Earth's surface, nor is it expected to reach the stratosphere. HCB is not, therefore, likely to be associated with global warming or stratospheric ozone depletion.

In several studies, HCB has been shown to cause cancer consistently in experimental animals, although available data are inadequate to determine whether HCB causes cancer in humans. It is, therefore, considered to be a "non-threshold toxicant" (i.e., a substance for which there is believed to be some chance of adverse health effect at any level of exposure). For such substances, estimated exposure is compared to quantitative estimates of potency to cause cancer, in order to characterize risk and provide guidance in establishing priorities for further action (i.e., analysis of options to reduce exposure). For hexachlorobenzene, such a comparison suggests that the priority for analysis of options to reduce exposure would be moderate to high.

Based on these considerations, the ministers of the Environment and of National Health and Welfare have concluded that the concentrations of HCB present in the Canadian environment may constitute a danger to the environment and to human life and health. HCB is, therefore, considered to be "toxic" as interpreted under section 11 of the *Canadian Environmental Protection Act* (CEPA).

1.0 Introduction

CEPA requires the ministers of the Environment and of National Health and Welfare 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 interpreted in 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 assessed to be "toxic" according to this section may be placed on Schedule I of the Act and considered for possible development of regulations, guidelines or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

The assessment of whether hexachlorobenzene is "toxic," as interpreted in CEPA, was based on the determination of whether it enters or likely enters 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.

For the human health-related portion of the assessment, a background review was prepared under contract by SRI International, Menlo Park, California, in February of 1990. For the period from 1983 to 1989, a literature survey was conducted by the contractor by searching a number of on-line bibliographic data bases from the National Library of Medicine in the United States [including Toxline, Medline, the Hazardous Substances Data Bank (HSDB) and the Registry of Toxic Effects of Chemical Substances (RTECS)], and consulting SRI's in-house data bases, chemical toxicity files, and standard reference sources. To identify other toxicological data relevant to the preparation of this Assessment Report, this initial search was supplemented by literature searches in the following computerized databases: HSDB, RTECS, IRIS, CCRIS (July, 1990); Toxline (1981 to March, 1992); Toxlit (1981 to March, 1992); and EMBASE (1981 to March, 1992). To identify data relevant to the estimation of exposure of the general population to HCB, literature searches were conducted on the following computerized data bases: Environmental Bibliography, Enviroline, Pollution Abstracts, Elias, Aquaref, Microlog, CODOC/GDOC (1981 to March, 1992); and Commonwealth Agricultural Abstracts, Food Science and Technology Abstracts and Agricola (1985 to 1990). Information on exposure is also included in some of the sources of toxicological data noted above, especially HSDB and Toxline. These were supplemented with manual searches of Current Contents throughout 1991.

Representatives of the Drinking Water Surveillance and of the Sport Fish Contaminant Monitoring Programs of Ontario were contacted for unpublished information. The Canadian Chemical Producers Association was consulted concerning relevant data for consideration.

Data relevant to the environmental portions of the assessment were identified through searches of commercial and government data bases, including: AQUALINE (1984 to 1990); AQUAREF (1984 to November, 1990); AQUIRE (1978 to 1989); ASFA (1984 to November, 1990); BIOSIS (1984 to October, 1991); CAB (1984 to November, 1990); CA Search (1984 to 1990); ENVIROFATE (1966 to 1983); Enviroline (1983 to 1990); Environmental Bibliography (1984 to 1990); Federal Register (1984 to 1990); Hazardous Substances Data Bank (1972 to 1987); IRPTC Legal Database (1971 to October, 1991); Life Sciences Collection (1984 to 1990); NTIS (1984 to November, 1990); Pollution Abstracts (1984 to 1990); Toxline (1984 to 1990); U.S. EPA Toxics Release Inventory (1987 to 1989); Water Resources Abstracts (1984 to 1990); and World Textiles (1984 to 1990). Additional information was identified in review documents. Relevant unpublished data were also acquired from the Canadian Wildlife Service. A background report on the fate and levels of HCB in the Canadian environment was prepared under contract by Diane Koniecki.

Data obtained after April, 1992 and relevant to the assessment of whether HCB is "toxic" to human health were not considered for inclusion. As well, data obtained after July, 1992 and relevant to the assessment of whether HCB is "toxic" to the environment have not been incorporated.

Although much of the research on HCB has been conducted outside of Canada, available Canadian data on sources, fate, levels and effects of HCB on the Canadian environment and human population were emphasized.

Review articles were consulted where considered appropriate; however, all original studies that form the basis for the determination of "toxic" under CEPA have been critically evaluated by the following Health and Welfare Canada staff (human exposure and effects on human health) and Environment Canada staff (entry, environmental exposure and effects):

R.L. Breton (Environment Canada)
R. Burnett (Health and Welfare Canada)
K. Lloyd (Environment Canada)
M.E. Meek (Health and Welfare Canada)
D.R.J. Moore (Environment Canada)
R. Newhook (Health and Welfare Canada)
L. Shutt (Environment Canada)

Following circulation and external peer review of the draft health-related sections by Dr. Michel Charbonneau of the Université de Montréal, Dr. Richard Kociba of Dow Chemical, U.S.A. (Supporting Document only), and BIBRA Toxicology International, these sections were approved by the Rulings Committee of the Bureau of Chemical Hazards of Health and Welfare Canada on June 9, 1992. The environmental portions of the Assessment Report were reviewed

by Dr. Lynn McCarty (CanTox Inc.), Dr. Barry Oliver (Zenon Consultants), Dr. Mike Whittle (Department of Fisheries and Oceans) and Dr. Bob Lane (Atmospheric Environmental Service). The final Assessment Report was reviewed and approved by the Environment Canada/Health and Welfare Canada CEPA Management Committee.

In this report, an overview of the findings is presented that will appear in the *Canada Gazette*. In addition, an extended summary of technical information critical to the assessment is presented in Section 2. The assessment of whether HCB is "toxic" under CEPA is presented in Section 3. A Supporting Document, in which the technical information is presented in greater detail, has also been prepared and is available upon request.

Copies of this Assessment Report and the unpublished Supporting Document are available upon request from:

Environmental Health Centre
Health and Welfare Canada
Room 104
Tunney' s Pasture
Ottawa, Ontario, Canada
K1A 0L2

Commercial Chemicals Branch
Environment Canada
Place Vincent Massey, 14th Floor
351 Saint-Joseph Boulevard
Hull, Quebec, Canada
K1A 0H3

2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production and Uses

The chemical formula of hexachlorobenzene is C_6C1_6, its Chemical Abstract Service (CAS) number is 118-74-1, and its molecular weight is 284.79. At ambient temperature, HCB is a white crystalline solid. It is virtually insoluble in water (0.005 mg/L at 25^0C), but is soluble in ether, benzene, chloroform and hot ethanol. HCB has a high octanol/water partition coefficient (log K_{ow} = 5.5), low vapour pressure (0.0023 Pa at 25^0C), and low flammability. Its Henry's Law constant is 131 Pa/m^3/mol (U.S. EPA, 1985; ATSDR, 1990; Mackay *et al*, 1992).

HCB was introduced in 1940 for use as a seed dressing for wheat, barley, oats and rye to prevent fungal disease. Between 1948 and 1972, 17 fungicidal formulations registered under the Canadian *Pest Control Products Act* contained HCB in amounts of up to 80% (Tuttle, 1979); however, the use of HCB in fungicides was discontinued in 1972, due to concerns about adverse effects on the environment and human health.

In industry, HCB has been used directly in the manufacture of pyrotechnics, tracer bullets and as a fluxing agent in the manufacture of aluminum. HCB has also been used as a wood preserving agent, a porosity control agent in the manufacture of graphite anodes, and as a peptizing agent in the production of nitroso and styrene rubber for tires (Mumma and Lawless, 1975).

Based on records available since 1980, HCB has not been produced as a commercial chemical in Canada (Statistics Canada, 1981; 1982; 1983; Camford Information Services, 1991). However, small quantities of HCB were imported and subsequently exported, either in pesticide formulations or as the parent compound. Five tonnes of HCB was imported into Canada in 1980, 7 tonnes in 1981, 8 tonnes in 1982 and 10 tonnes in 1983 (Statistics Canada, 1981; 1982; 1983). According to Camford Information Services (1991), HCB was not imported from 1984 to 1987, but was imported into Ontario in 1988 (36 tonnes), 1989 (27 tonnes) and 1990 (10 tonnes) from France and the United States. At this time, the identities of the supplier(s) and importer(s) and the use of the material imported between 1988 and 1990 are considered to be Confidential Business Information.

2.2 Entry into the Environment

Currently, the principal sources of hexachlorobenzene to the Canadian environment are estimated to be by-products from the manufacture and use of chlorinated solvents, application of HCB-contaminated pesticides, incineration of HCB-containing wastes, and long-range transport from other countries (Table 2.1).

Table 2.1 - Major Sources of Hexachlorobenzene to the Canadian Environment

Source	Release (kg/yr)
Manufacture of Chlorinated Solvents	24.0-69.7[a]
Use of Chlorinated Solvents	= 122[b]
Manufacture of Pesticides	0
Application of Pesticides	300-525[c]
Incineration of HCB-containing Wastes	Unknown
Long-range Transport and Deposition	510[d]
Manufacture of Chlorine and Sodium Chlorate	0[e]
Hazardous Waste Landfills	Unknown
Emissions from other Industries	Unknown
Effluents from Municipal Waste Water Treatment Plants	Unknown

[a] Estimated using emission factors from Brooks and Hunt (1984) multiplied by 1990 production figures in Canada (CPI, 1990a; 1990b; 1990c), assumes all wastes are incinerated with HCB destruction efficiency of 99.99% (Environment Canada, 1991a)

[b] Based on domestic demand in Canada multiplied by upper limit concentration of 5 mg/L; assumes 100% release to environment following solvent use

[c] Based on Canadian sales data for HCB-contaminated pesticides multiplied by HCB concentrations in the pesticides

[d] Based on annual HCB loading rate for the Great Lakes (Eisenreich and Strachan, 1992) multiplied by surface area of Canada

[e] HCB may be present in landfilled wastes due to past practices

HCB can be formed as a reaction by-product in the manufacture of chlorinated solvents, particularly carbon tetrachloride and tri- and tetrachloroethylene (Quinlivan *et al.,* 1975*;* Jacoff *et al.,* 1986). In Canada, there are two plants that manufacture carbon tetrachloride, and one plant that manufactures tetrachloroethylene (SRI International, 1990). In addition to generating HCB as a waste by-product during the manufacture of chlorinated solvents, HCB can also be found as a contaminant in the final products, at concentrations of up to 5 mg/L (Dow Chemical Canada Inc., 1991). Chlorinated solvents are used primarily in the manufacture of chlorofluorocarbons, metal cleaning and in dry-cleaning (CPI, 1990a; 1990b; 1990c).

A variety of chlorinated pesticides, including pentachlorophenol, dacthal, chlorothalonil, picloram, simazine, atrazine and pentachloronitrobenzene, are known to contain HCB as an impurity (Tobin, 1986). HCB is also generated as a by-product in the manufacture of these

pesticides, but there has been no manufacture in Canada of the pesticides suspected of generating HCB-containing wastes since the 1970s (Environment Canada, 1979; Gilbertson, 1979; Tuttle, 1979; Environment Canada and Agriculture Canada, 1990).

