ROTTERDAM CONVENTION

SECRETARIAT FOR THE ROTTERDAM CONVENTION
ON THE PRIOR INFORMED CONSENT PROCEDURE
FOR CERTAIN HAZARDOUS CHEMICALS AND PESTICIDES
IN INTERNATIONAL TRADE

UNEP

FORM FOR NOTIFICATION
OF FINAL REGULATORY ACTION TO BAN OR SEVERELY RESTRICT A CHEMICAL

Country: Canada

SECTION 1 IDENTITY OF CHEMICAL SUBJECT TO THE FINAL REGULATORY ACTION

1.1	**Common name**	Hexachlorobenzene (HCB)
1.2	**Chemical name according to an internationally recognized nomenclature (e.g. IUPAC), where such nomenclature exists**	Hexachlorobenzene
1.3	**Trade names and names of preparations**	amatin; Anticarie; Bunt-cure; Bunt-no-more; Ceku C.B.; co-op hexa; granox nm; HCB; hexa c.b.; julian's carbon chloride; No Bunt; no bunt 40; no bunt 80; pentachlorophenyl chloride; perchlorobenzene; sanocide; smut-go; Snieciotox
1.4	**Code numbers**	
1.4.1	CAS number	118-74-1
1.4.2	Harmonized System customs code	Not Available
1.4.3	Other numbers (specify the numbering system)	RTECS: DA2975000 UN: 2729 EPA Codes: K016; K150; K151; U127; D032

1.5 Indication regarding previous notification on this chemical, if any

1.5.1 ☐ This is a first time notification of final regulatory action on this chemical.

1.5.2 ☒ This notification replaces all previously submitted notifications on this chemical.
Date of issue of the previous notification: 2004/10/28

SECTION 2 FINAL REGULATORY ACTION

2.1 The chemical is: ☐ **banned** **OR** ☒ **severely restricted**

2.2 Information specific to the final regulatory action

2.2.1 Summary of the final regulatory action

Industrial: The *Prohibition of Certain Toxic Substances Regulations, 2005* prohibit the manufacture, use, sale, offer for sale and import of toxic substances listed in Schedules 1 and 2 to the Regulations. HCB is found on Schedule 2, which lists substances that are subject to prohibitions related to concentration or use.

Pesticide: In addition, pesticides may not be imported, sold or used in Canada unless registered under the Canadian *Pest Control Products Act.* HCB is no longer registered under this Act.

2.2.2 Reference to the regulatory document, e.g. where decision is recorded or published

Industrial: *Prohibition of Certain Toxic Substances Regulations, 2005* (SOR/2005-41) under the *Canadian Environmental Protection Act, 1999*

Pesticide: *Pest Control Products Act*

2.2.3 Date of entry into force of the final regulatory action

Industrial: May 15, 2005
Pesticide: December 31, 1976

2.3 Category or categories where the final regulatory action has been taken

2.3.1 All use or uses of the chemical in your country prior to the final regulatory action

Industrial: In industry, HCB was used directly in the manufacture of pyrotechnics, tracer bullets, and as a fluxing agent in the manufacture of aluminum. It was also used as a wood-preservative agent, a porosity-control agent in the manufacture of granite anodes, and as a peptizing agent in the production of nitroso compounds and rubber tires.

Pesticide: 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, 16 fungicidal formulations registered under the Canadian *Pest Control Products Act* contained HCB in amounts of up to 80%; however, the use of HCB in fungicides was voluntarily discontinued in 1976, due to concerns about adverse effects on the environment and human health.

2.3.2 Final regulatory action has been taken for the category ☒ Industrial

Use or uses prohibited by the final regulatory action

The Regulations prohibit the manufacture, use, sale, offer for sale or import of HCB, with the exceptions listed below.

Use or uses that remain allowed (only in case of a severe restriction)

The Regulations do not apply HCB that is:

- contained in a hazardous waste, hazardous recyclable material or non-hazardous waste;
- contained in a control product (e.g., pesticide);
- present as a contaminant in a chemical feedstock used in a process from which there are no releases of the substance and provided that the substance is destroyed or completely converted in that process to a substance that is not a toxic substance listed in the Regulations; or,
- used in a laboratory for analysis; in scientific research; or, as a laboratory analytical standard.

