LINDANE A REVIEW OF TOXICITY AND ENVIRONMENTAL FATE

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Hexachlorocyclohexane (HCH), also known as benzene hexachloride (BHC), is an organochlorine insecticide that is available in two formulations - technical grade HCH and lindane. Technical grade HCH is a mixture of different isomers: α-HCH (60-70%), β-HCH (5-12%), γ-HCH (10-15%), δ-HCH (6-10%), and ε-HCH (3-4%). Lindane is the γ-isomer (>99% pure) of HCH.

Uses
Lindane, as an insecticide and fumigant is used against a wide range of insects. Its main uses include treatment of seeds, on crops, in warehouses, in forestry, on domestic and agricultural animals, and for pest control of scabies and lice on humans.

Release to the Environment
Lindane is found in various compartments of the environment, with most in water, and the rest in soil, sediment and air. The most contaminated areas are locations where lindane is formulated, used or disposed of. Use of lindane in Canada has been estimated at up to 285,000 kg/year in 1990, with the majority of use in the prairie provinces. However, recent Environment Canada data estimated a total use of 455,000 kg for 1997 and 510,000 kg for 1998 in the prairie provinces alone, making the 1990 estimate rather obsolete. Lindane residues have been found in all environmental compartments, human and wildlife tissue as well as food products, including fruits, vegetables, meat, milk products, fish and other seafood.

Fate and Exposure
Lindane is relatively soluble in water and has a tendency to remain in the water column. Contamination of surface water may occur as a result of surface run-off from agricultural land or via rain, snow and dry deposition. Lindane is biodegraded in aquatic systems and the estimated degradation half-lives of lindane in rivers and lakes range from three to 300 days. While in the water column, lindane may be adsorbed or desorbed to sediment or other suspended materials. Bioconcentration factors for lindane vary in aquatic life, ranging from 63 to 1000, which suggests that lindane may bioaccumulate in some aquatic organisms, but not others. The half-life of lindane in sediment has been estimated at 90 days.

The major sources of lindane in the atmosphere are fugitive dust particles from wind erosion of contaminated soil, volatilization from treated agricultural soil and volatilization from plant foliage sprayed with lindane. Lindane is transported over long distances in the air, and has been found in Arctic air, distant from any sources of use.

With respect to soil, lindane is either adsorbed to the soil particles, volatilized to the atmosphere or leached into groundwater. The half-life of lindane in soil is temperature dependent; in warmer temperature, the lindane residence time in soil decreases considerably. The mean half-life for lindane in treated soils is estimated at 120 days. In soils and sediments, lindane is degraded primarily by biotransformation, however the major removal mechanism of lindane from soil is volatilization.
Lindane residues are also found in plants. Plants with high lipid content have a higher concentration of lindane than others.

Human Exposure
The most important route of human exposure to lindane is ingestion of food contaminated with this pesticide. Infants are exposed to lindane through ingestion of their mothers' milk. Higher concentrations of lindane and other HCH isomers have been found in human tissues and mothers' milk in developing countries, as compared with levels found in Canada and the US. In general, most Canadians are exposed to lindane at concentrations considered to be "acceptable". However, Inuit populations may be exposed to higher lindane concentrations. Farmers, pesticide applicators and individuals living in the vicinity of hazardous waste disposal sites contaminated with lindane may receive additional exposure through dermal contact and inhalation. Compared with the general population, higher concentrations are found in serum and adipose tissue of people occupationally exposed to lindane and other HCH isomers.

Acute Toxicity
Lindane is considered to be highly toxic to aquatic organisms, and moderately toxic to birds and mammals. People who are occupationally exposed to it are advised to avoid its contact with eyes, skin and via inhalation. Lindane has adverse effects on the central nervous system. Symptoms of acute toxicity in humans include headache, dizziness, seizures as well as effects on the gastrointestinal tract, cardiovascular and musculoskeletal systems.

Chronic Toxicity
A variety of sublethal effects have been observed in aquatic organisms, birds and mammals exposed to lindane in long-term studies. These include biochemical changes, which may affect growth and reproduction in aquatic organisms. Effects in mammals are mostly on the liver and kidney, although other organs may be affected, as well as the immune system and central nervous system. Lindane is considered to be a possible human carcinogen, and HCH is considered a probable human carcinogen by the US Environmental Protection Agency (EPA) and International Agency for Research in Cancer (IARC).

Reproductive Toxicity/Endocrine Effects
Both lindane and β-HCH have been shown to exert estrogenic activity in rodents, causing reduction in testes weight, disruption of the estrous cycling, and reduced pituitary and uterine weight, as well as vitellogenin induction in male fish. Lindane may also have anti-estrogenic characteristics that block the response of estrogen-dependent tissues to estradiol.

Neurotoxicity
Lindane may affect the central nervous system of mammals. Rats exposed to lindane at moderate concentrations showed effects on behaviour, motor activities and brain chemical levels. High doses of lindane have been shown to induce convulsions and seizures.

Immunotoxicity
A sublethal concentration of lindane adversely affects the immune systems of fish, birds and mammals. Effects include a reduction in hemoglobin, increase in kidney weight, and liver toxicity in addition to histopathological changes in liver and kidney.

Carcinogenicity

Dietary exposure of lindane and technical HCH promotes liver cancer in mice and rats under laboratory conditions. Both US EPA and IARC consider lindane as a possible human carcinogen, however, the US EPA did not provide a carcinogenicity assessment for lindane due to a lack of data.

Regulatory Status

Although the use of lindane and technical grade HCH is banned and/or restricted in many countries, there are a number of developing countries that still use them. Use of technical HCH is banned in North America; however, lindane is still used in Canada and the United States. Currently, in Canada, lindane is subject to Special Review under Section 19 of the Pest Control Products Regulations of the Pest Management Regulatory Agency (PMRA).

1.0 INTRODUCTION

Lindane is an organochlorine insecticide and fumigant which is used against a wide range of soil-dwelling and plant-eating insects. Lindane is used on crops, in warehouses, in public health measures to control insect-borne diseases and, together with fungicides, as a seed treatment agent. Lindane is also used in a variety of domestic and agricultural applications such as dips, sprays and dusts for livestock and domestic pets. The forestry industry also uses lindane to control pests on cut logs (Donald *et al.,* 1997). Other uses of lindane include lotions, creams and shampoos for the control of lice and mites (scabies) in humans (EXTOXNET, 1996; Bintein and Devillers, 1996; Health Canada, 1995).

Lindane and certain HCH isomers have been found to cause endocrine disrupting effects as well as reproductive and central nervous system damage (Warhurst, 1998; Sumpter, 1998; US EPA, 1998c, Willett *et al.*, 1998). Lindane and α- and β-HCH have been consistently found in various environmental compartments as well as human and wildlife tissue, blood and fat samples (Willett *et al.*, 1998). This review describes the environmental fate of lindane as well as its general toxicity with emphasis placed on the estrogenic activity of this pesticide. Other recent reviews of HCH isomers have been conducted by ATSDR (1997), the World Health Organization (1991a) and more recently by Willett *et al.* (1998).

2.0 CHEMICAL IDENTIFICATION

2.1 Chemical Profile

Hexachlorocyclohexane (HCH), also known as benzene hexachloride (BHC), is an organochlorine insecticide that is available in two formulations - technical grade HCH and lindane. Technical grade HCH is a mixture of different isomers: α-HCH (60-70%), β-HCH (5-12%), γ-HCH (10-15%), δ-HCH (6-10%), and ε-HCH (3-4%) (Kutz *et al*., 1991). Lindane is the γ-isomer (>99% pure) of HCH.