HCB can be emitted from incinerators as a result of incomplete thermal decomposition of a variety of substances, including Kepone, mirex, chlorobenzenes, polychlorinated biphenyls, pentachlorophenol, poly (vinyl chloride) and mixtures of chlorinated solvents (Ahling *et al.,* 1978; Dellinger *et al.,* 1991). In November, 1991, there were 16 large operational incineration facilities in Canada, excluding a plant that will come on-line in 1992 (Environment Canada, 199lb). The majority of these plants are located in Ontario and British Columbia and, except for the five plants in British Columbia, are equipped with air pollution control technology systems. In the only study available that quantified HCB emissions from a Canadian incinerator, Environment Canada (1987) estimated atmospheric HCB emissions of < 1 kg/year and HCB wastes in ash of < 1 kg/year from a Quebec City mass burner system.

Long-range transport plays a significant role as a continuing source and means of redistribution of HCB throughout the world and the Canadian environment. Wet deposition is the primary mechanism for transport of HCB from the atmosphere to aquatic and terrestrial systems in Canada (Eisenreich and Strachan, 1992).

Until the early 1970s, emissions from chlor-alkali and sodium chlorate plants using graphite anodes (which generate HCB as a by-product) were an important source of HCB (Quinlivan *et al.,* 1975; Mumma and Lawless, 1975; Alves and Chevalier, 1980; Christensen *et al,* 1989). Although current HCB production from this source is negligible, due to conversion to dimensionally stabilized anodes that do not produce HCB (Brooks and Hunt, 1984), unknown quantities of HCB may continue to be released from sites where wastes from these industries were landfilled.

HCB has been detected in emissions from a number of industries, including paint manufacturers, coal and steel producers, pulp and paper mills, textile mills, pyrotechnics producers, aluminum smelters, soap producers and wood-preservation facilities (Quinlivan *et al,* 1975; Gilbertson, 1979; Alves and Chevalier, 1980), likely reflecting the use of products contaminated with HCB. Municipal and industrial waste water facilities also discharge HCB-contaminated effluents (Environment Canada/Ontario Ministry of the Environment, 1986; King and Sherbin, 1986; UGLCCSMC, 1988; RAP, 1989), probably due to inputs from industrial sources. Although most of the hazardous waste landfill sites in Canada no longer accept HCB-contaminated wastes, leaching from sites where these wastes were previously landfilled continues to release HCB to the environment.

2.3 Exposure-related Information

2.3.1 *Fate*

Hexachlorobenzene is widely distributed throughout the Canadian environment because it is mobile and resistant to degradation. Volatilization from water to air and sedimentation

following adsorption to suspended particulates are the major removal processes from water. For example, Oliver (1984a) and Oliver and Charlton (1984) estimated that 80% of the HCB loading into Lake Ontario in 1982 was lost through volatilization, with the remainder removed by sedimentation (15%) and outflow to the St. Lawrence River (5%). Once in the sediments, HCB will tend to accumulate and become trapped by overlying sediments (Oliver and Nicol, 1982). However, desorption from resuspended bottom sediments does occur and may be an important and continuous source of HCB to water, even if inputs to the system cease (Oliver, 1984a; Oliver *et al.,* 1989). Chemical and biological degradation are not considered to be important removal processes of HCB from water or sediments (Callahan *et al.,* 1979; Mansour *et al.,* 1986; Mill and Haag, 1986; Oliver and Carey, 1986). In the troposphere, HCB is transported long distances by virtue of its persistence, but does undergo slow photolytic degradation ($t_{1/2}$ ~ 80 days; Mill and Haag, 1986), or is removed from the air phase via atmospheric deposition to water and soil (Bidleman *et al.,* 1986; Ballschmiter and Wittlinger, 1991; Lane *et al,.* 1992a; 1992b). Volatilization is the major removal process for soil at the surface (Kilzer *et al.,* 1979; Griffin and Chou, 1981; Schwarzenbach *et al.,* 1983; Nash and Gish, 1989), while slow aerobic ($t_{1/2}$ = 2.7-5.7 years) and anaerobic biodegradation ($t_{1/2}$ =10.6-22.9 years) are the major removal processes at lower depths (Beck and Hansen, 1974; Howard *et al.,* 1991).

Organisms generally accumulate HCB from water and from food, although benthic organisms may accumulate HCB directly from sediment (Oliver, 1984b; Knezovich and Harrison, 1988; Gobas *et al.,* 1989). The relative importance of the water and food uptake routes is not fully understood, but field studies indicate that exposure via food is important for organisms at higher trophic levels. Thus, several studies have shown that higher trophic level organisms in natural aquatic ecosystems accumulated HCB to levels greater than those at lower trophic levels (Oliver, 1987; Oliver and Niimi, 1988). In Lake Ontario, Oliver and Niimi (1988) observed that tissue residue concentrations increased from plankton (mean 1.6 ng/g wet weight) to mysids (mean = 4.0 ng/g wet weight) to alewives (mean = 20 ng/g wet weight) to salmonids (mean = 38 ng/g wet weight). Braune and Norstrom (1989) used field data on body burdens of HCB in the herring gull *(Larus argentatus)* and one of its principal food items, the alewife *(Alosa pseudoharengus)* in a Great Lakes food chain to calculate a biomagnification factor (whole body, wet weight basis) of 31.

2.3.2 *Concentrations*

Hexachlorobenzene is a widely distributed substance in the Canadian environment. It has been detected in air, water, sediment, soil and biota. In this section, concentrations of HCB in the Canadian environment are summarized, with particular emphasis on studies conducted between 1980 and 1992.

Air

Data on concentrations of HCB in ambient air in southwestern Ontario have been collected as part of the Detroit Incinerator Monitoring Program. On roughly 30 days during

1988-1989, HCB levels at a downtown Windsor site and at a rural site on Walpole Island each averaged 0.15 ng/m^3 [limit of detection (LOD) 0.03 ng/m^3] (Environment Canada, 1990; 1991c). Similar levels were reported for other sites in southern and central Ontario between 1985 and 1989 (Lane *et al.*, 1992a), and in surveys from the Canadian high Arctic in the summers of 1986 and 1987 (Patton *et al.*, 1988), highlighting the global long-range transport of HCB. No reports of HCB concentrations in indoor air were identified.

Drinking Water

HCB has been detected infrequently, and at low concentrations, in Canadian drinking water supplies. The substance was present in drinking water samples collected in 1980 from three Lake Ontario municipalities, at a mean concentration of 0.1 ng/L [LOD 0.01 ng/L] (Oliver and Nicol, 1982). HCH was not detected in a federal-provincial survey of roughly 600 municipal raw water sources in the maritime provinces between 1985 and 1988 (LOD 2 ng/L) (Environment Canada, 1989), nor in 86 drinking water sources analyzed during 1988-1989 under the Ontario Drinking Water Surveillance Program [LOD 1 ng/L] (Lachmaniuk, personal communication).

Surface Water

Of 1 042 surface water samples collected from lakes, streams, reservoirs, estuaries and coastal waters in the Atlantic provinces between 1979 and 1989, only six had concentrations above the LOD of 2.0 ng/L [maximum = 2.2 ng/L] (Leger 1991). Leger (1991), however, expressed reservations about the validity of these positive findings, since quality control testing was not used in 1980 when the six samples with HCB levels above the LOD were collected.

In numerous studies, the levels of HCB in surface water samples from the Great Lakes, their connecting channels and the St. Lawrence River have been measured. Of 189 surface water samples collected from the Great Lakes between 1980 and 1986, the concentration in only one, from Hamilton Harbour (4.0 ng/L), was found to exceed 1.0 ng/L (Oliver and Nicol, 1982; Neilson *et al.*, 1986; Poulton, 1987; Biberhofer and Stevens, 1987; Stevens and Neilson, 1989; IJC, 1989). Mean concentrations of HCB in 1986 for each of the Great Lakes were 0.026 ng/L for Lake Superior, 0.033 ng/L for Lake Huron, 0.041 ng/L for Georgian Bay, 0.078 ng/L for Lake Erie and 0.063 ng/L for lake Ontario (Stevens and Neilson, 1989). The levels observed in 1986 for lakes Huron and Ontario were similar to those observed in 1980.

In the connecting channels to the Great Lakes, HCB levels more frequently exceeded 1.0 ng/L, particularly near point sources. For example, in the St. Clair River near the Dow Chemical outfall, HCB concentrations as high as 87 ng/L in 1985 and 75 ng/L in 1986 were observed (Oliver and Kaiser, 1986; OME, 1987). In samples of suspended solids taken from this location in 1986, the mean concentration of HCB was 14 000 ng/g dry weight (Lau *et al.*, 1989). In the Niagara River near Niagara-on-the-Lake, mean concentrations of HCB in surface waters were 1.1 ng/L in a 1981 to 1983 survey [maximum = 29 ng/L] (Oliver and Nicol, 1984), and 0.1 ng/L in a 1988/1989 survey [maximum = 0.2 ng/L] (DIG, 1990).

No recent (1980-1992) data were available concerning HCB levels in surface waters for any province west of Ontario.

Industrial and Municipal Waste Water

In a long-term monitoring program of effluents from the Sarnia industrial complex in 1986, the mean level of HCB detected was 117 ng/L in the Dow 42-inch sewer and 28 ng/L in the Polysar Cole drain (OME, 1987). HCB concentrations as high as 2 800 ng/L were observed in the Dow sewer in a short-term effluent study in 1985 (King and Sherbin, 1986).

HCB has also been detected in effluents from the Welland Water Pollution Control Plant (OME, 1989), Stelpipe Welland Tube Works (OME, 1989), Rainy River bleached kraft pulp and paper mill (Merriman, 1988), Sarnia municipal waste water treatment plant (Marsalek, 1986), and chlor-alkali industries in British Columbia (Wilson and Wan, 1982). Mean HCB levels in these effluents were generally low, ranging from < 1 to 11.6 ng/L.

Sediment

In sediment samples collected from 1979 to 1989 in the Atlantic provinces, HCB was reported to be below the limit of detection of 0.2 ng/g (dry weight) in 140 of 152 samples (Leger, 1991). HCB levels ranged from 0.4 to 10 ng/g (dry weight) in 12 sediment samples from the Annapolis River (Nova Scotia), Restigouche River (New Brunswick), Scales Pond (Prince Edward Island) and Deer Lake (Newfoundland). All 12 samples in which HCB was detected were collected from 1980 to 1982. Higher HCB levels have been reported in studies conducted near point sources. For example, HCB levels ranged from 19 to 273 ng/g (dry weight) in 1979 in sediment samples from the East River (Nova Scotia) near a chlor-alkali plant discharge (MacLaren Marex Inc., 1979).

In surveys conducted from 1980 to 1983, HCB levels in sediments were much higher in lakes Ontario and Erie than in lakes Huron and Superior. The observed ranges were 0.02 to 4.1 ng/g for Lake Superior, 0.4 to 5.2 ng/g for Lake Huron, 0.7 to 63 ng/g for Lake Erie, and 7.6 to 840 ng/g for Lake Ontario [dry weight] (Oliver and Nicol, 1982; Fox *et al.*, 1983; Kaminsky *et al.*, 1983; Oliver and Bourbonniere, 1985; Bourbonniere *et al.*, 1986; Oliver *et al.*, 1989; IJC, 1989). Analyses of sediment cores from Lake Ontario indicated that HCB levels have declined from the peak levels observed in the mid-1960s (mean ˜ 60 to 80 ng/g dry weight) to the early 1980s [mean ˜ 30 to 50 ng/g dry weight] (Oliver and Nicol, 1982; Oliver *et al.*, 1989). More recent data are not available to determine if this downward trend has continued.