In addition, the Regulations do not apply in respect of the manufacture, use, sale, offering for sale or import of HCB if it is present, incidentally or not, in a mixture or product listed below if the concentration of HCB in the mixture or product is below the specified limit:

- Trichloroethylene, Concentration limit = 20 ppb
- Tetrachloroethylene, Concentration limit = 20 ppb
- Tetrachloromethane, Concentration limit = 20 ppb
- Magnesium salt (by-product from the magnesium industry), Concentration limit = 20 ppb
- Magnesium sludge (by-product from the magnesium industry), Concentration limit = 20 ppb

- Hydrochloric acid (by-product), Concentration limit = 20 ppb
- Ferric chloride, Concentration limit = 20 ppb
- Ferrous chloride, Concentration limit = 20 ppb

The Regulations also establish a permit system that provides a mechanism for temporarily exempting certain applications of a substance listed in the Regulations. A permit may be granted only if the Minister of the Environment is satisfied that there is no technically or economically feasible alternative or substitute available for the substance. In addition, the Minister must be satisfied that measures have been taken to minimize or eliminate any harmful effects of the substance on the environment and human health. Finally, the applicant must provide an implementation plan that identifies specific timelines for eliminating the substance. Each permit lasts for 12 months, and can be renewed only twice.

2.3.3 Final regulatory action has been taken for the category ☒ Pesticide

Formulation(s) and use or uses prohibited by the final regulatory action

All uses and formulations are prohibited.

Formulation(s) and use or uses that remain allowed
(only in case of a severe restriction)

Not Applicable

2.4 Was the final regulatory action based on a risk or hazard evaluation? ☒ **Yes**

☐ **No** (If no, you may also complete section 2.5.3.3)

2.4.1 If yes, reference to the relevant documentation, which describes the hazard or risk evaluation

Industrial: *Canadian Environmental Protection Act* Priority Substances List Assessment Report: Hexachlorobenzene (1993)

2.4.2 Summary description of the risk or hazard evaluation upon which the ban or severe restriction was based.

2.4.2.1 Is the reason for the final regulatory action relevant to human health? ☒ Yes

☐ No

If yes, give summary of the hazard or risk evaluation related to human health, including the health of consumers and workers

Industrial: Note that the information on the hazard and risk evaluation relates to the industrial regulatory action. No information is available on the hazard and risk evaluation conducted for

the pesticide regulatory action.

The *Canadian Environmental Protection Act* (CEPA) requires the Ministers of the Environment and of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents and wastes that may be harmful to the environment or constitute a danger to human health. HCB was placed on this list and was given priority for assessment to determine whether it is "toxic" under CEPA. As HCB was assessed under the original CEPA (CEPA was reviewed and updated in 1999), it was assessed against the definition for "toxic" as interpreted in section 11 of the 1988 Act, which stated:

"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;

(*c*) constituting or that may constitute a danger in Canada to human life or health."

The assessment of whether HCB is "toxic," as interpreted in CEPA 1988, was based on the determination of whether it entered or likely entered the Canadian environment in a concentration or quantities or under conditions that could have 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 in February of 1990. For the period of 1983 to 1989, a literature survey was conducted by the contractor by searching a number of databases to identify toxicological data and data relevant to the estimation of exposure of the general population to HCB. 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.

Although much of the research on HCB was 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 formed the basis for the determination of "toxic" under CEPA were critically evaluated by staff of Health Canada (human exposure and effects on human health) and Environment Canada (entry, environmental exposure and effects).

Human Life or Health

Population Exposure

Based on the most representative concentrations of HCB in air, water, food and soil, and

standard values for body weights and intakes of these environmental media, the mean daily intakes of HCB were estimated for various age classes of the general population (Table 4, attached). In addition, estimates were made for more highly exposed subgroups of the population, including recreational fishermen who consumed salmonids from Lake Ontario, and Inuit from the high Arctic who consumed large quantities of marine mammals. Exposure of populations in the vicinity of industrial sources may also have been 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 were also calculated based on these age-specific intakes.

Effects

HCB was 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". 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. HCB was, therefore, considered to be "toxic" to human life or health.

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.

Overall Conclusion

The data presented indicated that HCB, at the concentrations found in Canada, had potential to cause adverse effects on the environment and on human life or health. Therefore, HCB was considered to be "toxic" to the environment and to human life or health.

Expected effect of the final regulatory action

Industrial

Sources addressed by the Industrial Regulations protect the health of Canadians and ecosystems by ensuring that future production, importation and the use of HCB is prohibited with very limited exemptions.

Note that sources of HCB emissions addressed by the Industrial Regulations are relatively small compared to the principal sources, identified as being the application of chlorinated pesticides containing HCB as a micro contaminant, and the incineration of wastes. Sources not addressed are subject to various non-regulatory initiatives contributing to the reduction of HCB releases.