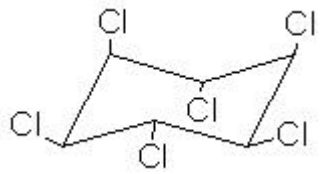
Technical grade HCH was first synthesized in 1825 through the chlorination of benzene in the presence of ultraviolet light (IARC, 1973). The insecticidal properties of HCH were first discovered in Europe in 1941-1942, however, in 1944 it was found that the γ-isomer is the only HCH isomer responsible for these properties (Hardie, 1964). Lindane is extracted from HCH by using selected solvents, most commonly methanol, and then using nitric acid for odour removal. The use of technical grade HCH has been banned in Canada and the United States since the 1970s, however it is still used in a few developing countries.

2.2 Trade Names

Trade names for lindane include: Agrocide, Ambrocide, Aparasin, Aphitiria, Benesan, Benexane, Benhexachlor, Benzene Hexachloride, BHC, BoreKil, Borer-Tox, Exagama, Gallogama, Gamaphex, gamma-BHC, Gamma-Col, gamma-HCH, Gammex, Gammexane, Gamasan, Gexane, Hexachlorocyclohexane, HCH, Isotox, Jacutin, Kwell, Lindafor, Lindagronox, Lindaterra, Lindatox, Lintox, Lorexane, New Kotol, Noviagam, Quellada, Steward, Streunex, and Tri-6 (EXTOXNET, 1996).

2.3 Physical and Chemical Properties

Common name: Lindane
Chemical name: 1,2,3,4,5,6-hexachlorocyclohexane, γ-isomer; γ-HCH
CAS Registry number: 58-89-9
Chemical formula: $C_6H_6Cl_6$
Molecular weight: 290.83
Chemical Structure:



Melting point: 112.5°C
Boiling point: 323.4°C
Odour: musty (odourless when pure), with an odour threshold of 12 ppm (NTP, 1998)
Solubility in water at 25°C: 7.52 mg/l
Partition coefficients:
Log K_{OW}: 3.3, 3.61
Log K_{OC}: 3.0, 3.57
Bioaccumulation factor:
in human fat: 19 ± 9
in aquatic animals: 2.5 ± 0.4
Vapour Pressure at 20°C or 25°C: 5.3 ± 1.4 x 10^{-3} Pa
Henry's law constant at 25°C: 3.2x10^{-4} KPa m^3/mol
Conversion Factors:
air 1 ppm = 1.18 mg/m^3
water 1ppm = 1 mg/L

2.4 Mode of Action

Lindane is a contact insecticide with stomach and respiratory action. It acts as a stimulant to the nervous system causing epileptiform convulsions and death.

In the nervous system, lindane interferes with γ-aminobutyric acid (GABA) neurotransmitter function by interacting with the $GABA_A$ receptor-chloride channel complex at the picrotoxin binding site (ATSDR, 1997).

Other effects include renal and liver damage. Lindane and ß-HCH interact with cellular membranes and may produce several generalized cytotoxic effects associated with impaired membrane function. For example, glucose uptake and cyclic AMP accumulation in rat renal cortical tubules were altered by exposure to lindane (López-Aparicio *et al.,* 1994).

2.5 Worldwide Production and Use

Lindane and technical HCH are banned from use in a number of countries and restricted in several others (Bintein and Devillers, 1996). Generally, there were two significant drops in global production and usage of technical HCH. First, in 1983, when China banned the use of HCH. Second, in 1990, when the former Soviet Union banned the use of technical HCH, and India stopped using HCH on agricultural crops. Global use of lindane and technical HCH was estimated to be 720,000 and 550,000 metric tonnes/year respectively (Voldner and Li, 1995; Isnard and Lambert, 1987). However, earlier reports on total global technical HCH and lindane production were grossly underestimated. Obtaining new information, Li reported revised global consumption levels for lindane and technical HCH as high as 6,000,000 and 11,000,000 metric tonnes, respectively. The two estimates for global usage of technical HCH and lindane are shown in Table 1. Information in this table was extracted from Li *et al*. (1996) and Li (1996, 1999). Both estimates were calculated based on data provided by each country and then mapped according to a global climate model in a 1° x 1° longitude/latitude grid system.

The use of technical HCH is banned in Canada, China, Egypt, France, Russia and the US. Currently, the largest consumer of technical HCH is India, with an estimated 51,000 tonnes consumed in 1990 (Li, 1999). Lindane is not currently manufactured in the US or Canada. The basic manufacturers of lindane worldwide are: Agrolinz (Austria); All India Medical Corp. (India); Celamerck GmbH KG Ingelheim (Germany); Inquinosa (Spain); Mitsui, Inc. (Japan); Rhône-Poulenc; Phytosanitaire (China) (FAO-UNEP/PIC, 1997).

Table 1: Worldwide usage/production of technical HCH and lindane in 1990s

COUNTRY	Tech. HCH tonnes/year (Li *et al.,* 1996)	α-HCH[a] tonnes/year (Li *et al.,* 1996)	γ-HCH[b] tonnes/year (Li *et al.,* 1996)	Tech. HCH tonnes/year (Li 1999)	α-HCH[a] tonnes/year (Li 1999)	γ-HCH[b] tonnes/year (Li 1999)
Algeria	67	47	14	405	315	72
Argentina	6	4	0.6	0	0	0.6
Australia	NA	-	-	3,700	2590	555
Belgium	0	0	66	0	0	-
Brazil	NA	-	-	2,080	1456	312
Canada	0	0	285	-	-	285
Central African Republic	NA			1	0.7	0.15
China	0	0	100	0	0	100
Colombia	NA	-	-	6	4	0.9
Former USSR	0	-	-	4,528	3170	679
France	0	0	1863	0		
Gambia	NA	-	-	0.3	0.21	0.05
Germany	120	84	94	120	84	94
Honduras	NA	NA	137	2	0.8	0.3
India	28,400	19,880	4,260	51,000	35,700	7,650
Ivory Coast	NA	-	-	16	11	2.4
Italy	5	3	600	15	11	600
Mexico	262	183	54	1,740	1,218	276
Myanmar	NA	1	6	1	0.7	6
Niger	NA	358	397	3	2	397
Pakistan	3	2	0.5	20	14	3
Philippines	NA	-	-	126	88	19
South Africa	NA	-	-	13	9	2
Spain	NA	0	96	0		96
Sri Lanka	NA	-	-	18	13	3
Sudan	NA	-	-	3	2	0.5
Suriname	NA	-	-	60	42	9
Ukraine	240	168	36	-	-	36
UK	NA	0	77	0		77
Uruguay	NA	-	-	140	98	21
USA	NA	-	114	-	-	114

(Li *et al.,* 1996; Li 1999)

a) Values were calculated assuming that technical grade HCH contains 70% α-HCH

b) Values were calculated based on reported lindane consumption with addition of 15% of the HCH consumption (assuming that technical grade HCH contains 15% γ-HCH).