The highest levels of HCB have been observed in samples of sediment from the St. Clair, Detroit and Niagara rivers, particularly near point sources. In the St. Clair River, HCB levels in the 5-km stretch downstream of the Dow Chemical sewer discharges were found to be as high as 24 000 ng/g in 1984 (mean ˜ 5 200 ng/g) and 280 000 ng/g in 1985 [dry weight] (Oliver and Pugsley, 1986). The mean HCB concentration in a 35-km stretch of the

St. Clair River downstream of the industrial complex was found to be 370 ng/g (dry weight) in 1985 (Oliver and Pugsley, 1986). HCB levels in bottom sediment observed in the late 1970s and early 1980s ranged from below the limit of detection (LOD) [1.0 ng/g] to 360 ng/g (dry weight) for the Detroit River (Hamdy and Post, 1985; UGLCCSMC, 1988), below the LOD (1.0 ng/g) to 250 ng/g (dry weight) for the Niagara River (NRTC, 1984), below the LOD (1.0 ng/g) to 351 ng/g (dry weight) for the St. Lawrence River (Merriman, 1987; Kuntz, 1988; Kauss *et al.*, 1988; OME, 1989; Kaiser *et al.*, 1990), and 0.4 to 170 ng/g (dry weight) for Lake St. Clair (Oliver and Bourbonniere, 1985; UGLCCSMC, 1988).

No recent (1980-1992) data were available concerning HCB levels in sediments for any province west of Ontario.

Soil

Levels of HCB in soil from agricultural areas of British Columbia were determined. Of 24 samples from cereal seed treatment areas, where HCB seed treatment had last been applied between 10 and 15 years prior to the survey, six had detectable HCB residues (LOD 1 ng/g dry weight) of between 1.3 and 2.2 ng/g. Due to use of HCB-contaminated herbicides, mean HCB levels in soil at forest nurseries and vegetable-growing areas were 11.2 and 2.3 ng/g, respectively (Wilson and Wan, 1982).

Biota

HCB has been detected in invertebrates, fish, reptiles, birds and mammals across Canada since the 1960s, when monitoring of organochlorines began. Based on data from long-term monitoring studies in various species of birds, HCB levels peaked in the mid-1970s and then declined from the late 1970s through the 1980s and into the 1990s (CWS, unpublished data base; Noble and Elliott, 1986). This section will focus on recent and ongoing surveys (i.e., 1980 to present) of HCB levels in Canadian biota.

Data on levels of HCB in tissues of invertebrates in Canada are limited. In studies conducted since 1981 in the Great Lakes and connecting channels, HCB levels in freshwater mussels *(Elliptio complanata)* have ranged from 0.1 ng/g wet weight in Lake St. Clair to 24 ng/g wet weight in the St. Clair River near Sarnia (Kauss and Hamdy, 1985; Innes *et al.*, 1988; Muncaster *et al.*, 1989). A similar range (0.1 to 26 ng/g wet weight) was observed in marine invertebrates from the Beaufort Sea (Hargrave *et al.*, 1989).

In a 1981-1982 survey of watersheds in New Brunswick and Nova Scotia, HCB levels in brook trout *(Salvelinus fontinalis)* and yellow perch *(Perca flavescens)* ranged from below the limit of detection (4.2 ng/g in 1981; 0.2 ng/g in 1982) to 54 ng/g for trout and 15 ng/g wet weight for perch (Peterson and Ray, 1987). Relatively high body burdens of HCB have been observed in fish in Lake Ontario and connecting channels. For example, HCB was not detected (ND) in juvenile spottail shiners *(Notropis hudsonius)* from lakes Superior and Erie [LOD = 1 ng/g wet weight] (Suns *et al.*, 1983; Environment Canada/Department of Fisheries

and Oceans/Health and Welfare Canada, 1991), while mean body burdens in shiners in Lake Ontario were between ND and 13 ng/g wet weight, and those in the Detroit and Niagara rivers averaged 5 ng/g wet weight and ND to 8 ng/g wet weight, respectively (Suns *et al.,* 1985). The highest levels were reported in the St. Clair River, particularly near Sarnia where a mean of 231 ng/g wet weight was observed in 1983 (Suns *et al.,* 1985). Mean concentrations in the muscle tissue of Lake Ontario salmonids were 37 ng/g wet weight for lake trout (S. *namaycush),* 10 ng/g for brown trout *(Salmo trutta),* 5 and 16 ng/g for small and, large rainbow trout *(Oncorhynchus mykiss)* respectively, and 10 and 13 ng/g for small and large coho salmon *(O. kisutch)* respectively (Niimi and Oliver, 1989). Similar values were reported for Lake Ontario fish species through the Ontario Sport Fish Contaminant Monitoring Program, while concentrations in the muscle tissue of species from the other Great Lakes were somewhat lower (mean across ail species 1.4 ng/g wet weight, assuming 0.5 ng/g [one half of LOD] for ND). HCB was rarely detected in the other Ontario lakes surveyed (Cox and Ralston, 1990, Cox, personal communication). Limited recent information exists on HCB levels in fish in other parts of Canada. In the only recent study found for marine fish species, the mean concentration of HCB in arctic char (S. *alpinus)* was 6.9 ng/g wet weight in a 1987 survey (Hargrave *et al.,* 1989).

There are limited data on levels of HCB in reptiles in Canada. In snapping turtle *(Chelydra s. serpentina)* eggs collected since 1986, mean levels of HCB were found to range from 1.0 ng/g wet weight in Algonquin Park to 25 ng/g wet weight in Hamilton Harbour in 1988 (Bishop *et al.,* 1991).

The levels of HCB in birds have been similar across the various regions of Canada since the 1980s, likely as a combined result of emission reductions and the long-range transport of HCB to remote locations. For example, concentrations of HCB in herring gull eggs in 1991 were relatively uniform in the Great Lakes (two colonies per lake): Lake Michigan (37 & 71 ng/g wet weight); Lake Superior (34 & 41 ng/g); Lake Ontario (28 & 39 ng/g); Lake Huron (28 & 28 ng/g); and Lake Erie (16 & 30 ng/g) [Environment Canada/Department of Fisheries and Oceans/Health and Welfare Canada, 1991; CWS, unpublished data base]. These levels are approximately two orders of magnitude lower than in 1971. Recent surveys have indicated similar HCB residue levels in eggs of five other predatory bird species (means range from 10 to 53 ng/g wet weight) [Noble and Elliott, 1986; Pearce *et al.,* 1989; Noble *et al.,* 1992; CWS, unpublished data base]; however, the mean level of HCB in peregrine falcon *(Falco peregrinus anatum)* eggs collected across Canada from 1980 to 1987 was 279 ng/g wet weight, and ranged as high as 1 060 ng/g wet weight (Peakall *et al.,* 1990). In breast muscle tissue samples from various species of birds, HCB concentrations tend to be progressively greater at higher trophic levels [i.e., piscivores > molluscivores > omnivores > grazers] (CWS, unpublished data base).

In the blubber of marine mammals, observed mean levels of HCB were 19 ng/g wet weight for ringed seals *(Phoca hispida)* and 491 ng/g wet weight for beluga whales *(Delphinapterus leucas)* in the Canadian Arctic (Norstrom *et al.,* 1990), while male belugas sampled in the Gulf of St. Lawrence contained up to 1 340 ng/g (Béland *et al.,* 1991). Male and female white-beaked dolphin blubber *(Lagerorhunchus albirostris)* collected near the

Newfoundland coast had 1110 ng/g and 880 ng/g HCB wet weight. Lower levels (290 ng/g and 100 ng/g wet weight) were observed in blubber from male and female pilot whales *(Globicephala me/eana),* also collected near the Newfoundland coast (Muir *et al.,* 1988a). The higher levels observed in the dolphin may reflect greater exposure to HCB because of overwintering and feeding in the Gulf of St. Lawrence.

Limited data are available on HCB levels in terrestrial mammals. Mean concentrations of HCB in the livers of adult male river otters *(Lutra canadensis)* in Alberta in 1983 were 25 ng/g (lipid basis) and 4 ng/g wet weight (Somers, 1985*).* HCB levels in livers of adult mink *(Mustela vison)* and river otter collected in 1991 along the Columbia River in British Columbia, Washington and Oregon ranged from 0.2 ng/g to 9.8 ng/g wet weight (CWS, unpublished data base). Levels of HCB in mink carcasses collected in Ontario in the late 1970s and early 1980s ranged from < 0.5 to 10 ng/g (Proulx *et al.,* 1987) while burdens in the fat of coyotes *(Canis latrans)* and grey wolves *(Canis lupis)* collected in Alberta in the early 1970s were <0.5 ng/g wet weight (CWS, unpublished data base). In the Canadian north, the mean level of HCB in the fat of polar bears *(Ursus maritimus)* hunted between 1982 and 1984 was 296 ng/g wet weight (Norstrom *et al.,* 1990).

The results of some studies of the levels of HCB in human tissues and fluids, and in foods, indicate that exposure of the general population in Canada declined from the 1970s to the mid-1980s (Frank and Ripley, 1990; Mes, 1990), while there has been no clear trend in other studies (Frank *et al.,* 1988). In the most recent available national survey of organochlorine compounds in the breast milk of Canadians, from 1982, the mean concentration of HCB was 2 ng/g of whole milk (54 ng/g fat). The substance was present in all 210 samples analysed (Mes *et al.,* 1986). (The data from a more recent national breast milk survey were not available at the time of writing.)

Food

In a limited number of recent surveys, HCB levels in commercial foods available in Canada have been determined. Davies (1988) reported the levels of organochlorines in composites of foods purchased in Toronto in 1985 and combined in proportion to the amounts purchased by Ontario residents. A composite of fresh meat and eggs contained 0.17 ng/g wet weight of HCB, a root-vegetables and potatoes composite 0.04 ng/g, a leafy and other above ground vegetables composite 0.02 ng/g and a 2%-milk composite 0.16 ng/g. No HCB was detected in a composite of fresh fruit (LOD 0.01 ng/g). In a subsequent Ontario survey designed to verify these findings (OMAF/MOE, 1988), HCB was not found in supplies of peaches, tomatoes, potatoes, wheat, eggs, pork or chicken (LOD 0.2 ng/g), but was present in some samples of apples, hamburger and prime beef.

The results of the U.S. Total Diet Study indicate that HCB is detected in a small fraction of food items, most often dairy products, meats, and peanuts/peanut butter. Mean levels over all surveys from 1982-1986 were less than 1 ppb (ng/g) for all products except for peanuts (3.2 ng/g), peanut butter (3.0 ng/g), frankfurters (1.2 ng/g) and butter (2.4 ng/g) [Gunderson, undated].

2.4 Effects-related Information

2.4.1 Experimental Animals and In Vitro

Exposure to hexachlorobenzene causes a wide range of effects in several species of mammals, with similar lowest-observed-effect levels (LOELs) and no-observed-effect levels (NOELs) for a number of end-points (Table 2.2). This section summarizes the extensive literature on the toxicity of HCB to laboratory mammals, with emphasis on the lowest reported effect levels.

Acute, Short-term and Subchronic Toxicity

The acute toxicity of HCB in experimental animals is low; reported oral LD_{50} values for various species range from > 1 000 mg/kg b.w. for the guinea pig to between 3 500 and > 10 000 mg/kg b.w. for the rat. Reported LC_{50} values for inhalation exposures range from 1 600 mg/m^3 for the cat to 4 000 mg/m^3 for the mouse (IARC, 1979; Strik, 1986; Sax, 1989). It is important to note that because the volatility of HCB is not high (vapour pressure is only 0.0019 Pa at 25^{0}C) and its solubility in oil is limited (approximately 10 mg/mL in corn oil), it is unlikely that some of very high doses reported in acute and short-term toxicity studies were actually achieved (Charbonneau, personal communication).