2.4.2.2 Is the reason for the final regulatory action relevant to the environment? ☒ Yes ☐ No

If yes, give summary of the hazard or risk evaluation related to the environment

Industrial: Note that the information on the hazard and risk evaluation relates to the industrial regulatory action. No information is available on the hazard and risk evaluation conducted for the pesticide regulatory action.

The *Canadian Environmental Protection Act* (CEPA) requires the Ministers of the Environment and of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents and wastes that may be harmful to the environment or constitute a danger to human health. HCB was placed on this list and was given priority for assessment to determine whether it is "toxic" under CEPA. As HCB was assessed under the original CEPA (CEPA was reviewed and updated in 1999), it was assessed against the definition for "toxic" as interpreted in section 11 of the 1988 Act, which stated:

"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;

(*c*) constituting or that may constitute a danger in Canada to human life or health."

The assessment of whether HCB is "toxic," as interpreted in CEPA 1988, was based on the determination of whether it entered or likely entered 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.

Data relevant to the environmental portions of the assessment were identified through searches of commercial and government databases. 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.

Although much of the research on HCB was 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 formed the basis for the determination of "toxic" under CEPA were critically evaluated by staff of Health Canada (human exposure and effects on human health) and Environment Canada (entry, environmental exposure and effects).

Environment

The highest concentrations of HCB were observed near point sources in the Great Lakes and connecting channels. Levels in air, water and forage fish from this area at the time the assessment was conducted had the potential to cause harmful effects to fish-eating mammals, such as mink. The available data on these levels further indicated that HCB ha the potential to cause reproductive impairment to predatory bird species across Canada, including the endangered peregrine falcon.

Conclusion

On the basis of the available data on levels of HCB in Canadian air, water and forage fish, and the potential effects of exposure at these levels on predatory birds and fish-eating mammals, HCB was considered to be "toxic" to the environment.

Environment on Which Human Life Depends

HCB 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 ($t_{½}$ ~ 80 days) and deposition to soil and water, and thus levels of HCB in the atmosphere at the time the assessment was conducted were low (< 0.2 ng/m^3). HCB was, 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, indicated that little, if any, HCB was expected to reach the stratosphere. HCB is, therefore, unlikely to be associated with stratospheric ozone depletion.

Conclusion

Therefore, on the basis of available data, HCB was not considered to be "toxic" to the environment on which human life depends.

Overall Conclusion

The data presented indicated that HCB, at the concentrations found in Canada, had potential to cause adverse effects on the environment and on human life or health. Therefore, HCB was considered to be "toxic" to the environment and to human life or health.

Expected effect of the final regulatory action

Industrial: Sources addressed by the Industrial Regulations protect the health of Canadians

and ecosystems by ensuring that future production, importation and the use of HCB is prohibited with very limited exemptions.

Note that sources of HCB emissions addressed by the Industrial Regulations are relatively small compared to the principal sources, identified as being the application of chlorinated pesticides containing HCB as a micro contaminant, and the incineration of wastes. Sources not addressed are subject to various non-regulatory initiatives contributing to the reduction of HCB releases.

2.5 Other relevant information regarding the final regulatory action

2.5.1 Estimated quantity of the chemical produced, imported, exported and used

	Quantity per year (MT)	Year
produced	0	1991
imported	0.005, 0.007, 0.008, 0.010	1980, 1981, 1982, 1983
	0	1984-1987
	0.036, 0.027, 0.010	1988, 1989, 1990
exported	Not Available	Not Available
used	Not Available	Not Available

2.5.2 Indication, to the extent possible, of the likely relevance of the final regulatory action to other states and regions

Industrial: Because HCB was not used as a commercial chemical in Canada, the Regulations were put in place as a precautionary measure to ensure future production, importation and use of HCB was prohibited, with limited exemptions. The Regulations therefore represent no change in the use in Canada. Any state and region in a similar situation may find these Regulations relevant.

Pesticide: There is no further impact from the prohibition of pesticide uses likely to take place as the product was banned several years ago.

2.5.3 Other relevant information that may cover:

2.5.3.1 Assessment of socio-economic effects of the final regulatory action

Industrial: The reduction and eventual virtual elimination of HCB releases contribute to

reducing the health risk to the Canadian population, and to protecting the Canadian environment. As HCB was not used as a commercial chemical in Canada at the time the Regulations were published, the cost to the private sector was negligible.