NA = not available

2.5.1 Lindane Use in Canada

The estimated total lindane use in Canada for 1990 is 285,000 kg (Li *et al.,* 1996). However, this estimate for total Canadian use is grossly underestimated. A recent estimate by Environment Canada's scientists suggested an estimate of total use for the three prairie provinces as 455 tonnes for 1997 and 510 tonnes for 1998. These estimates were calculated based on the average canola seeding rate of 6.5 kg canola per ha, and total planted area of 4,819,500 ha in 1997 and 5,402,575 ha in 1998 (Don Waite, personal communication).

Canadian uses of lindane include:

1) Seed treatment for wireworms and for seed-borne diseases in wheat, oats, barley and rye. Sometimes also used on field crops such as peas, soybeans, beans, cucumbers, sugar beets;
2) Seed treatment for control of flea beetles in canola, rapeseed, mustard and cole crops;
3) Topical application on livestock for ticks, lice, mange, etc., and also in feed and industrial establishments;
4) Topical application for fleas on domestic pets, e.g. shampoos, sprays and flea collars;
5) Soil application against wireworms in tobacco fields;
6) Direct plant application for pests of spruce, pine and balsam fir logs and Christmas trees;
7) Dip or spray to control wood-destroying beetles in logs; and
8) Direct plant application for control of greenhouse, industrial and home insects such as aphids, thrips and whiteflies.

The estimated use of lindane in various Canadian prairies is summarized in Table 2.

Table 2: Use of lindane in various Canadian provinces

PROVINCE	LINDANE KG/YEAR	REFERENCE
British Colombia	272**	B.C. Ministry of Environment, Lands and Parks and Environment Canada¸ Technical Report DOE FRAP#1997-16, Survey of Pesticide Use in British Columbia: 1995. 1997.
New Brunswick	Minor usage	Cathy Stapleton, New Brunswick Department of Environment
Newfoundland	None used	
Nova Scotia	?	
North West Territories	None used	Harvey Gaukel, Environmental Protection Service, Department of Resources, Wildlife and Economic Development
Ontario	?	
Quebec	1,339**	Marcel Guacher, Ministry of Environment
Prince Edward Island	None used	Dan Reeves, Pesticides Regulatory Program
Prairies Provinces (Saskatchewan, Alberta, Manitoba)	455,000 (1997)*** 510,000 (1998)***	Don Waite, Environment Canada
Yukon	Minor usage	Bengt Pettison, Environmental Protection and Assessment Branch, Department of Renewable Resources

* Based on seeding rates; seed treatment rates; assuming average 50% lindane in seed treatment product by weight; 90% of canola seed treated; 1996-1998 canola acreage planted, assuming that canola use is 85% of all agricultural use.
** Sales figures.
*** Based on canola seeding rates; acreage planted; assuming average 95% of the canola seeds were treated with lindane.

2.5.2 Lindane Use in the United States

Lindane is registered in the US for use on fruit and vegetable crops, ornamentals, seed treatments for grains, legumes and oilseed crops, tobacco, greenhouse vegetables, lawns, forestry, domestic outdoor and indoor uses by homeowners (including dog dips, house sprays), commercial food and

feed storage areas and containers, fallows, barrier strips, livestock and farm animal premises, wood or wooden structure sites (WinSpirs Pestbank database, 1997).

While lindane is no longer produced in the US, it is imported from France, Germany, Spain, Japan and China (US EPA, 1985). In 1990, total lindane use in the US was estimated at 114,000 kg based on available usage data and on a global climate model developed by Li *et al.* (1996). More recent data, by United States Geological Survey (USGS) estimated the total agricultural use as 32,000 kg (USGS, 1992). This usage data was back calculated based on state-wide estimates of pesticide use rates on cropland and pesticide use information collected by state and federal agencies. These data represent only agricultural use of lindane and do not include non-cropland applications (i.e. home use, green house use, etc.) Table 3 lists the total kilograms applied on each crop and the per cent national use of lindane in 1992.

Table 3: Estimated annual agricultural use of lindane in the United States

CROPS	TOTAL KG APPLIED	PER CENT NATIONAL USE
Pecans	26,079	81
Squash	2,845	8.88
Safflower	1,484	4.41
Sugar beets for sugar	969	3.03
Lettuce	243	0.90
Sweet peppers	131	0.41
Melons	115	0.36
Cantaloupes	54	0.17
Cauliflower	54	0.17
Hot peppers	28	0.09
Total	**32,002**	

(USGS - Pesticide National Synthesis Project, 1992)

3.0 FATE, RESIDUES AND EXPOSURE

Lindane is a persistent organochlorine compound that is widely distributed in the environment with a long half-life in various environmental compartments (Simonich and Hites, 1995; Bro-Rasmussen, 1996; Bintein and Devillers, 1996). The presence of lindane and other HCH isomers (namely α- and ß-HCH) in the environment and human and wildlife tissues, as well as the environmental fate and exposure routes of lindane, have been documented in detail in many scientific studies and literature reviews. Therefore, in this report, the following sections will only briefly capture some of these findings.

Because of the importance of HCH in the Arctic, the levels found in various environmental compartments, humans and wildlife are discussed separately in section 3.4.

3.1 Fate and residues

3.1.1 Global movement and isomerization

Lindane, as well as α- and ß-HCH, has the potential to bioaccumulate in organisms and to be transported over long distances. Isomerization of lindane to other HCH isomers which are either more environmentally stable HCHs, such as α-HCH, or more bioaccumulative, such as β-HCH, is of great concern. In the environment, lindane is potentially transformed into a variety of chemicals, most of which are volatile. These include γ-pentachlorocyclohex-1-ene, γ-3,4,5,6-tetrachlorocyclohex-1-ene, α-HCH, β-HCH, and δ-HCH (Bintein and Devillers, 1996; Cornacoff *et al.,* 1988). The ratio of α-HCH to γ-HCH concentration in air has been used as an indicator to estimate the possible origin of the air mass in the long-range transportation of contaminants (Iwata *et al.,* 1993). The study by Iwata and coworkers recognised considerable latitudinal variations of HCH isomer composition in air. In general, they observed a lower α/γ ratio in the southern hemisphere, South China Sea, Mediterranean Sea and North Atlantic, which may indicate the sporadic use of lindane in these areas. On the contrary, higher α/γ ratios were found in northern air samples including Chukchi Sea, Bering Sea, and the northern and central part of the North Pacific, where ratios higher than 10 were observed (Iwata *et al*., 1993). There are several assumptions regarding higher levels of α-HCH in the atmosphere in cold climates. One possibility is the photochemical isomerisation of γ-HCH to α-HCH. Although photoisomerization of both ß-HCH and γ-HCH to α-HCH is possible under experimental conditions (Hamada *et al*., 1981; Steinwandter, 1976), it has never been proven under environmental conditions. Iwata and coworkers (1993) argued that if the photoisomerization phenomenon is true, then higher ratios of α-/γ-HCH should also be found at the emission sites. Poissant and Koprivnjak (1996), working on seasonal fluctuations of α-/γ-HCH ratios in Quebec, found no increase in α-HCH levels during lindane application, suggesting that perhaps photoisomerisation is not the main factor in the fluctuation of α/γ ratios in various geographical regions of the world. In fact, they found the spring-summer ratio of α-/γ-HCH to be particularly low, especially during the early spring corn seeding period, indicating the local usage of lindane (a maximum concentration of lindane of up to 367 ng/m^3 was noted in May 20th), and a high
α-/γ-HCH ratio (up to 14) during the winter (indicating background lindane levels). They suggested that the winter high ratio may be influenced by the air mass current originating from the Arctic. During the summer, the current from the Arctic is cut off from mid-altitudinal exchange, therefore, the HCH concentration ratios in Quebec are more influenced by the volatilization of recently applied lindane. Similar temporal variations in α-/γ-HCH ratios have also been observed in other areas, including Ontario (Poissan *et al*., 1996), Saskatchewan (Don Waite, personal communication), Southern Norway (Haugen *et al*., 1998) and the Canadian and Norwegian Arctic (Fellin *et al*., 1996).