The effects of short-term, repeated exposure to HCB are primarily hepatotoxic and neurologic. In a number of studies, the effects of HCB on rats exposed to oral doses in the range from 30-250 mg/kg b.w./day include altered body weight, cutaneous lesions, tremors and other neurological signs, hepatomegaly, liver damage and, in some cases, early alterations in porphyrin or heme metabolism (U.S. EPA, 1985; Courtney, 1979; Strik, 1986). Short-term exposures induce a variety of Phase I (both cytochrome P450 IIB and cytochrome P450 I, as well as other mixed-function oxidases) and Phase II enzymes (Wada *et al*, 1968; Courtney, 1979*;* Denomme *et al*., 1983; U.S. EPA, 1985*;* Linko *et al.*, 1986; Strik, 1986*;* Vos *et al.*, 1988; Green *et al.*, 1989; Rizzardini *et al.*, 1990; D'Amour and Charbonneau, 1992); reported effect levels for this end-point in rats have been as low as 50 mg/kg feed (approximately 2.5 mg/kg b.w./day) [den Tonkelaar and van Esch, 1974].

The effects produced by subchronic exposure to HCB are similar to those observed in short-term studies, but are generally evident at lower doses (Courtney, 1979; U.S. EPA, 1985; ATSDR, 1990). At relatively high doses (32 mg/kg b.w./day and higher for periods from several weeks to 90 days), reported effects include deaths, skin lesions, behavioural and neurological changes, reduced body weight gain, increased organ weights, and altered thyroid function and serum levels of thyroid hormones. At lower doses, hepatotoxic effects are commonly reported, including histological alterations, the induction of a variety of hepatic microsomal enzymes, and porphyria. The lowest doses producing effects on the liver in a subchronic study were reported by den Tonkelaar *et al.* (1978). Pigs exposed for 90 days to doses of 0.5 mg/kg b.w./day and up in diet were porphyric, and had altered liver histology and microsomal enzyme activities, while no effects were observed at 0.05 mg/kg b.w./day.

Table 2.2 - Lowest No-Observed-Effect and Low-Observed-Effect Levels (NOELs and LOELs) in Mammals Exposed to HCB

Reference	Effects	NOEL (mg/kg b.w./day)	LOEL (mg/kgb.w./day)
Den Tonkelaar *et al.* (1978)	Increased urinary coproporphyrin and microsomal liver enzyme activity in pigs with subchronic exposure to HCB in diet	0.05	0.5
Andrews *et al.* (1988; 1989; 1990)	Alterations in Ca metabolism (increased serum 1,25-dihydroxyvitamin D, levels, alterations in femur density, bone morphometry and strength), increased liver weights, with subchronic gavage exposure to HCB	0.07	0.7
Babineau *et al.* (1991); Sims *et al,* (1991); Singh *et al.* (1990a)	Ultrastructural changes in ovarian surface epithelium and follicular cells, ovarian follicles and developing ovum in monkeys with subchronic exposure to HCB in gelatin capsules	---	0.1
Vos *et al.* (1983)	Increased cell-mediated and humoral immune function, intraalveolar macrophage accumulation, microsomal EROD[b] activity, in rats exposed to HCB *in utero*, via nursing and in the diet to five weeks of age	---	0.2[a]
Barnett et al. (1987)	Depressed delayed-type hypersensitivity response to oxazolone in mice exposed to HCB in peanut butter *in utero* (throughout gestation) and via nursing to 45 days of age	---	0.5[a]
Loose *et al.* (1981); Loose (1982)	Increased susceptibility to *Leishmania* infection, and reductions in resistance to a challenge with tumour cells and in the cytotoxic macrophage activity of the spleen in mice with subchronic exposure to HCB in diet	---	0.6
Gralla *et al.* (1977)	Nodular hyperplasia of gastric lymphoid tissue in beagles with chronic exposure to HCB in gelatin capsules	---	0.12
Arnold *et al.* (1985);Arnold and Krewski (1988)	Increased organ weights (heart, brain and liver) in F_0 males, compound-related histological changes in liver of both sexes of f_1 rats with chronic exposure to HCB in diet	0.05-0.07[a]	0.27-0.35[a]
Mollenhauer *et al.* (1975;1976)	Ultrastructural changes in livers (proliferation of SER, altered mitochrondria, increase in numbers of storage vesicles) of rats with chronic exposure to HCB in diet	0.05-0.06	0.25-0.30
Grant *et al.* (1974)	Induction of *in vivo* mixed function oxidase activity in rats with chronic exposure to HCB in diet	---	0.5-0.6
Rush *et al.* (1983); Bleavins *et al.* (1984[a];1984[b])	Increased serotonin concentrations in hypothalamus of mink dams with chronic dietary exposure to HCB, decreased dopamine levels in hypothalamus, reduced birth weights, increased mortality to weaning, no significant hepatic or renal damage, in mink kits with *in utero* plus lactational exposure to HCB	---	0.16[a]

[a] Doses reported are those received by dams; actual doses received *in utero* or via nursing are unknown

[b] Ethoxyresorufin-O-deethylase

Subchronic exposure to relatively low doses of HCB has also caused changes in calcium homeostasis and bone morphometry. Male Fischer 344 rats administered HCB by gavage in corn oil had elevated serum levels of 1,25-dihydroxy-vitamin D3 and reduced calcium excretion after 5 weeks, and increased femur density, weight and strength after 15 weeks. These effects were evident at 0.7 mg/kg b.w./day, but not at 0.07 mg/kg b.w./day (Andrews *et al.,* 1989; 1990). While technical HCB is known to be contaminated with chlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls (Villenueva *et al.,* 1974; Goldstein *et al.,* 1978), the effects of subchronic dietary exposure of rats to either pure or technical HCB were virtually identical, indicating that the effects observed in this study were due to the parent compound (Goldstein *et al.,* 1978).

HCB-induced porphyria has been well-studied, and has been reported for all species examined except the dog. It is most often manifested as increased levels of porphyrins and/or porphyrin precursors in the liver, other tissues and excreta. Female rats exposed to doses of several mg/kg b.w./day in diet or by gavage for periods of three to four months developed a marked porphyria, which was absent or much reduced in males (Kuiper-Goodman *et al.,* 1977; Rizzardini and Smith, 1982; Smith *et al.,* 1985). This sex-related difference may be related to differences between male and female rats in the induction of specific cytochrome P-450 isoenzymes (Smith *et al.,* 1990), in the importance of glutathione conjugation (Rizzardini and Smith, 1982; D'Amour and Charbonneau, 1992) or perhaps in steroid hormones (Grant *et al,* 1975).

Chronic Toxicity, Carcinogenicity, and Genotoxicity

The non-neoplastic effects reported from chronic exposure to HCB, which are primarily hepatotoxic, are observed at relatively low doses (Table 2.2). In a two-generation study with Sprague-Dawley rats, increased heart and liver weights and histopathological changes in the liver and kidney were seen in F1 animals exposed to a maternal dose of 0.27-0.35 mg HCB/kg b.w./day in diet *in utero,* through nursing, and then continued on the same diet as their parents for their lifetimes. The no-effect level in this study was 0.05-0.07 mg/kg b.w./day (Arnold *et al.,* 1985; Arnold and Krewski, 1988). Dietary exposures of Sprague-Dawley rats to 10 ppm and above (roughly 0.5-0.6 mg/kg b.w./day; NIOSH, 1985) for 9-10 months induced *in vivo* mixed-function oxidase activity, as indicated by reductions in drug-induced sleeping times (Grant *et al.,* 1974). Exposure of Sprague-Dawley rats to 5 ppm HCB in diet (roughly 0.25-0.30 mg/kg b.w./day; NIOSH, 1985) for 3-12 months caused proliferation of smooth endoplasmic reticulum, altered mitochondria, and increased numbers of storage vesicles; these effects were not evident at 1 ppm in diet [roughly 0.05-0.06 mg/kg b.w./day; NIOSH, 19851 (Mollenhauer *et al.,* 1975; 1976). Bleavins *et al.* (1984a) reported that exposure of female mink to a dietary concentration of 1 ppm HCB (estimated to yield a dose of 0.16 mg/kg b.w./day) for 47 weeks significantly increased serotonin concentrations in the hypothalamus of dams, and depressed hypothalmic dopamine concentrations in kits exposed *in utero* and through nursing.

The carcinogenicity of HCB has been assessed in several bioassays in rats, mice and hamsters. The following discussion is limited principally to the four studies in which adequate numbers of animals of both sexes were exposed for a sufficient length of time to more than one dose level (Cabral *et al.,* 1977; Cabral *et al.,* 1979; Arnold *et al.,* 1985; Lambrecht *et al.,* 1983a; 1983b).

Cabral *et al.* (1977; see also Cabral and Shubik, 1986) reported a statistically significant increase of "liver cell tumours (hepatomas)" in male and female Syrian golden hamsters fed 50, 100 or 200 ppm (4, 8 or 16 mg/kg b.w./day) HCB in their diets for life. Survival of both sexes and weight gain of males were reportedly reduced at 200 ppm. The incidence of "haemangioendotheliomas" of the liver was significantly increased in both sexes at 200 ppm and in males at 100 ppm, and of alveolar adenomas of the thyroid in males at 200 ppm. The authors reported that three of the hepatic "haemangioendotheliomas" (which are benign by definition) metastasized.

HCB was administered in the diet to outbred male and female Swiss mice at concentrations of 0, 50, 100 and 200 ppm (0, 6, 12 and 24 mg/kg b.w./day [U.S. EPA, 1985]) for 120 weeks (Cabral *et al.*, 1979; Cabral and Shubik, 1986). At 90 weeks, 4% of the males and none of the females survived, compared to survival rates of 50% for control males and 48% for control females. The rate of body weight increase was reportedly reduced in dosed females (at 50 and 200 ppm) and males (at 100 and 200 ppm). In females exposed to 200 ppm, a statistically significant increase in the incidence of "liver cell tumours (hepatomas)" was noted. "Hepatomas" were also elevated, although not significantly, in males at this dose and in both sexes at 100 ppm. The incidence of "hepatomas" for both sexes showed a dose dependency not only in the number of tumour-bearing animals but also in the latent period, and in multiplicity and size of tumours.

Arnold *et al.* (1985; see also Arnold and Krewski, 1988) investigated the potential carcinogenicity to rats of *in utero*, lactational and oral exposure to analytical-grade HCB. Weanling male and female Sprague-Dawley rats were fed diets containing 0, 0.32, 1.6, 8 or 40 ppm HCB. (Mean doses for males 0, 0.01, 0.05, 0.27 and 1.39 mg/kg b.w./day and for females 0, 0.01, 0.07, 0.35 and 1.72 mg/kg b.w./day [California Department of Health Services, 1988]). After 3 months, the F_0 rats were bred, and 50 F_1 pups of each sex were randomly selected from each group. From weaning, the F_1 animals were continued on the same diet for their lifetimes (up to 130 weeks). In exposed F_1 females, increased incidences of neoplastic liver nodules and adrenal phaeochromocytomas were noted at the highest dose. A significantly increased incidence of parathyroid adenomas was noted in males receiving 40 ppm HCB in their diet.