2.5.3.2 Information on alternatives and their relative risks, e.g. IPM, chemical and non-chemical alternatives

Not Available

2.5.3.3 Basis for the final regulatory action if other than hazard or risk evaluation

Not Applicable

2.5.3.4 Additional information related to the chemical or the final regulatory action, if any

Toxic Substances Management Policy – Track 1 Assessment

HCB was also assessed against the criteria for selection of Track 1 substances under the Canadian federal *Toxic Substances Management Policy* (TSMP). The policy presents a management framework based on two key objectives: virtual elimination from the environment of toxic substances that are persistent, bioaccumulative and primarily the result of human activity (Track 1); and life-cycle management of other toxic substances and substances of concern to prevent or minimize their release into the environment (Track 2).

This analysis was based on the information summarized in the assessment report for HCB and the unpublished supporting document, taking into consideration additional scientific information published since that date. Expert judgement was used to analyse the scientific and technical evidence available for this substance, and a conclusion was drawn using the accumulated weight of evidence to establish whether the criteria of the TSMP were met.

The TSMP presents four criteria to be used in identifying substances for management under Track 1. The following analysis documents the evidence considered and whether the criteria were satisfied for HCB.

1. Predominantly Anthropogenic

For a substance to be "predominantly anthropogenic", its concentration in the environment has to result largely from human activity. Although the generation of HCB by natural processes can not be excluded, such contributions to the total levels existing in the environment are considered to be negligible. The analysis of sediment core samples revealed that HCB was not detectable in Lake Ontario before the 1940s. This demonstrates that the concentrations of HCB are correlated with the industrial production of chlorine and chlorinated compounds.

Conclusion

On the basis of the available information, it was concluded that the concentration of HCB in the environment was due largely to the quantities of this substance used or released as a result of human activity.

2. Persistence

To be managed under Track 1, a substance must be determined to be persistent in at least one environmental medium. In assessing if a substance is persistent in the environment, only transformation processes are taken into account; dilution or transportation to other media are not considered.

Air: HCB released into the atmosphere will partition between the vapour and solid phases. It has been estimated that the direct photolysis half-life of HCB in the vapour phase is approximately 80 days. Photo-oxidation half-lives (i.e., indirect photolysis) were estimated to range from 156.4 days to 4.2 years. A half-life of between two and six years for HCB in the atmosphere was suggested. Like other chlorinated substances, HCB adsorbed onto particulate matter in the atmosphere will not be transformed but will be removed via wet and dry atmospheric deposition.

Long-range atmospheric transport of HCB to the Arctic and other remote areas is a well-recognized phenomenon. The substance has been detected in Arctic air, snow, seawater, vegetation and biota. HCB has also been observed in other remote areas such as the North Pacific Ocean and in rainfall of two remote islands on Lake Superior.

Soil: A half-life greater than six years for HCB in soil was suggested. Other reported half-lives for the aerobic biodegradation of HCB in soil ranged from 2.7 to 5.7 years. Other results reported indicated that HCB was still detectable 10 to 10 years after it had been used as a fungicide for cereal seed treatment.

Water: A half-life greater than six years for HCB in water was suggested. Using scientific judgement based on unacclimated aerobic biodegradation, the half-life of HCB was predicted to range from 2.7 to 5.7 years. The unacclimated aqueous aerobic half-lives of HCB in groundwater was estimated to range between 5.3 and 11.4 years.

Sediment: Using fugacity modeling and published reaction rates, the half-life of HCB in sediment was suggested to be greater than six years. A good correlation was reported to exist between sediment concentrations of HCB in Lake Ontario and the production and use of the substance

Conclusion

On the basis of the available information, it was concluded that HCB is persistent in air, water,

soil and sediment.

3. Bioaccumulation

To be managed under Track 1 of the TSMP, a substance must either have a bioaccumulation or a bioconcentration factor higher than 5000, or a log K_{ow} (octanol/water partition coefficient) ≥ 5.0.

Bioconcentration factors (BCF) were measured in freshwater and marine biota. Whole-body BCFs were reported for freshwater algae (*Chlorella fusca*), 24 800; worm (*Lumbriculus variegates*), 106 840, and green sunfish (*Lepomis cyanellus*), 21 900.

Bioconcentration factors for marine biota were measured up to 11 458 for grass shrimp, 6692 for sheephead minnows, and 21 000 for pinfish.