Biological degradation of γ-HCH to α-HCH may be another possible explanation for the global variability of the α/γ ratios. However, although early workers have shown that bioisomerization of γ-HCH to α-HCH is possible under experimental conditions (Newland *et al*., 1969; Benezet and Matsumura, 1973), current field studies have found that only a small percentage of γ-HCH is converted to α-HCH as a result of biological activities (Waliszewski, 1993; Singh *et al.,* 1991). Other explanations for the higher global presence of α-HCH and higher α/γ ratios in some places could be attributed a) to their variable physical-chemical properties, for example the Henry's law

constant for α-HCH is 0.524 Pa m^3/mol and for γ-HCH it is 0.257 Pa m^3/mol at 20°C indicating water solubility of lindane and its tendency to partition faster from a gas phase into the water phase. Therefore, during global atmospheric transportation of HCH isomers, lindane will be more readily removed from the air by rain, leaving proportionally higher levels of α-HCH in the air (Walker *et al*., 1999). And b) to different degradation rates of HCH-isomers which may contribute to the variable accumulation of α-HCH. Brubaker and Hites (1998) found an approximately 25 per cent longer atmospheric residence time for α-HCH than for lindane. (See Walker *et al.,* 1999 for more information on HCH isomerization.) Also, Wania and Mackay (1999) suggested that because of a ban on technical HCH (containing 70% α-HCH) in many countries in temperate regions, the current global inventory of α-HCH is confined to higher altitudes and the Arctic region, where there is less potential for degradation. They predicted an atmospheric residence time of 280 days.

3.1.2 Fate and residue in the atmosphere

The major sources of lindane to the atmosphere are fugitive dust particles from wind erosion of contaminated soil, volatilization from treated agricultural soil and from plant foliage sprayed with lindane. In addition, lindane and other HCH isomers may be emitted into the atmosphere during the manufacturing and reformulation process. Both α- and γ-HCH have been found in air samples in the vicinity of formulation plants (ADSTR, 1998; US EPA, 1998a).

Lindane is removed from the atmosphere by rain and dry deposition. The residence time of lindane was estimated in air as 119 days and the removal rates by rainfall and dry deposition were estimated at 2.5 per cent per week and 3.5 per cent per week, respectively (Atkins and Eggleton, 1971). More recently, the atmospheric life-times of lindane and α-HCH, based on hydroxyl radical reactions using a rate constant model, were estimated as 96 days and 120 days, respectively (Brubaker and Hites, 1998). Similarly, van Pul and coworkers also calculated the atmospheric residence time of lindane as 85 days, using a rate constant model based on first-order and time averaged reaction rates for the removal processes, including dry deposition, wet deposition and degradation in air (van Pul *et al*., 1998).

As a result of the ban on technical HCH, most of the α-HCH current inventory now resides in the northern hemisphere, and therefore subject to a lower degradation potential. Wania *et al*. (1999) suggest that since the zonal and compartmental distribution changed in time, the persistence of α-HCH also changed with time. They predicted a resident time of 280 days for α-HCH, based entirely on the degradation process.

Levels of lindane in the atmosphere are seasonal and temperature dependent. For example, high summer concentrations of lindane found in southern Ontario may be indicative of recent usage as well as the movement of warm air from the lower parts of the US and the Canadian prairie provinces to the Great Lakes region (Hoff *et al.,* 1992, Don Waite, personal communication). In Sweden and other Scandinavian countries, a higher concentration of lindane has been recorded in spring and summer, whereas concentrations of α-HCH remained constant (Haugen *et al*., 1998). Similarly, yearly concentrations were found to vary in US and Canadian cities, with highest air concentrations in the summer and lowest in the winter, as would be expected from agricultural use (Whitmore *et al.,* 1994). In Saskatchewan, Waite and co-workers (1997-98, unpublished data), found that lindane concentrations in air above a canola field are elevated during the first

week of planting, reach their peak in the second week and then decrease with time. The highest concentration at a height of 100 cm above canola field was 16.1 ng/m^3 in 1997 and 7.4 ng/m^3 in 1998. The authors attributed the lower concentration in 1998 to severe draught conditions which reduced the volatilization rate of lindane from soil (Don Waite, personal communication).

Similarly, in Villeroy, Quebec, Poissant and Koprivanjak (1996) also reported a seasonal variation of lindane concentrations in air as well as variation during and a few days after corn seedings. They attributed the springtime high air concentrations mainly to usage of lindane on corn seeds. Some atmospheric concentrations of lindane and α-HCH and their seasonal variations are summarized in Table 4.

Table 4: Global seasonal variations in atmospheric concentrations of lindane and α-HCH

LOCATION	SAMPLING YEAR	γ-HCH pg/m^3	α-HCH pg/m^3	REFERENCE
Lista, southern Norway	1991-1995	37-60	47-84	Haugen *et al*., 1998
Karvatn, central Norway	1992 (Mar-May)	77	88	Oehme *et al*., 1995
Svanvik, northern Norway	1992(Mar-May)	46	97	Oehme *et al*., 1995
Ny-Ålesun, Spitsbergen	1992 (Mar-May)	32	144	Oehme *et al*., 1995
	1993(Apr-Dec)	14	77	Oehme *et al*., 1996
Rörvik, southern Sweden	1990 (Feb)	134	76	Brorström-Lundén *et al*., 1994
	1990 (May)	693	370	Brorström-Lundén *et al*., 1994
Rörvik, Nidingen, southern Sweden	1991 (May-Apr)	98	43	Brorström-Lundén, 1996
	1991 (Nov-Dec)	61	75	Brorström-Lundén *et al*., 1995
	1991 (May-Jun)	128	77	Brorström-Lundén *et al*., 1995
	1992 (Nov-Dec)	22	36	Brorström-Lundén *et al*., 1995
North Atlantic	1990 (Oct)	79	105	Schreitmüller & Ballschmitter, 1995
	1991 (Apr-May)	66	63	
Paris, France	1989-90 (Jan-Dec)	1500	-	Granier & Chervreuil, 1992
Saskatchewan, Canada	1997 (May-July)	3700-16100	-	Waite, 1999
	1998 (May-July)	1700-7400	-	
Turkey Lake, Ontario, Canada	1987 (May)	94	288	Lane *et al*., 1992
	1987 (July)	48	418	
	1987 (Sept)	26	197	
Point Petre, Ontario, Canada	1988 (Nov)	14	153	Lane *et al*., 1992
	1989 (Mar)	18	63	
Villeroy, Quebec, Canada	1992 (May 14)	55	23	Poissant and Koprivanjak, 1996
	1992 (May 20)	367	40	
	1992 (May 26)	64	29	
Saskatchewan, Canada*	1997 (May-July)	3.7-16.1x10^3	-	Waite, 1999
	1998 (May-Aug)	1.7-7.4 x10^3		
Green Bay, USA	1989 (June)	138	333	McConnell *et al*., 1993
Great Lakes, USA & Canada	1990 (Aug)	40	219	McConnell *et al*., 1993
Asia and Oceania		5.5 to 4.0x10^6		Iwata *et al.,* 1994
Jacksonville, USA		0.6 - 22.1x10^3	0 - 1.2x10^3	Whitmore *et al.,* 1994
Springfield, USA		0 - 9.5 x10^3	0 - 0.2x10^3	Whitmore *et al.,*1994