In a study by Lambrecht *et al.* (1983a; 1983b; Peters *et al.*, 1983, in U.S. EPA, 1985; Ertürk *et al.*, 1986), weanling Sprague-Dawley rats were fed diets containing 0,75 or 150 ppm of HCB (4 and 8 mg/kg b.w./day for males and 5 and 9 mg/kg b.w./day for females, respectively) for up to 2 years. Body weights were reportedly not affected by treatment until the final stages of the study. Statistically significant increases in the incidence of "hepatomas/hemangiomas" and of renal cell adenomas were noted at both doses in animals of both sexes surviving beyond 12 months. Incidences of hepatocellular carcinomas and bile duct adenomas/carcinomas were also elevated in females at both doses. In female rats, significant increases in the incidences of adrenal cortical adenomas at 75 ppm and phaeochromocytomas at both doses were reported in reviews of this study (U.S. EPA, 1985; California Department of Health Services, 1988). Lambrecht *et al.* (1983b) reported a generalized leukemia involving the thymus, spleen, liver and kidney in rats exposed to HCB in this study, but did not present any quantitative data.

High incidences of liver tumours have also been reported in some more limited studies in which single dietary concentrations were administered to very small groups of females of

three strains of rats (Smith and Cabral, 1980; Smith *et al,* 1985*);* in one strain (Fischer 344), hepatocellular carcinomas were observed (Smith *et al,* 1985). HCB has not, however, been carcinogenic in several other bioassays (Theiss *et al.,* 1977; Shirai *et al.,* 1978; Arnold *et al,* 1985; Smith *et al.,* 1989), perhaps as a results of limitations in the design of these studies, including the low doses and/or small group sizes employed.

Results from a number of studies have indicated that HCB is a cocarcinogen or promoter of cancer. Concomitant exposure to HCB in diet enhanced the induction of liver tumours by polychlorinated terphenyl in mice (Shirai *et al.,* 1978). Dietary exposure of rats to HCB promoted the development of liver tumours from prior exposure to iron (Smith *et al,* 1989), and of hepatocellular carcinomas and/or hepatic gamma-glutamyltranspeptidase-positive foci initiated by diethylnitrosamine (Pereira *et al.,* 1982; Herren-Freund and Pereira, 1986; Stewart *et al,* 1989). Short-term exposures (< 1 day) of Sprague -Dawley rats to sublethal doses of HCB produced a 1.3-fold increase in ornithine decarboxylase activity, a marker for promotion (Kitchin and Brown, 1989).

In the majority of a large number of studies in which various end-points have been examined both *in vitro* and *in vivo,* HCB has not been genotoxic (Khera, 1974; Simon *et al.,* 1979; Haworth *et al.,* 1983; Górski *et al,* 1986; Kuroda, 1986; Kitchin and Brown, 1989; Rizzardini *et al.,* 1990; Siekel *et al.,* 1991). A questionable positive response was reported by Gopalaswamy and Aiyar (1986) in the Ames test. There have been reports of mutagenic activity for HCB in eukaryotic cells *in vitro,* but these appear questionable because of the small magnitude of the observed increase (Guerzoni *et al,* 1976; Kuroda, 1986), and because of limitations in the design of the study by Guerzoni *et al.*

Reproductive and Developmental Toxicity

In recent studies conducted by Health and Welfare Canada, relatively low doses of HCB affected the reproductive tissues in female monkeys. Oral exposure of cynomolgus monkeys to 0.1 mg HCB/kg b.w./day for 90 days caused degenerative ultrastructural changes in the ovarian surface epithelium (Babineau *et al,* 1991), and in the follicular cells, ovarian follicles and the developing ovum (Singh *et al.,* 1990a). In parallel light microscopic investigations, HCB-induced histological alterations in the surface epithelium were observed (Sims *et al.,* 1991). Alterations were more severe in animals receiving 1 and 10 mg/kg b.w./day (Babineau *et al.,* 1991; Singh *et al,* 1990b; 1991; Sims *et al.,* 1991). Further studies are required to establish the effects of the damage observed at the low dose on reproductive performance, although the higher doses used in these studies have been shown to affect circulating levels of reproductive hormones (Foster *et al.,* 1992a; 1992b).

In contrast, the results of studies on a variety of species have indicated that repeated exposure to HCB can affect male reproduction, but only at relatively high doses (between 30 and 221 mg/kg b.w./day) [den Tonkelaar *et al.,* 1978; Elissalde and Clark, 1979; Simon *et al,* 1979; Borzelleca and Carchman, 1982].

Placental and lactational transfer of HCB, demonstrated in a number of species, can adversely affect both the foetus and nursing offspring. Maternal doses in the range from 1.4 to 4 mg/kg to rats and cats have been hepatotoxic and/or affected the survival or growth of nursing offspring. In some cases, these or higher doses have reduced litter sizes and/or

increased numbers of stillbirths (Grant *et al.,* 1977; Mendoza *et al.,* 1977; 1978; 1979; Hansen *et al,* 1979; Kitchin *et al.,* 1982; Arnold *et al.* 1985). Mink are particularly sensitive to the effects of prenatal and perinatal exposure to HCB; the offspring of mink fed diets containing concentrations as low as 1 ppm of HCB (approximately 0.16 mg/kg b.w./day) for 47 weeks (prior to mating and throughout gestation and nursing) had reduced birth weights and increased mortality (Rush *et al.,* 1983; Bleavins *et al*., 1984b; Table 2.2).

Adverse effects on suckling infants (most often on the liver or pup survival) have generally been observed more frequently, and at lower doses, than effects resulting from *in utero* exposure to HCB (Mendoza *et al,* 1977; 1978; 1979; Kitchin *et al,* 1982; Arnold *et al.,* 1985). However, Bleavins *et al*. (1984b) reported the results of a cross-fostering study with mink in which mortality to weaning was higher in kits exposed to HCB *in utero* than in those exposed through nursing.

The available data, although limited, indicate that HCB is not a potent developmental toxicant. The skeletal and renal abnormalities that have been reported in rats and mice exposed to HCB during gestation were not clearly related to treatment, or occurred at doses that were also maternally toxic (Khera, 1974; Courtney *et al*., 1976; Andrews and Courtney, 1986).

Immunotoxicity

The results of a number of studies have indicated that HCB affects the immune system. In rats or monkeys exposed to several mg HCB/kg b.w./day or more, histopathological effects in the thymus, spleen, lymph nodes, and/or lymphoid tissues of the lung have been observed (Kimbrough and Linder, 1974; latropoulos *et al*., 1976; Goldstein *et al*., 1978; Vos *et al.,* 1979; Kitchin *et al.,* 1982). GralIa *et al.* (1977) observed that chronic exposure to as little as 1 mg/day of HCB (equivalent to a dose at the start of the experiment of roughly 0.12 mg/kg b.w./day [ATSDR, 1990J) caused nodular hyperplasia of the gastric lymphoid tissue in beagle dogs (Table 2.2).

In a series of studies with Wistar rats summarized by Vos (1986), humoral immunity, and to a lesser extent cell-mediated immunity, were enhanced by several weeks exposure to HCB in diet, while macrophage function was unaltered. In these studies, the developing immune system was particularly sensitive to the effects of HCB. Rat pups that were exposed to 4 mg/kg of HCB in the maternal diet (approximately 0.2 mg/kg b.w./day [NIOSH, 1985]) during gestation, through nursing, and then in their own diet to 5 weeks of age had significant increases in humoral and cell-mediated immune responses, and accumulated macrophages in lung tissue (Vos *et al.,* 1983; Table 2.2).

In contrast, HCB has been immunosuppressive in most studies with mice (Vos, 1986). Balb/C mice exposed to 5 mg HCB/kg diet (roughly 0.6 mg/kg b.w./day [NIOSH, 1985]) were more susceptible to *Leishmania* infection (Loose, 1982) and had reductions in resistance to a challenge with tumour cells and in the cytotoxic macrophage activity of the spleen (Loose *et al.,* 1981) [Table 2.2]. Barnett *et al.* (1987) reported that the delayed-type hypersensitivity response was depressed in Balb/C mice exposed to HCB *in utero* (maternal dose of 0.5 mg/kg b.w./day) and through nursing (Table 2.2).

2.4.2 Humans

More than 600 cases of a condition called porphyria cutanea tarda (PCT) were identified, primarily in children, following an accidental poisoning incident in Turkey between 1955 and 1959. Hexachlorobenzene-treated grain had been ground into flour and made into bread (Cam and Nigogosyan, 1963; Courtney, 1979; Peters *et al.*, 1982; U.S. EPA, 1985; Gocmen *et al.*, 1989). Clinical manifestations (primarily dermal lesions) and disturbances in porphyrin metabolism were associated with an estimated dose of 50-200 mg/day for a number of months (Cam and Nigogosyan, 1963). In addition, the infants of mothers who either had PCT or had eaten HCB-contaminated bread had a disorder called *pembe yara* ("pink sore"), involving cutaneous lesions and clinical symptoms; at least 95% of these children died within a year of birth. In 20- to 30-year follow-ups of exposed individuals, neurological, dermatological and orthopaedic abnormalities persisted, and there were elevated levels of porphyrins in excreta of some individuals (Gocmen *et al.*, 1989).

There have been case reports of workers developing PCT as a result of direct contact with HCB (Gombos *et al.*, 1969, in Currier *et al.*, 1980; Mazzei and Mazzei, 1972, in Courtney, 1979), although there was no association between exposure to HCB and PCT in three cross-sectional studies of very small populations of exposed workers (Morley *et al.*, 1973; Burns *et al.*, 1974; Currier *et al.*, 1980). There was no evidence of cutaneous porphyria in a cross-sectional study of the general population in Louisiana exposed to HCB through the transport and disposal of "hex" waste; however, plasma concentrations of HCB were significantly correlated with levels of coproporphyrin in urine and of lactic dehydrogenase in blood (Burns and Miller, 1975). Enriquez de Salamanca *et al.* (1990) have speculated that exposure to HCB could be responsible for annual variations in the incidence of PCT in Spain between 1977 and 1988, based on an association between the levels of HCB in human milk fat and adipose tissue and the numbers of cases of PCT reported annually.

Available data on the carcinogenicity of HCB in humans are restricted to one study of a cohort of magnesium metal production workers in Norway. Although the incidence of lung cancer was significantly elevated compared to that of the general population, workers were exposed to numerous other agents in addition to HCB (Heldaas *et al.*, 1989).

2.4.3 Ecotoxicology

Data on the acute and chronic toxicity of hexachlorobenzene are available for species from a number of trophic levels, including protozoans, algae, invertebrates and fish, for both the freshwater and marine environments. For the terrestrial environment, toxicity data are available only for birds and mammals.

Since HCB is nearly insoluble in water (Section 2.1), and tends to partition from water to the atmosphere (Section 2.3.1), the substance disappears rapidly from open-test solutions. Hence, it is difficult to maintain test concentrations for a sufficient time to establish concentration-effects profiles for aquatic organisms. Further, HCB tends to bind to suspended solids in the water column and thus may not be bioavailable to test organisms. The discussion of the toxicity of HCB to aquatic organisms will therefore focus on tests conducted under flow-through conditions, static renewal conditions, or using closed vessels with minimal

headspace. As well, no consideration has been given to tests in which HCB concentrations were well above the solubility limit of HCB in water of 5 µg/L at 25^0C.

Acute

Aquatic Biota

Of four freshwater algal species tested, only one, *Chlorella pyrenoidosa*, was affected by concentrations of HCB in water at or below its limit of aqueous solubility. Reduced production of chlorophyll, dry matter, carbohydrate and nitrogen was observed for *C. pyrenoidosa* after exposure to 1 µg/L HCB (unmeasured) for 46 hours in a static-closed system (Geike and Parasher, 1976a). A no-effect concentration (NOEC) was not determined in this study.