Several studies showed that organisms from higher trophic levels in natural aquatic ecosystems accumulated HCB to levels higher than would be predicted based on its chemical properties. In Lake Ontario, it was observed that concentrations of HCB in tissue increased from plankton, to mysids, to alewives, to salmonids. Concentrations of HCB were also observed in fish-eating birds (e.g., herring gull eggs in 1991 in the Great Lakes). Levels of HCB in five other predatory bird species have been detected in other surveys; in particular, HCB was detected in eggs of peregrine falcon at concentrations as high as 1 060 ng/g wet weight. These studies indicated that HCB biomagnifies through the food chain.

The log K_{ow} for HCB was estimated to be 5.5, with most reported values ranting between 5 and 6.

Conclusion

On the basis of the available information, it was concluded that HCB is a bioaccumulative substance.

4. CEPA-toxic or Equivalent

As reported earlier, HCB was assessed under the priority substances provisions of CEPA. Based on the assessment findings, HCB was considered to be "toxic" as defined by the Act.

Conclusion

HCB was determined to be toxic under CEPA.

Overall Conclusion

On the basis of the available information, it was concluded that HCB is predominantly anthropogenic, persistent, bioaccumulative and CEPA-toxic. HCB satisfied all four criteria for

the selection of Track 1 substances under the Canadian federal *Toxic Substances Management Policy*.

SECTION 3 PROPERTIES

3.1 Information on hazard classification where the chemical is subject to classification requirements

International classification systems e.g. WHO, IARC, etc.	**Hazard class**
Not Available	Not Available
Not Available	Not Available

Other classification systems e.g. EU, USEPA	**Hazard class**
Not Available	Not Available
Not Available	Not Available

3.2 Further information on the properties of the chemical

3.2.1 Description of physico-chemical properties of the chemical

The chemical formula of HCB is C_6Cl_6. At ambient temperature, HCB is a white crystalline solid. It is virtually insoluble in water, but is soluble in ether, benzene, chloroform and hot ethanol. HCB has:

- vapour pressure of 0.0023 Pa at 25 °C
- water solubility of 0.005 mg/L at 25 °C [1] or 0.0062 mg/L[2]
- octanol/water partition coefficient (K_{ow}) of 5.5
- Henry's Law constant of 131 Pa/m^3/mol
- relative density of 2.044 (ratio of mass of HCB to the mass of an equal volume of distilled water at 4 °C)
- molecular weight of 284.784
- flash point of 242 °C
- melting point of 230 °C
- boiling point of 332 °C

- low flammability

Reference

[1] *Canadian Environmental Protection Act* Priority Substances List Assessment Report: Hexachlorobenzene (1993)

[2] ChemFinder.com Database and Internet Searching (www.chemfinder.com)

3.2.2 Description of toxicological properties of the chemical

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. 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. 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.

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. 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 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).

The effects produced by subchronic exposure to HCB are similar to those observed in short-term studies, but are generally evident at lower doses. 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. 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.

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. While technical HCB is known to be contaminated with chlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls, 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.

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. This sex-related difference may be related to differences between male and female rats in the induction of specific cytochrome P-450 isoenzymes, in the importance of glutathione conjugation or perhaps in steroid hormones.

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 1, attached). 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 F_1 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. Dietary exposures of Sprague-Dawley rats to 10 ppm and above (roughly 0.5-0.6 mg/kg b.w./day) for 9-10 months induced *in vivo* mixed-function oxidase activity, as indicated by reductions in drug-induced sleeping times. Exposure of Sprague-Dawley rats to 5 ppm HCB in diet (roughly 0.25-0.30 mg/kg b.w./day) 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]. It was 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.

A statistically significant increase of "liver cell tumours (hepatomas)" was reported 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) for 120 weeks. 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.

The potential carcinogenicity to rats of *in utero*, lactational and oral exposure to analytical-grade HCB was investigated. 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). 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, 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. A generalized leukemia involving the thymus, spleen, liver and kidney in rats exposed to HCB was reported 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; in one strain (Fischer 344), hepatocellular carcinomas were observed. HCB has not,

however, been carcinogenic in several other bioassays, perhaps as a result 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. Dietary exposure of rats to HCB promoted the development of liver tumours from prior exposure to iron, and of hepatocellular carcinomas and/or hepatic gamma-glutamyltranspeptidase-positive foci initiated by diethylnitrosamine. 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.

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. A questionable positive response was reported 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, and because of limitations in the design of the study.