3.1.3 Fate and residue in water

Lindane is more soluble in water than most other organochlorine compounds, therefore has a tendency to remain in the water column. Contamination of surface water may occur as a result of surface run-off (as dissolved chemicals are absorbed to particles) and atmospheric depositions. Three major transport pathways for atmospheric inputs to surface waters are wet deposition, dry deposition and gas exchange across the air-water interface. Despite its high vapour pressure, evaporative loss of lindane from surface water is not considered significant. It depends on water temperature and occurs only during the warmest months of the year. Lindane biodegradation in aquatic systems is considered the most dominant process in the removal mechanism from water. The estimated degradation half-lives of lindane in rivers, lakes and groundwater are 3-30 days, 30-300 days, and >300 days, respectively (Zoetemann *et al.,* 1980). Others have estimated the half-life of lindane in surface water to be 151 days (Mackay and Leinonen, 1975).

While in the water column, lindane may be adsorbed to and desorbed from sediment or other suspended materials. The adsorption and desorption rate of lindane to sediment is related to the physical characteristics of the sediment as well as its organic carbon content. Lindane in sediment may also be recycled back into the water column as a result of bacterial activity (Fendinger *et al.,* 1992). The half-life of lindane in sediment has been estimated at 90 days (Bintein and Devillers, 1996).

Agricultural run-off is the major contamination route of lindane and other HCH isomers to surface water. In Saskatchewan, run-off from canola fields (where lindane is heavily used to treat canola seeds) is reported to contaminate surface water with maximum concentrations of 11 ppt and 4 ppt for lindane and α-HCH, respectively. However, there were no reports regarding the contamination of groundwater (Donald *et al.,* 1997). In Alberta, α-HCH was found in rivers due to atmospheric deposition (Donald *et al.,* 1997). In the Great Lakes region, deposition of total HCH into water from air is balanced by the evaporation of HCH from the water. The net atmospheric loading of total HCH was estimated to be from 0 (± 150) kg/year in Lake Ontario up to 600 (± 450) kg/year in Lake Erie (Hillery *et al.,* 1998). Significantly higher α/γ ratios in water from upper Great Lakes are reported, indicating the long range transportation of technical HCH whereas the lower α/γ ratios in the lower Great Lakes suggest contamination from local sources. Lindane and α-HCH concentrations and ratios in the Great Lakes water are presented in Table 5.

Table 5. Lindane and α-HCH concentrations in the Great Lakes

SAMPLING AREA	α-HCH (ppt)	Lindane (γ-HCH) (ppt)	α/γ	REFERENCE
Lake Superior, May 1986 Lake Huron, May 1986 Lake Erie, April 1986 Lake Ontario, April 1986	8.07 6.16 3.96 4.12	1.09 0.81 1.08 1.31	7.4 7.6 3.67 3.14	Stevens and Neilson, 1989
Lake Ontario, 1987	4.83-8.81	0.81-1.85		Biberhofer *et al*. 1987
Green Bay, June 1989 Lake Michigan, August 1990 Lake Huron, August 1990 Lake Erie, August 1990 Lake Ontario, August 1990	1.11 1.33 1.40 1.04 0.98	0.41 0.31 0.36 0.45 0.37	3.3 4.5 4.0 2.4 2.7	McConnell *et al*., 1993

Low concentrations of lindane have also been found in surface and groundwater in other parts of the world (Table 6).

Table 6: Examples of lindane concentrations in surface water in other parts of the world

SAMPLING AREA	CONCENTRATION (ppt)	REFERENCE
French estuaries	5-50	Marchand, 1989
Surface water in France	13.6-95.2	Bintein and Devillers, 1996
Groundwater in France	9.5 to 183.8	Bintein and Devillers, 1996
Scheldt estuaries	17-125	van Zoest and van Eck, 1991
Sable Island	1.2-2.1	Bidleman *et al.,* 1992*
Baltic Sea and North Sea	1.0-7.7	Huhnerfuss *et al.,* 1992

* total HCHs

Apart from atmospheric deposition and surface run-off, point source discharges are also major contributors of surface water contamination. For example, Uniroyal Chemical Limited operates a plant in Elmira, Ontario, which formulates lindane products for seed treatment. The Ontario Ministry of Environment and Energy entered into an agreement with Uniroyal in November 1993, which requires Uniroyal to report concentrations of lindane and other substances in Canagigue Creek, which traverses the Uniroyal plant. The MOE stipulates that the maximum level of lindane be 0.006 ppb; the Provincial Water Quality Objective (PWQO) for lindane in Ontario is 0.01 ppb. For the period of January 1997 to September 1998, the PWQO was exceeded in 12 of 39 samples, and the IPWQO was exceeded in 19 of 39 samples.

3.1.4 Fate and residue in soil

With respect to soil, lindane is either adsorbed to the soil particles, volatilized to the atmosphere, taken up by crop plants or leached into groundwater. In soils and sediments, lindane is degraded primarily by biotransformation, however the major removal mechanism of lindane from soil is volatilization. High temperatures and flooding are considered the key elements in increasing the

volatilization rate of lindane from soil surfaces (Bintein and Devillers, 1996; Rudel, 1997; ADSTR, 1998). Warmer temperatures decrease the half-life of lindane under all soil and moisture conditions. The estimated half-lives of lindane from soil and plant surfaces at 10°C and 20°C are 2.3-24.8 days and 0.29-0.73 days, respectively (Dorfler *et al.,* 1991). The mean half-life of lindane in treated soils is estimated at 120 days (Bintein and Devillers, 1996). Also, it has been reported that HCH isomers degrade faster under anaerobic soil conditions (Singh *et al.*, 1991). Singh *et al*. (1991) investigated the residence time of HCH isomers in soil under cropped and uncropped conditions. Their study showed that the persistence of all HCH isomers (except for α-HCH) was higher in uncropped plots. The half-life for Σ-HCH residues was 58.8 days in cropped and 83.8 days in uncropped plots. Among the different isomers, β-HCH was found to be most persistent (half-life = 184 days) under uncropped conditions followed by lindane (half-life = 107 days) and α-HCH (half-life = 54.4 days). The corresponding half-life values under uncropped conditions were 100 days for β-HCH, 62 days for lindane and 56 days for α-HCH (Singh *et al*., 1991).

Depending on use patterns, exposure length, moisture, temperature, and seasonal variation, lindane soil levels vary widely. Singh *et al*. (1991) reported that the concentrations of HCH isomers, in experimental plots, have declined gradually during the two year study. However, α isomer dissipated from soil faster than the other HCH isomers. This could be attributed to its higher vapour pressure and hence, its higher volatilization rate compared with others. Also, they noted that the rates of dissipation of HCH isomers were much faster from the soil under crop conditions than from uncropped soil. Table 7 is a summary of their work.