At concentrations equal to its aqueous solubility in water (5 µg/L), HCB was not lethal to the freshwater water flea, *Daphnia magna*, in a flow-through test in which concentrations of HCB were measured (Nebecker *et al.*, 1989). In 96-hour flow-through tests on marine invertebrates, exposure to HCB caused 13% mortality in pink shrimp *(Penaeus duorarum)* at a measured concentration of 7 µg/L HCB, and 10% mortality in grass shrimp *(Palaemonetes pugio)* at 17 µg/L. The NOECs in these species were 2.3 µg/L and 6.1 µg/L, respectively (Parrish *et al*, 1974). In a static-closed system, there was a 10% reduction in reproduction of the ciliate protozoan, *Euplotes vannus*, after an exposure to 10 µg/L HCB (unmeasured) for 48 hours (Persoone and Uyttersprot, 1975).

The available data on freshwater fish species indicated no harmful effects at concentrations at or near the limit of solubility of HCB in water during acute exposures (Call *et al.*, 1983; Ahmad *et al.*, 1984). In the only available study for marine fish species, there were no harmful effects to sheepshead minnow *(Cyprinodon variegatus)* after a flow-through exposure to a measured concentration of 13 µg/L HCB for 96 hours (Parrish *et al.*, 1974).

Limited data are available concerning the toxic effects of HCB in sediment to freshwater and marine biota. In a 96-hour sediment toxicity test on the marine shrimp, *Crangon septemspinosa*, no mortality was observed at the highest concentration of HCB tested, 300 µg/L wet weight (McLeese and Metcalfe , 1980).

Several studies have confirmed that there is a relatively constant body residue associated with acute lethality in freshwater fish, invertebrates and algae exposed to mono-through pentachlorobenzene (McCarty *et al.*, 1992a and citations therein; Ikemoto *et al.*, 1992). The acute LC_{50} critical body residue for chlorobenzenes is 2 µM/g wet weight, or 569.6 µg/g wet weight for HCB, assuming that HCB has the same mode of action as the other chlorobenzenes (McCarty *et al.*, 1992b).

Terrestrial Biota

The LD_{50} for HCB in herring gull *(Larus argentatus)* embryos injected on day 4 and tallied on day 25 was 4.3 µg/g b.w. (Boersma *et al*, 1986). At a dose of 1.5 µg/g b.w., there were significant reductions in embryonic weight. Five-day LC_{50} values (i.e., 5 days of HCB-containing diet followed by 3 days of untreated diet) were 617 µg/g diet for 10-day-old

ring-necked pheasants (*Phasianus colchicus*) and > 5 000 µg/g diet for 5-day-old mallards (*Anas platyrhynchos*) [Hill *et al*., 1975]. Induction of porphyria has been observed in several short-term studies of Japanese quail following administration of 500 µg/g b.w./day HCB either in food or via intraperitoneal injection (Buhler and Carpenter, 1986; Lambrecht *et al*., 1988). The significance of porphyria to potential effects at the population level (e.g., lethality, reproductive impairment) is unknown. The acute and short-term toxicity of HCB to mammals are discussed in Section 2.4.1.

Long-term

Aquatic Biota

The growth of sensitive freshwater algae and protozoa is affected by concentrations of 1 µg/L HCB, while slightly higher concentrations (near the aqueous solubility of the compound) had effects on sensitive fish and invertebrates. Cultures of the alga *Chlorella pyrenoidosa* exhibited increased growth compared to controls after having been incubated for 3 months with a nominal concentration of 1 µg/L HCB (Geike and Parasher, 1976b), while growth of the protozoan, *Tetrahymena pyriformis*, was decreased after a 10-day exposure to a nominal concentration of 1 µg/L HCB (Geike and Parasher, 1976b).

After an exposure to 5 µg/L HCB for 10 days in a static-renewal system, crayfish (*Procambarus clarki*) experienced an increase in damage to the hepatopancreas (Laseter *et al*., 1976). The fertility of *Daphnia magna* was reduced by 50% after an exposure for 14 days to a measured concentration of 16 µg/L HCB in a static-closed system (Calamari *et al*., 1983). Significantly increased mortality was observed after the amphipod, *Gammarus lacustris*, was exposed to a measured concentration of 3.3 µg/L HCB for 28 days under flow-through conditions (Nebecker *et al*., 1989); however, the results of this study indicated a weak-dose response relationship. The results of two other flow-through studies indicated no observed effects to survival, growth and reproduction of the amphipod, *Hyallela azteca*, and the worm, *Lumbriculus variegatus*, at a measured concentration of 4.7 µg/L HCB (Nebecker *et al*., 1989).

Fathead minnows (*Pimephales promelas*) and rainbow trout (*Oncorhynchus mykiss*) were not adversely affected by exposure to levels of HCB approaching its aqueous solubility (Ahmad *et al*., 1984; Carlson and Kosian, 1987; Nebecker *et al*., 1989; U.S. EPA, 1988). After an exposure for 10 days to 3.5 µg/L of HCB under flow-through conditions, however, large-mouth bass (*Micropterus salmoides*) had liver necrosis (Laseter *et al*, 1976).

No acceptable long-term toxicity data for HCB were found for marine algae, invertebrates or fish.

There are no data from sediment toxicity tests available for HCB. A number of jurisdictions have, however, developed approaches to estimate the levels at which HCB in sediment will have effects on benthic organisms, based on correlations between benthic community composition and HCB sediment concentrations in field samples. Persaud *et al*. (1991) applied the Ontario Screening Level Concentration Approach to data from the Great Lakes and estimated a lowest-effect level for HCB of 20 ng/g sediment (dry weight, normalized to 1% total organic carbon content). The authors also estimated that benthic communities would be seriously impacted at sediment concentrations of 240 ng/g HCB dry

weight and higher. For marine sediments, a similar approach, known as the Apparent Effects Threshold (AET) approach, was used to estimate the sediment concentration of HCB above which significant effects to benthic community composition are expected (Tetra Tech Inc., 1986). The marine sediment AET for HCB was estimated to be 3.8 ng/g dry weight (normalized to 1% total organic carbon content) on the basis of co-occurrence data collected from Puget Sound, Washington (Washington State Department of Ecology, 1990).

Quantitative structure-activity relationships (QSAR) have also been used to determine the sediment HCB level at which 95% of species in the freshwater community are unlikely to be affected (Van Leeuwen *et* al., 1992). The QSAR-derived level for HCB was 5 814 ng/g dry weight (20.4 nM/g in the reference) for sediments with 5% total organic carbon content. The adjusted level for sediment with 1% total organic carbon content (i.e., ÷ 5) is 1 163 ng/g, which is 58 times higher than the estimated lowest-effect level, based on the co-occurrence data described above.

The critical body residue for aquatic biota after a chronic exposure to chlorobenzene substances is approximately 0.2 µM/g wet weight, based on a limited data set for mono-through pentachlorobenzene (McCarty, 1986). If these data are applicable to HCB, the critical body residue after a chronic exposure would be 57.0 µg/g wet weight.

Terrestrial Biota

In adult Japanese quail (*Coturnix japonica*) fed diets containing HCB for 90 days, mortality was increased at 100 µg/g wet weight HCB in diet, and hatchability of eggs was significantly reduced at 20 µg/g HCB (Vos *et al.*, 1971; 1972). At 5 µg/g HCB, increased liver weight, slight liver damage and increased fecal excretion of coproporphyrin were observed. The significance of these effects to those at the population level in the field is unknown. Eurasian kestrels (*Falco tinnunculus*) fed 50 and 200 µg/g wet weight of HCB in contaminated mice for 65 days had significant weight loss, ruffling of feathers, tremors, increased liver weight and decreased heart weight at the higher dose (Vos *et al.*, 1972). The available long-term toxicity data for mammals are discussed in Section 2.4.1.

3.0 Assessment of "Toxic" under CEPA

Hexachlorobenzene is not used commercially in Canada, but is released to the Canadian environment as a by-product from the manufacture and use of chlorinated solvents and pesticides, through long-range transport and deposition, and in emissions from incinerators and other industrial processes. This entry results in measurable concentrations of HCB in the various media to which humans and other organisms may be exposed.

3.1 CEPA 11(*a*): Environment

HCB is a persistent substance that has been dispersed throughout the Canadian environment. HCB accumulates in aquatic sediments and also biomagnifies, suggesting that benthic biota and those at higher trophic levels (e.g., predatory birds and fish-eating mammals) are the most likely to be exposed to high concentrations of this substance.

Mink *(Mustela vison)* are opportunistic carnivores, with aquatic organisms comprising up to 100% of their diet. Based on the data presented in Table 3.1, the potential total daily intake of HCB by mink in the St. Clair River area is estimated to be 36 509 ng/kg b.w./day. Reproductive impairment of mink exposed to HCB in their diet was shown to occur at 210 000 ng/kg b.w./day (Bleavins *et al,* 1984b), assuming that a 1 kg mink eats 210 grams of food per day in the wild with an HCB content of 1 000 ng/g. This value was divided by 10 in order to convert this effect level to a no-effects level and to account for differences between laboratory and field conditions. This results in a tolerable daily intake (TDI) of 21 000 ng/kg b.w./day for mink. The total daily intake calculated for mink in the St. Clair River area (36 509 ng/kg b.w./day) exceeds the TDI and therefore HCB has the potential to cause harmful effects to mink and possibly other fish-eating mammals in the St. Clair River area.

Table 3.1 - Estimated Total Daily Intake of HCB for a 1 Kg Adult Mink in the St, Clair River Area

Medium	Concentration[a]	Intake of Medium[b]	Daily Intake
Air	0.15 ng HCB/m^3	0.55 m^3/day	0.0825 ng/kg b.w./day
Water	87 ng/L	0.1 L/day	8.7 ng/kg b.w./day
Fish	231 ng/g	158 g/day	36 500 ng/kg b.w./day
TOTAL	——	——	36 509 ng/kg b.w./day

a Air concentration from Environment Canada (1990; 1991c), water concentration from Oliver and Kaiser (1986), and fish tissue concentration from Suns *et al.* (1983)

b Rate of consumption data for air from Stahl (1967), for water from Calder and Braun (1983), and for fish from Nagy (1987), with additional assumption that fish comprise 75% of mink diet

Injection studies in eggs have shown that tissue levels of 1 500 ng/g HCB wet weight caused reduced embryo weights in herring gulls [*Larus argentatus*] (Boersma *et al,* 1986). For many bird species, reduced embryo weights are associated with lower survival of chicks,

although the severity of this effect on populations in the field cannot be determined. The effects level was divided by a factor of 10 in order to derive a no-effects level and to account for potential differences in species sensitivity and laboratory versus field conditions. Therefore, the no-effects level for HCB in tissues of sensitive bird species is estimated to be 150 ng/g wet weight. HCB concentrations in peregrine falcon eggs *(Falco peregrinus anatum)* collected between 1980 and 1987 across Canada had a mean concentration of 279 ng/g wet weight. HCB has the potential, therefore, to cause harmful effects to egg embryos of peregrine falcons in Canada. The potential for effects to peregrine falcons from exposure to HCB is considered to be a serious threat to the long-term survival of this species, given its current status as an endangered species in Canada. The levels of HCB observed in eggs of most other bird species [e.g., herring gulls, common murre *(Uria aalge)*, northern gannet *(Sula bassana)*] in Canada indicate that harmful effects to these species are less likely.

The available information suggests that the lowest-observed-effect level for HCB in freshwater sediments (normalized to 1% total organic carbon content) lies between 20 and 1 163 ng/g dry weight. No additional information is available to further refine this estimate. Similarly, the estimated LOEL for HCB in fish tissues (57 µg/g wet weight) is based on limited toxicity testing that did not include HCB. Therefore, the available data are considered inadequate to assess whether HCB is "toxic" to benthic organisms or bottom-feeding fish.