Reproductive and Developmental Toxicity

In studies conducted by Health 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, and in the follicular cells, ovarian follicles and the developing ovum. In parallel light microscopic investigations, HCB-induced histological alterations in the surface epithelium were observed. Alterations were more severe in animals receiving 1 and 10 mg/kg b.w./day. 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.

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).

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. 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.

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. However, the results of a cross-fostering study with mink were reported, 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.

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. It was 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 caused nodular hyperplasia of the gastric lymphoid tissue in beagle dogs.

In a series of studies with Wistar rats, 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) 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.

In contrast, HCB has been immunosuppressive in most studies with mice. Balb/C mice exposed to 5 mg HCB/kg diet (roughly 0.6 mg/kg b.w./day) were more susceptible to *Leishmania* infection and had reductions in resistance to a challenge with tumour cells and in the cytotoxic macrophage activity of the spleen. It was 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.

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. 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. 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.

There have been case reports of workers developing PCT as a result of direct contact with HCB, although there was no association between exposure to HCB and PCT in three cross-sectional studies of very small populations of exposed workers. 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. It was 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.

Reference

Canadian Environmental Protection Act Priority Substances List Assessment Report: Hexachlorobenzene (1993)

3.2.3 Description of ecotoxicological properties of the chemical

Data on the acute and chronic toxicity of HCB 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, and tends to partition from water to the atmosphere, 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°C.

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. 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. 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. 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.

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. 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.

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.

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. 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.

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. 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*). 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. The significance of porphyria to potential effects at the population level (e.g., lethality, reproductive impairment) is unknown.

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, while growth of the protozoan, *Tetrahymena pyriformis*, was decreased after a 10-day exposure to a nominal concentration of 1 µg/L HCB.

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. 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. 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; 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.

Fathead minnows (*Pimephales promelas*) and rainbow trout (*Oncorhynchus mykiss*) were not adversely affected by exposure to levels of HCB approaching its aqueous solubility. 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.

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. The Ontario Screening Level Concentration Approach was applied 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. 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.

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. 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. 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. 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.

Reference

Canadian Environmental Protection Act Priority Substances List Assessment Report: Hexachlorobenzene (1993)

SECTION 4 DESIGNATED NATIONAL AUTHORITY

Institution	Environment Canada Environmental Stewardship Branch Chemical Sectors Directorate Chemical Management Division
Address	Place Vincent Massey 351 St. Joseph Blvd., 12th Floor Gatineau, Quebec K1A 0H3 CANADA
Name of person in charge	France Jacovella
Position of person in charge	Executive Director, Chemical Management Division
Telephone	(819) 956-5263
Telefax	(819) 994-0007
E-mail address	CDS-SDC@ec.gc.ca

Date, signature of DNA and official seal: France Jacovella

PLEASE RETURN THE COMPLETED FORM TO:

Secretariat for the Rotterdam Convention
Food and Agriculture Organization
of the United Nations (FAO)
Viale delle Terme di Caracalla
00100 Rome, Italy
Tel: (+39 06) 5705 3441
Fax: (+39 06) 5705 6347
E-mail: pic@pic.int

OR

Secretariat for the Rotterdam Convention
United Nations Environment
Programme (UNEP)
11-13, Chemin des Anémones
CH – 1219 Châtelaine, Geneva, Switzerland
Tel: (+41 22) 917 8177
Fax: (+41 22) 917 8082
E-mail: pic@pic.int

Definitions for the purposes of the Rotterdam Convention according to Article 2:

(a) 'Chemical' means a substance whether by itself or in a mixture or preparation and whether manufactured or obtained from nature, but does not include any living organism. It consists of the following categories: pesticide (including severely hazardous pesticide formulations) and industrial;

(b) 'Banned chemical' means a chemical all uses of which within one or more categories have been prohibited by final regulatory action, in order to protect human health or the environment. It includes a chemical that has been refused approval for first-time use or has been withdrawn by industry either from the domestic market or from further consideration in the domestic approval process and where there is clear evidence that such action has been taken in order to protect human health or the environment;

(c) 'Severely restricted chemical' means a chemical virtually all use of which within one or more categories has been prohibited by final regulatory action in order to protect human health or the environment, but for which certain specific uses remain allowed. It includes a chemical that has, for virtually all use, been refused for approval or been withdrawn by industry either from the domestic market or from further consideration in the domestic approval process, and where there is clear evidence that such action has been taken in order to protect human health or the environment;

(d) 'Final regulatory action' means an action taken by a Party, that does not require subsequent regulatory action by that Party, the purpose of which is to ban or severely restrict a chemical.