Samuel and Pillai (1990) demonstrated the significant influence of temperature, humidity and solar radiation on the rapid dissipation of HCH isomers from Indian sub-tropical soils. Kaushik (1989) also reported that, under sub-tropical conditions, the loss of HCH isomers from soil is dependent on soil moisture content, based on two experimental plots, where one plot was kept under dry conditions, whereas the other was regularly watered. Similar to the Singh *et al*. work, they found that among HCH isomers, α-HCH is the fastest isomer to dissipate from soil, followed by γ-HCH. They also noted that the rate of dissipation of all isomers was greater under wet soil conditions than under dry conditions.

Lindane and other HCH isomers will stay on the upper layer of the soil and generally, there is very little movement of lindane and other HCH isomers to lower soil layers (Martijn *et al*., 1993).

Table 7. Periodic concentrations of HCH isomers in soil from cropped and uncropped plots

TIME LAG (days)	HEXACYCLOHEXANE ISOMERS IN SOIL (μg/g) α-HCH	β-HCH	γ-HCH
Cropped			
0	6.5	0.12	1.3
127	2.2	0.07	0.9
210	0.4	0.004	0.4
300	0.3	0.03	0.3
346	0.2	0.005	0.12
466	0.03	0.004	0.06
533	0.004	0.005	0.002
682	0.003	0.001	0.001
Uncropped			
0	6.5	0.26	1.5
127	2.8	0.098	1.01
210	0.15	0.095	0.86
300	0.16	0.08	0.55
346	0.14	0.065	0.48
466	0.09	0.05	0.32
533	0.002	0.03	0.033
682	0.001	0.01	0.021

(Singh *et al*., 1991)

Seasonal variation of HCH isomers in soil has been recorded in various countries. In the tropical environment of South India, where large-scale application of technical HCH on rice is practiced, higher levels of HCH have been found in soil and sediments during the wet season, than during the dry season (Ramesh *et al*., 1991). The levels of total HCH in paddy soils were found to be in the range of 3.7-1100 ng/g in the wet season and 1.1-190 ng/g in the dry season. The relatively low levels of HCH isomers in soil and sediments of South India have been related to the rapid volatilization of HCH from soil, causing 99.6 per cent of applied HCH to become airborne (Takeoka *et al*., 1991).

3.1.5 Fate and residue in plants

Plants are exposed to lindane during direct application and from the air and water (EXTOXNET, 1996). There are several pathways through which lindane and other organic pollutants may enter plants, including a) partitioning from contaminated soil to the roots and from there to other parts, b) through the atmosphere by gas-phase and particle phase deposition onto the leaf surface and c) by direct uptake through the stomata. Metabolism of lindane in plants is not well understood and it depends on plant type and lipid content. For example, carrots are estimated to metabolize lindane with a half-life of over 10 weeks, whereas in lettuce the metabolic half-life may only last for 3 to 4 days (Ulman, 1972).

Lindane residues have been found in a number of different edible plants, including carrots and lettuce, with lower levels in cauliflower and spinach. More lindane is found in plants with higher lipid content, such as carrots. All HCH isomers have been found in all plant and grain samples growing in experimental plots treated with technical HCH (Sing *et al*., 1991). Table 8

demonstrates the concentration of lindane and other HCH isomers in various stages of experiment in both wheat plants and grain samples.

Lindane has also been found in tree bark samples collected in various countries and regions around the world (Simonich and Hites, 1995). Both lindane and α-HCH were detected in pine needle samples collected from various countries in Europe (Calamarie *et al*., 1994).

Table 8. HCH isomers in wheat samples during various experimental stages

HCH ISOMERS	DAYS AFTER TREATMENT					
	127		466		847	
	Plant	Grain	Plant	Grain	Plant	Grain
α-HCH	0.125	0.116	0.056	0.050	0.036	0.010
β-HCH	NA	NA	0.014	0.036	0.031	ND
γ-HCH	0.125	0.027	0.031	0.039	0.023	0.003
Σ-HCH	0.340	0.143	0.114	0.124	0.104	0.013

(Singh *et al*., 1991)
ND = not detected
NA = not analysed

3.1.6 Fate and residue in laboratory animals and wildlife

Lindane may break down to a number of metabolites in mammals. In rabbits, the potential metabolites of lindane include chlorobenzenes, chlorophenols, pentachlorocyclohexene, hexachlorocyclohexene, pentachlorobenzene, 2,4,6-trichlorophenol and 2,3,4,5-tetrachlorophenol (Karpally *et al.,* 1973; Pompa *et al.,* 1994). In humans, lindane is metabolized and excreted in urine; metabolites include 2,4-dichlorophenol, 2,4,6-trichlorophenol, 2,3,5-trichlorophenol, 2,4,5-trichlorophenol, 2,3,4,6-tetrachloro acids and 2,4-dimercaptic (Starr and Clifford, 1972). Different isomers of HCH are metabolized differently in the body and have variable retention times. For instance, β-HCH has a relatively long half-life of seven to eight years (Jung *et al.,* 1997).

Lindane residues have been found in liver, fat, blood, brain and muscle tissue of exposed rats (DeJongh and Blaauboer, 1997). Male rats exposed to lindane (6 ppm bw) during lactation were found to have lindane concentrations in brain, liver, kidney and testes tissue, with the greatest concentrations in the liver (Dalsenter *et al.,* 1997b). The mean concentration was over 800 ppb wet weight in the liver, while in the brain, kidney and testis, levels were less than 400, 700 and 400 ppb, respectively.

An unborn fetus may be exposed to lindane *in utero* via placental transfer, as shown in rat and mouse models (Khanna *et al.,* 1991; Srivastava and Raizada, 1993). In rats, oral exposure to lindane during gestation resulted in lindane residues in the fetal brain, liver and carcass tissue (Khanna *et al.,* 1991). Female mice exposed to technical grade HCH levels of up to 50 ppm bw/day during gestation were found to have HCH residues in the blood, liver, brain and fat (Srivastava and Raizada, 1993). The highest concentrations were in fat tissue, with levels of up to 25 ppm. In the fetuses, detectable HCH residues were found in the liver, brain, placenta and amniotic fluid, with levels in the brain up to 2.5 ppm and placenta levels of 2 ppm. Additionally,

pentachlorobenzene, a metabolite of lindane, may be transferred from a pregnant animal to the infant via the placenta and higher concentrations are transferred to the newborn in milk (Pompa *et al.,* 1994). In rabbits that were given lindane orally, lindane and pentachlorobenzene were found in muscle, liver, brain and adipose tissue, with the highest concentrations again in the liver. In fetuses and newborns, lindane and pentachlorobenzene concentrations were found in the body, liver, brain, lung and gastric contents, with the largest concentration in the brain.

Lindane is stored in tissues and then excreted over time. Lindane concentrations were found in the liver, whole blood, plasma and adipose tissue of rats exposed to 60 ppm bw (Junqueira *et al.,* 1997). Initial concentrations in the liver and adipose on the day after exposure were 8.64 and 437 ppb, respectively, and down to 0.56 and 11 ppb by the seventh day. Levels in whole blood and plasma ranged from 1.5 and 2.21 on the first day to 0.22 to 0.09 ppm, respectively, on the seventh day (Junqueira *et al.,* 1997). Similarly, lindane residues decreased over time following administration in rabbits. For instance, rabbits given 4.21 ppm bw/day lindane orally were found to have fat tissue residues of lindane of 38.51-61.85 ppm at 28 days, with lower levels of lindane (12.31-21.52 ppm fat) in rabbits sacrificed seven days following the last dosing (Ceron *et al.,* 1995). Rabbits receiving 500 ppm lindane in drinking water had plasma levels of approximately 20 ppb (Wasserman *et al.,* 1972). Mink exposed to lindane in the diet at a concentration of 1 ppm bw/day for three generations had increased lindane concentrations in the adipose tissue (Beard and Rawlings, 1998). The concentration of lindane in the adipose of third-generation female mink was 4.42 ppm.