Conclusion

On the basis of the available data on levels of hexachlorobenzene in Canadian air, water and forage fish, and the potential effects of exposure at these levels on predatory birds and fish-eating mammals, HCB is considered to be "toxic" as interpreted under paragraph 11(*a*) of CEPA.

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

Hexachlorobenzene absorbs infrared light at several wavelengths (7, 13 and 14 µm) characteristic of trace gases associated with global warming. Substances that absorb strongly between 7 and 13 µm act to absorb thermal radiation from the Earth's surface that would otherwise escape into space. HCB is, however, removed from the troposphere by photolysis ($t_{1/2}$ ~ 80 days) and deposition to soil and water, and thus current levels of HCB in the atmosphere are low (< 0.2 ng/m^3). HCB is, therefore, unlikely to have a significant impact on global warming.

In general, substances such as HCB with tropospheric sinks or removal processes (e.g., photolysis, deposition to soil or water) are not transported to the stratosphere. These processes, combined with the low levels of HCB in the troposphere, indicate that little, if any, HCB is expected to reach the stratosphere. HCB is, therefore, unlikely to be associated with stratospheric ozone depletion.

Conclusion

Therefore, on the basis of available data, hexachlorobenzene is not considered to be "toxic" as interpreted under paragraph 11*(b)* of CEPA.

3.3 CEPA 11(*c*): Human Life or Health

Population Exposure

Based on the most representative concentrations of HCB in air, water, food and soil presented in Section 2, and standard values for body weights and intakes of these environmental media, the mean daily intakes of HCB have been estimated for various age classes of the general population (Table 3.2). In addition, estimates have been made for more highly exposed subgroups of the population, including recreational fishermen who consume salmonids from Lake Ontario, and Inuit from the high Arctic who consume large quantities of marine mammals. Exposure of populations in the vicinity of industrial sources may also be greater than that for the general population, but the available data were considered inadequate as a basis for quantitative estimation. Since intakes vary considerably during the course of the lifespan and the critical toxicological effect is associated with long-term exposure to HCB, estimates of the average daily intake of HCB over a lifetime have also been calculated based on these age-specific intakes.

Table 3.2 - Estimated Intakes of Hexachlorobenzene (ng/kg b.w./day) for the Canadian General Population

Medium	0-6 mo[a]	7 mo-4 yr[b]	5-11 yr[c]	12-19 yr[d]	20+ yr[e]
Air[f]	0.04	0.06	0.07	0.06	0.05
Drinking water[g]	0[i]	0.006	0.003	0.002	0.002
Soil[h]	0.004	0.003	0.001	0.0003	0.0002
Food[j]	214.3[i]	17.7	9.8	4.8	2.7
TOTAL[k]	214.3	17.8	9.9	4.8	2.8

[a]Assumed to weigh 7 kg, breathe 2 m^3 of air, and ingest 35 mg of soil per day (EHD, 1992)
[b]Assumed to weigh 13 kg, breathe 5 m^3 of air, drink 0.8 L of water and ingest 50 mg of soil per day (EHD. 1992)
[c]Assumed to weigh 27 kg, breathe 12 m^3 of air, drink 0.9 L of water and ingest 35 mg of soil per day (EHD, 1992)
[d]Assumed to weigh 57 kg, breathe 21 m^3 of air, drink 1.3 L of water and ingest 20 mg of soil per day (EHD, 1992)
[e]Assumed to weigh 70 kg, breathe 23 m^3 of air, drink 1.5 L of water and ingest 20 mg of toil per day (EHD, 1992)
[f]Intakes via air based on mean airborne concentrations (0.15 ng/m^3) reported by Environment Canada (1990; 1991c) for both Walpole Island and Windsor sites; in absence of data on indoor air, assumed equal to ambient
[g]Intakes via drinking water based on mean concentration (0.1 ng/L) for three Lake Ontario cities reported by Oliver and Nicol (1982)
[h]Intakes via soil based on levels in B.C. agricultural soils treated 10-15 years prior with HCB cereal seed treatments (Wilson and Wan, 1982). Estimated mean soil concentration is 0.8 ng/g (assume mean concentration in soils with detectable HCB (6/24) is as midpoint of reported range (1.75 ng/g), and sites with no detectable HCB had mean concentration of one-half of the EOD of 1 ng/g, or 0.5 ng/g)
[i]Assumed that infant is exclusively breast-.fed for first six months. Drinking water intake is assumed to be zero. as "exclusively breast-fed infants do not require supplementary liquids". Estimated intake via breast milk based on mean HCB concentration from 1982 Health and Welfare Canada survey (2 ppb, whole milk basis; Mes et al., 1986), breast milk consumption of 750 ml per day and body weight of 7 kg
[j]Intakes via food estimated based on the concentrations of HCB reported by Davis (1988) for 2% milk (0.16 ng/g), fresh meat and eggs (0.17 ng/g), leafy above-ground vegetables (0.02 ng/g), root vegetables (0.04 ng/g), and fruit (0.005 ng/g = one-half LOD); by Gunderson (undated) for cheese (0.90 ng/g), cottage cheese (0.10 ng/g), processed cheddar (0.70 ng/g), butter (2.40), marine fish (0.20 ng/g), peanuts and peanut butter (3.10 ng/g), canned fish, shellfish, soups, grain-based foods, foods primarily sugar, fats and oils (all ND, use 0.05 ng/g = one-.half LOD); data for freshwater fish (1.10 ng/g) are average for all species monitored by Sport Fish Contaminant Monitoring Program (Cox, personal communication) from Crest Lakes other than Lake Ontario, and from several other major recreational Ontario lakes, assuming that ND are 0.5 ng/g (= one-half LOD). The concentration of HCB in each food has been multiplied by its consumption in the Nutrition Canada Survey for each age class (EHD, 1992).
[k]Total may not equal sum of medium-specific intakes, because of rounding off

Virtually all (>98%) of the estimated intake of HCB by members of the Canadian general population is via food (Table 3.2), primarily through such dairy products as milk, butter and ice cream, and to a lesser extent through fresh meat and eggs and peanuts/peanut butter. HCB accumulates in breast milk, and the estimated intake for breast-fed infants is greater than in other age groups of the general population. Mean intakes of HCB by the Canadian general population are estimated to range from 214 ng/kg b.w./day for breast-fed infants to 2.8 ng/kg b.w./day for adults. Assuming a 70-year lifespan, the daily intake of HCB for members of the general population averaged over a lifetime is estimated to be 6.2 ng/kg b.w./day.

Although judged to be the best available, the monitoring data on which the estimated intakes are based are relatively limited. In particular, the intakes through most dairy products have been derived from levels of HCB in milk from a single study, and data on the remainder of dairy products are from the U.S. Total Diet Study. In addition, no data on HCB concentrations in indoor air were identified. These estimated intakes are based on mean concentrations in the general environment. Elevated levels of HCB present in ground water, for example, as a result of leaching from landfill sites were not considered relevant to estimation of exposure for the general population.

Sport fishermen who consume their catch from Lake Ontario, the Great Lake with the highest concentrations of HCB in fish tissues (Section 2.3.2), would be expected to have some of the highest intakes among recreational anglers. The mean consumption of Lake Ontario salmonids by fishermen responding to a questionnaire circulated in conjunction with the *Toronto Star* Great Salmon Hunt was 14.24 g/person/day (Cox and Johnson, 1990). Based on the mean concentrations in muscle for salmonid species reported by Niimi and Oliver (1989) [12 ng/g for chinook salmon; assume same for coho; 11 ng/g for rainbow trout; 10 ng/g for brown trout; and 37 ng/g for lake trout], weighted by the frequency of consumption for these species reported by Cox and Johnson (1990) [71.0%; 64.9%; 90.5%; 50.0%; and 9.4%,. Respectively], the mean concentration of HCB in fish muscle consumed by these respondents is estimated to be 12.2 ng/g wet weight. Assuming a 70 kg body weight, the intake via these fish would be 25 ng/kg b.w./day. In combination with the 2.8 ng/kg b.w./day received on average from other sources (Table 3.2), the total calculated intake for people who consume salmonid species from Lake Ontario is estimated to be 5.3 ng/kg b.w./day. This is almost twice the intake of adults from the general population. Assuming that the intake of HCB for age classes other than adults is the same as for the general population, the total daily intake for these recreational fishermen averaged over a 70-year lifespan is estimated to be 8.0 ng/kg b.w./day.

Intakes of HCB by people consuming large quantities of Inuit food were estimated using data from a study of residents of an isolated island community on the east coast of Baffin Island (Kinloch *et al*, 1992; Muir *et al*, 1988b; Kuhnlein, 1989). The primary source of food in this community is subsistence hunting and fishing. Marine mammals, which accumulate relatively high body burdens of lipophilic contaminants such as HCB (Section 2.3.2), are consumed in large quantities. The calculated intake includes only those species that were consumed in the largest quantities (seal, caribou, narwhal and fish, which comprised 90% of Inuit food intake) and those food types that had greater than 1% frequency of mention across all surveys in the study (Kuhnlein, 1989). Based on the reported intake of Inuit food by all consumers (Kinloch *et al.*, 1992), and assuming a 1:1 sex ratio, it is estimated that 320.3 g of meat, 53.1 g of mattak, 42.5 g of fish, 32.5 g of fat and 24.3 g of blubber were consumed on average per person/day. The mean concentrations of HCB in these food groups, derived from

the individual food types determined by Muir *et al.* (1988b), are calculated to be 2.9 ng/g, 20.3 ng/g, 2.1 ng/g, 21.8 ng/g, and 119.5 ng/g, wet weight, respectively. Based on an assumed body weight of 62 kg for Inuit (calculated from values in NHW, 1980, assuming a 1:1 sex ratio), the mean intake for adult consumers of Inuit food in this community is calculated to be 92 ng/kg b.w./day. Roughly one-half of this intake is consumed in blubber, with significant contributions from meat, mattak (skin) and fat. Although this intake of HCB was calculated for adults, it has been assumed to approximate the exposure over the total lifespan. While younger study participants had a lower consumption of Inuit foods than adults, a number of other minor pathways of exposure are not included in this estimate, and adulthood comprises the majority of the lifespan.

Effects

Potentially, the most sensitive end-point for assessment of whether or not HCB is toxic" under paragraph 11*(c)* of CEPA is carcinogenicity. Hence, the initial step in evaluation of whether or not HCB is "toxic" under paragraph 11*(c)* of CEPA is an assessment of the weight of evidence for carcinogenicity, an effect for which it is generally believed there is no threshold.

The available information is inadequate to assess the carcinogenicity of HCB in humans. No neoplasms have been reported in long-term follow-up studies of a population accidentally poisoned in Turkey between 1955 and 1959 as a result of HCB-treated wheat grain being ground into flour and made into bread (Peters *et al.,* 1982; Cripps *et al.,* 1984; Gocmen *et al.,* 1989). These follow-up studies included only small numbers of individuals, however, and were not designed specifically to assess neoplastic end-points. Other epidemiological studies relevant to the carcinogenicity of HCB are limited to a single report of an increased incidence of lung cancer in a cohort of magnesium workers exposed to HCB and numerous other substances (Heldaas *et al,* 1989).

In the four carcinogenesis bioassays of adequate design, HCB has been tumourigenic in three species of rodents, inducing several tumour types rarely observed in control animals. Thus, administration of HCB in the diet (the principal source of exposure of humans) produced hepatomas in hamsters (Cabral *et al.,* 1977), mice (Cabral *et al.,* 1979) and rats (Arnold *et al.,* 1985; Lambrecht *et a/.,* 1983a). (The incidence of hepatomas in the control groups in all of these studies was zero.) In addition, there were increases in adenomas of the thyroid in hamsters (Cabral *et al.,* 1977) and tumours of the kidney, bile duct (Lambrecht *et al.,* 1983a; 1983b; Ertürk *et al.,* 1986), parathyroid (Arnold *et al.,* 1985) and adrenal glands (Arnold *et al.,* 1985; data from Lambrecht *et al.* study reported by Peters *et al.,* 1983, in U.S. EPA, 1985) in rats. In two of the critical bioassays, there was a dose-response relationship between exposure to HCB and tumour incidence (Cabral *et al.,* 1977; Lambrecht *et al.,* 1983a; 1983b), and in the other two there was a significant increase at the highest dose (Cabral *et al.,* 1979; Arnold *et al.,* 1985). Moreover, in two of the studies, there were dose-related trends in tumour latency and multiplicity (Cabral *et al.,* 1977; Cabral *et al.,* 1979). In some of the studies, increases in tumour incidence were observed at doses that were not clearly toxic in other respects (Cabral *et al.,* 1977; Lambrecht *et al.,* 1983a; 1983b; Ertürk *et al.,* 1986), although effects on body weight gain and survival were inadequately reported in two of the bioassays (Cabral *et al,* 1977; Cabral *et al.,* 1979).

Although the majority of neoplasms observed in these bioassays was benign, there were also excesses of some malignant tumours. Significant increases in hepatocellular carcinomas in rats were observed (Lambrecht *et al.,* 1983a; Ertürk *et al.,* 1986). In addition, there were other malignant tumours which, while evidently not significantly increased, were only observed in exposed animals, including bile duct carcinomas (Lambrecht *et al.,* 1983a; Ertürk *et al.,* 1986), and renal cell carcinomas (Lambrecht *et al.,* 1983b; Ertürk *et al.,* 1986). Lambrecht *et al.* (1983b) also reported a generalized leukemia involving the thymus, spleen, liver, and kidney in HCB-exposed rats, although they did not present any quantitative data. Cabral *et al.* (1977) also reported metastases of three of the "haemangioendotheliomas" (which are, by definition, benign) observed in hamsters. It seems likely, therefore, that these tumours were malignant, though misclassified.

The results of some more limited assays have confirmed the neoplastic effects of HCB. High incidences of liver tumours have been reported in studies in which single dietary concentrations were administered to very small groups of females of three strains of rats (Smith and Cabral, 1980; Smith *et al.,* 1985); in one strain (Fischer 344), hepatocellular carcinomas were observed (Smith *et al,* 1985). Moreover, Lambrecht *et al.* (1982a; 1982b; Ertürk *et al.,* 1982; 1986) reported that following dietary exposure to HCB for more limited periods (i.e., 90 days, with serial sacrifices every 6 weeks thereafter), mice, hamsters and rats developed tumours in the liver, bile duct, kidney, thymus, spleen and lymph nodes. Although the information provided in the summary accounts of these studies was inadequate for evaluation, results showing dose-related increases in thymic, splenic and nodal lymphosarcomas were reported for male and female mice (Ertürk *et al.,* 1982). Lymphatic and renal neoplasms were observed as early as the end of the 90-day exposure period.

Bouthillier *et al.* (1991) presented the results of studies of Sprague-Dawley rats exposed to HCB by gavage for periods of several weeks, which indicated that the observed increase in renal tumours in male Sprague-Dawley rats following exposure to HCB (Lambrecht *et al.,* 1983b; Ertürk *et al.,* 1986) is related to protein droplet nephropathy. The mechanism by which structurally diverse hydrocarbons induce hyaline droplet nephropathy in male rats has been well documented and involves accumulation of alpha-2-u-globulin, resulting in necrosis, regeneration and, in some cases, tumours. This response is sex- and species-specific, and hence is unlikely to be relevant to humans. This mechanism does not, however, explain the increased (but lower) incidence of renal tumours in females also reported by Lambrecht *et al* (1983b). In addition, mechanistic studies that address the relevance to humans of the remaining tumour types induced in rodents by HCB have not been identified.

Thus, HCB has induced tumours, some of which were malignant and several of which occurred at dietary concentrations that were not overtly toxic in other respects, at multiple sites in three species of rodents following administration for a large proportion of the lifespan. In addition, although information in the published accounts was insufficient for evaluation, tumours (some of which were malignant) have been observed in rodents following exposures for much shorter periods (i.e., 90-day).

Based on these considerations, HCB is classified in Group II (probably carcinogenic to man) of the classification scheme developed by the Bureau of Chemical Hazards for use in the derivation of the "Guidelines for Canadian Drinking Water Quality" (NHW, 1989).

Although data on the mechanism of induction of most tumours by HCB are lacking, it is possible that the compound may induce tumours through an epigenetic mechanism. HCB has not been genotoxic in *in vitro* and *in vivo* assays of a range of genetic end-points (Section 2.4.1), and acts as a promoter in *in vivo* assays (Smith *et al.*, 1989; Stewart *et al*, 1989). (It should be noted, however, that the pattern of tumour development in carcinogenicity bioassays for HCB is not entirely similar to that of other epigenetic carcinogens.) Carcinogens that act by an epigenetic mechanism are generally classified in Group IIIB (possibly carcinogenic to humans) of the classification scheme developed for use in the derivation of the "Guidelines for Canadian Drinking Water Quality" (NHW, 1989). For substances in this group, a tolerable daily intake (TDI) is derived on the basis of a no- or lowest-observed-(adverse)-effect level (NO[A]EL or LO[A]EL) in humans or animal species divided by an uncertainty factor which, when considered appropriate, takes into account the evidence of carcinogenicity. Although available information on the mechanisms of induction of tumours by HCB is insufficient to classify it in this category, even if such an approach were adopted, the estimated mean lifetime exposure of some subgroups of the population would exceed a TDI derived on the basis of data on non-neoplastic effects.

For non-neoplastic effects, the lowest reported NOELs and LOELs for severaldifferent types of effects, such as those on the liver, calcium metabolism, ovarian morphology, immune function and perinatal survival, fall within a very small range (Table 2.2). The lowest NOELs compiled in this table range from 0.05 to 0.07 mg/kg b.w/day and the lowest LOELs range from 0.1 to 0.7 mg/kg b.w./day. Based on the lowest reported NOELs included in the table [0.05 mg/kg b.w./day based primarily on hepatic effects in two species observed at higher doses (den Tonkelaar *et al.*, 1978; Arnold *et al*, 1985*;* Mollenhauer *et al.*, 1975*;* 1976)], a TDI of 50 ng/kg b.w./day could be derived, based on incorporation of an uncertainty factor of 1 000 (x 10 for intraspecies variation; x 10 for interspecies variation; x 10 for evidence of carcinogenicity). This value is less than the estimated mean lifetime exposure of some subgroups in the population.

For substances classified in Group II, where data permit, quantitative estimates of carcinogenic potency, expressed as the dose that induces a 5% increase in the incidence of relevant tumours ($TD_{0.05}$) are compared to the estimated total daily intake in order to characterize risk and provide guidance for further action (i.e., analysis of options to reduce exposure).

There are four carcinogenesis bioassays with HCB that are of adequate design. These are studies in which adequate numbers of hamsters (Cabral *et al.*, 1977), mice (Cabral *et al.*, 1979), and rats (Arnold *et al.*, 1985; Lambrecht *et al.*, 1983a; 1983b; Ertürk *et al.*, 1986) were exposed for a large proportion of the lifespan to several concentrations of HCB in the diet. The study by Arnold *et al.* (1985) has been selected for the purpose of estimating the carcinogenic potency of HCB, owing to the increased sensitivity and relevance to the nature of exposure of humans of the design of this study, which involved dietary exposure to relatively low concentrations of HCB in diet over two generations (including *in utero* and lactational exposure). Moreover, tumour pathology was inadequately reported in the studies in hamsters and mice conducted by Cabral *et al.* (1977) and Cabral *et al.* (1979), respectively, and there is some concern that in the study conducted by Lambrecht *et al.* (1983a; 1983b; Ertürk *et al.*, 1986), rats may also have been exposed to some HCB (which was incorporated in diet as a powder) by inhalation.

The estimates of carcinogenic potency of HCB derived from the results of the study by Arnold *et al.* (1985) are based on the multistage model. The tumour incidences in the pups were analyzed in the same manner as data from a single-generation study, due to the lack of information on individual litters. Owing to the lack of information about the extent of metabolism to unidentified active metabolite(s) and the possible role of such metabolites in carcinogenicity, a surface area to body weight correction was incorporated. The $TD_{0.05}$ values calculated in this manner from the results of the study in rats by Arnold *et al*. (1985) range from 0.06 mg/kg b.w./day for hepatic neoplastic nodules in females to 0.17 mg/kg b.w./day for parathyroid adenomas in males.

The exposure/carcinogenic potency indices (EPI) have been calculated on the basis of the results of the study by Arnold *et al.* (1985) and the estimated total daily intake, averaged over a lifetime, by the general population of Canada and by high-exposure subpopulations. The indices for the general population in Canada range from 3.6 x $l0^{-5}$ to 1.0 x $l0^{-4}$ (6.2 x $l0^{-6}$ mg/kg b.w./day ÷ 0.06-0.17 mg/kg b.w./day). The corresponding values for recreational fishermen consuming salmonids from Lake Ontario range from 4.7 x 10^{-5} to 1.3 x 10^{-4} (8.0 x 10^{-6} mg/kg b.w./day ÷ 0.06-0.17 mg/kg b.w./day), and those for people consuming large quantities of Inuit food range from 5.4 x 10^{-4} to 1.5 x $l0^{-3}$ (92 x 10^{-6} mg/kg b.w/day ÷ 0.06-0.17 mg/kg b.w./day). Based on these EPIs, the priority for further action (i.e., analysis of options to reduce exposure) is considered to be moderate to high.

Conclusion

Substances classified in Groups I and II on the basis of the weight of evidence of carcinogenicity are considered non-threshold toxicants, substances for which there is some probability of harm for the critical effect at any level of exposure. **Hexachlorobenzene *is*, therefore, considered to be "toxic" as interpreted under paragraph 11(*c*) of CEPA**.

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 determination of "toxic" under the Act.

3.4 Overall Conclusion

The data presented in this section indicate that hexachlorobenzene, at the concentrations found in Canada, has potential to cause adverse effects on the environment and on human life or health. Therefore, HCB is considered to be "toxic" as interpreted under paragraphs 11(*a*) and 11(*c*) of CEPA.

4.0 Recommendations for Research and Evaluation

Although several data gaps have been identified in conducting this assessment, these data are not considered to be critical to the determination of "toxic" under CEPA, and the priority for the research recommended below is considered to be low.

1. Since no sediment toxicity bioassays have been conducted for hexachlorobenzene, studies to determine the effects of HCB on benthic organisms at environmentally relevant concentrations in sediment are desirable.

2. Since limited data were available to estimate food chain biomagnification in the St. Clair River system, a modelling and field validation exercise to estimate tissue residue levels at each trophic level in this system is desirable. The results of this exercise would be useful in conducting a more rigorous assessment of the potential effects of HCB on piscivorous birds and mammals in the St. Clair River.

3. In order to ascertain the relevance of the neoplasms observed in animals exposed to HCB to humans, additional data on the mechanisms of induction of these tumours in animal species by HCB are desirable.

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