Wildlife exposed to lindane in the natural environment were found to accumulate lindane in fatty tissues (Bro-Rasmussen, 1996). In female roe deer caught in a field habitat in Poland, the mean concentration of lindane was 0.5 ppm in fatty tissue (Krynski *et al.,* 1982). This compared with an average concentration of 0.096 ppm fatty tissue in deer from forest habitats. The authors suggested that deer in fields are exposed to higher concentrations of lindane due to pesticide use on plants. Mink collected in Iowa (1970-71) had lindane concentrations of less than 0.001 ppm in adipose tissue but up to 0.04 ppm in brain tissue (Franson *et al.,* 1974). Higher levels of β-HCH were found in these mink, with 0.11 and 0.08 ppm in adipose and brain tissue, respectively (Franson *et al.,* 1974). These levels of lindane are lower than those found in laboratory animals exposed to 1 ppm bw/day (Beard and Rawlings, 1998). Neither lindane nor β-HCH were detected in liver samples.

HCH was detected in the fat tissue of northern female fur seals collected in Japan from 1971 through 1988, as well as in the breast muscle tissue of double-crested cormorants in Lake Michigan and Lake Superior in 1990 (Iwata *et al.,* 1998). Mean concentrations of lindane in the fat tissue of seals was 38-67 ppb, with higher concentrations of α-HCH (159-208 ppb) and β-HCH (376-467 ppb). In the breast muscle tissue of cormorants, mean lindane concentrations were 58-72 ppb fat. Lower concentrations of lindane were found in the brain, bone, liver, skin and carcass.

Lindane residues have also been found in the eggs of water birds on the Danube River delta, with increasing concentrations found in birds higher on the food chain (Walker and Livingstone, 1992). Higher levels were found in the common cormorant which is a bottom feeder, as compared to the white pelican which feeds at the surface. This is due to increased exposure of cormorants since sediments are generally higher in lindane than surface water.

Table 9: Lindane residues in the eggs of water birds

SPECIES	LINDANE RESIDUES (ppb dry weight)
mallard eggs	0.27
glossy ibis eggs	0.28
grey heron eggs	0.65
night heron eggs	0.52
pygmy cormorant eggs	0.46
white pelican eggs	1.15
common cormorant eggs	2.01

(Walker and Livingstone, 1992)

3.2 Human Exposure

General public can be exposed to lindane through eating food sprayed with lindane, breathing air contaminated with lindane, as well as dermally following skin contact. Almost all human exposure to lindane is from dietary intake (>99 per cent), with the rest coming from drinking water, from dermal contact with contaminated soil, and some inhalation of contaminated water (Ragas and Huijbregts, 1998; Bintein and Devillers, 1996). In addition to agriculture, lindane is also used in the treatment of scabies and pubic lice in Canada, in the form of a one per cent cream or lotion (Health Canada, 1995). Lindane can be absorbed by the skin through the use of scabies control lotions as well as through contact with contaminated soil or occupational exposure (Duff and Kissel, 1996; Franz *et al.,* 1996; Dick *et al.,* 1997a,b; Meinking and Taplin, 1996; Downs, 1997).

The daily intake of total HCH from 1969 through 1978 for the average Canadian decreased from 2.49 to 0.60 µg/person-day. For a 70 kg person, this can be expressed as 0.036 to 0.0086 ppb bw/day. These levels are much lower than the recommended WHO temporary ADI of 1 ppb bw/day (FAO, 1998).

A study of adult dietary intake of table-ready foods in the US in 1990 estimated the mean intake of lindane at 0.2 µg/day, with a maximum of up to 3.2 µg/day (MacIntosh *et al.,* 1996). The mean and maximum intakes can be expressed as 0.003 and 0.05 ppb bw/day which again are much lower than the oral reference dose (RfD) for lindane of 0.3 ppb bw/day set by US EPA (US EPA, 1988b).

Similar to Canada and the US, dietary exposure to lindane in France was also below acceptable daily intake levels and levels in foods were below the maximum residue levels (MRLs) (Venant *et al.,* 1989; Klein *et al.,* 1986). Further to this, in 1992 it was estimated in China that people had an intake of 0.0224 ppb bw/day lindane from food (Zhang *et al.,* 1997). This level is higher than that in developed countries, but still lower than the WHO temporary ADI for lindane (1 ppb bw/day).

Exposure of workers occupationally exposed to lindane is different from that of the general public. It was estimated that the exposure to total HCH for workers following an eight hour forest spraying was between 0.35 and 5.59 ppm bw via inhalation and 7.40 to 38.82 ppm bw from dermal exposure (Wasserman *et al.,* 1960). These exposure levels are well above the WHO

temporary acceptable daily intake (1 ppb bw/day). Therefore, occupational exposures may potentially result in adverse health effects if precautions are not taken.

Table 10: Lindane residues in foods in various countries

COUNTRY/FOOD	RESIDUE LEVEL (ppm)	MRL (ppm)	REFERENCE
China			
processed grain	0.013	0.3	Zhang *et al.,* 1997
vegetables and fruits	0.005	0.2	Zhang *et al.,* 1997
meat and poultry	0.008	0.4	Zhang *et al.,* 1997
aquatic products	0.011	2	Zhang *et al.,* 1997
eggs and egg products	0.045	1.0	Zhang *et al.,* 1997
milk and milk products	0.018	0.1	Zhang *et al.,* 1997
Hong Kong			
milk	0.068	-	Wong and Lee, 1997
Nigeria (1989/90)			
cereals	0.008-0.017	0.5	Osibanjo and Adeyeye, 1995
Ireland (1971/72)			
milk fat and dairy products	< 0.1 fat	-	Downey *et al.,* 1975
animal feed	0.0001	-	Downey *et al.,* 1975
France			
fish	0.011 - 0.029	-	Bintein and Devillers, 1996
Greece			
bovine milk fat	0.0008 - 0.007	0.008	Mallatou *et al.,* 1997
cheese fat	0.0008 - 0.002	0.008	Mallatou *et al.,* 1997

3.3 Residues in Human Tissue and Breast Milk

People who are occupationally exposed to HCH through spraying have higher concentrations of the α-, β- and γ-isomers in their blood and skin lipid samples than the general population (Dua *et al.,* 1998).

Table 11: HCH isomers in human blood and lipid samples from India

TISSUE	α-HCH	γ-HCH	β-HCH	δ-HCH
Whole Blood (ppm)				
Workers	0.34	0.32	0.36	0.17
General Population	0.28	0.20	0.28	0.13
Skin Lipid (ppm)				
Workers	9.69	12.00	22.04	10.84
General Population	3.63	3.54	5.98	4.77

(Dua *et al.,*1998)

Lindane and other HCH isomers may be found in the fat tissue of people, as shown in Table 12.

Table 12: Concentration of HCH isomers in human adipose tissue and serum samples

COUNTRY	SEX	CONCENTRATION (ppm fat)	REFERENCE
Lindane in Adipose Tissue			
India	-	1.9	Jani *et al.,* 1988
Greenland/Denmark	-	0 to 0.01**	Jensen and Clausen, 1979
Italy	-	0.104	Gallelli *et al.,* 1995
United States	-	less than 0.1	Kutz *et al.,* 1977
β-HCH in Adipose Tissue			
Finland	-	0.06 to 0.13	Mussalo-Rauhamaa *et al.,* 1990
United States		0.20	Redetzle and Applegate, 1993
United States	-	0.21 to 0.31	Kutz *et al.,* 1977
Total HCH in Adipose Tissue			
India	males	4.054	Kashyap *et al.,* 1993
	females	3.144	Kashyap *et al.,* 1993
HCH in Serum		**Concentration (ppb)**	
India	males	70.051	Kashyap *et al.,*1993
	females	65.44	Kashyap *et al.,*1993

** median concentration (90th decile concentration is 0.06 ppm fat)

HCH residue levels were found to be the highest in people aged 41 to 50 years, with lower residues in younger and older adults (Kashyap *et al.,* 1993). It was also found that concentrations of the β-HCH isomer were the highest in both adipose and serum samples.

Lindane and HCH residues have also been found in maternal serum, the placenta, the umbilical cord and cord serum (Saxena *et al.,* 1983; Nair *et al.,* 1996). This suggests the potential for exposure of the unborn fetus to HCH.

HCH isomers have been found in human breast milk in many areas of the world, including Asia, Africa, Europe and America (Kroger, 1972; Downey *et al.,* 1973; Saleh *et al.,* 1996; Ejobi *et al.,* 1996; Banjeree *et al.,* 1997). Levels of lindane and other HCH isomers were much higher in women from India, where use of technical grade HCH is widespread, than those reported for women in developed countries (WHO, 1991a, 1992). This was seen especially for the α- and β-isomers which could be attributed to a greater use of technical grade HCH in India. Table 13 is a summary of HCH isomer concentrations in the breast milk of women from various countries.

Table 13: Mean concentrations of HCH isomers in human breast milk samples

Location/ year of sampling	α-HCH Concentration (ppm, lipid)	β-HCH Concentration (ppm, lipid)	γ-HCH Concentration (ppm, lipid)	∑HCH Concentration (ppm, lipid)	Reference
Australia Victoria, 1993	0.071	0.345	0.108	-	Quinsey, 1995
Belarus	-	-	-	0.416	Barkatina *et al*., 1998
Brazil Ribeirao Preto Region, 1983-84 Porto Alegre	- 0.04	- 0.90	0.044 0.02	- -	Matuo *et al*., 1992 Beretta & Dick, 1994
Canada	0.00031	0.00103	0.0226	-	Newsome *et al*., 1995
China, 1982	-	6.6	0.03	-	From: Atuma, 1986
Czech Republic Prague	-	0.071	-	-	Schoula *et al*., 1996
France, 1990	0.052	0.287	0.037	-	Bordet *et al*., 1995
Germany (East), 1990/91 (West), 1990/91 Lower Saxony, 1992/93	 0.0008 <0.01 -	 0.083 0.075 0.045	 0.0098 0.016 0.016	-	Schlaud *et al*., 1995
India Delhi	1.83	8.83	2.31	-	Banjeree *et al*., 1997
India Punjab Fairidkot	 0.65 1.76	 4.37 8.20	 0.21 0.41	-	Kalra *et al*., 1994
Jordan* Amman, 1989/90	0.12	0.40	0.23	-	Alawi *et al*., 1992
Kazakstan, 1994	0.078	2.210	-	-	Hooper *et al*., 1997
Mexico Veracruz,1994/95	0.018	0.561	0.22	-	Waliszewski *et al*., 1996
Nigeria Bebdel State, 1981/82	-	0.47	0.05	-	Atuma, 1986
Norway Oslo, 1991	-	-	-	0.036	Johansen *et al*., 1994
Russia Kola, 1993	-	-	-	0.858	Polder *et al*., 1996
Russia 5 different regions, 1989/90	0.129	1.589	0.0094	-	Schecter *et al*., 1990
Saudi Arabia Al-Kharj	-	-	0.0233	-	Al-Saleh *et al*.,1998
Spain Madrid, 1991	0.0342	0.235	0.0105	-	Hernandez *et al*.,1993
Sweden Uppsala, 1990	-	0.02	-	-	Vaz *et al*., 1993
Thailand Bangkok, 1985/87	0.001	0.119	0.003	-	Schecter *et al*., 1989
Turkey Kayseri, 1989	0.096	0.522	0.156	-	Ustuntas *et al*., 1994

Location/ year of sampling	α-HCH Concentration (ppm, lipid)	β-HCH Concentration (ppm, lipid)	γ-HCH Concentration (ppm, lipid)	∑HCH Concentration (ppm, lipid)	Reference
Turkey Van, 1995/96 Manisa, 1995/96	 0.05 0.067	 0.417 0.355	 0.016 0.017	 - -	Çok *et al*., 1997
UK	-	0.08	<0.02	-	Dwarka *et al*., 1995
USA New York, 1985/87	0.001	0.020	0.002	-	Schecter *et al*., 1989
USA Pennsylvania	-	-	0.08	-	Kroger, 1972
Uganda	0.1	0.07	0.44	-	Ejobi *et al*., 1996
Vietnam (South) Ho Chi Minh, 1985/87	0.003	0.221	0.023	-	Schecter *et al*., 1989

*Median

The infants of humans and wildlife may be exposed to lindane through breast milk (Pompa *et al.,* 1994; Nair *et al.,* 1996); some potential exposure levels were calculated and are outlined in Table 14. For these calculations, it was assumed that an average infant would weigh 5 kg and ingest 0.8 L milk/day [e.g., 0.8 L/d x lindane concentration (mg/L) / 5 kg bw].

Table 14: Exposure of Infants to Lindane from Mothers Milk

COUNTRY	LINDANE IN BREAST MILK (ppm)	EXPOSURE OF INFANT (ppm bw/day)	REFERENCE
Delhi, India	0.06	0.0096	Banjeree *et al.,* 1997
Delhi, India	0.084	0.0134	Nair *et al.,* 1996
Egypt	0.00842	0.00135	Saleh *et al.,* 1996
Ireland	0.00003	0.0000048	Downey *et al.,* 1973

Not all of these estimated intake values for infants are lower than the acceptable daily intake (ADI) of 0.001 ppm body weight/day. For example, values in India suggest higher exposure for infants. Banjeree *et al.* (1997) could not assess the toxicological implications of infant exposure to these levels of lindane. It is anticipated that exposures of infants to lindane in the developed world, including Canada, would be much lower, as indicated by exposures in Ireland.

3.4 Residues in the Arctic Environment

HCH is the most abundant pesticide in the Arctic environment. This results from the volatilization of HCH compounds after their application in tropical or sub-tropical countries and transportation by air masses and water currents to the Arctic and other remote regions (Takeoka *et al.,* 1991). Long-range transportation of lindane and other HCH isomers is evident by their presence in Arctic air and seawater samples from remote areas such as Resolute Bay in Nunavut Territory, Canada (Bidleman *et al.,* 1995).

3.4.1 Residues in Arctic Air and Water

Following atmospheric transport to the Arctic, HCH isomers, because of their low Henry's Low constant, particularly at cold temperatures (0.03 and 0.1 for lindane and α-HCH, respectively, at -2°C, the freezing point of seawater), have a tendency to partition from air into water (CACAR, 1997). This is evident by the high concentration ratio of HCH isomers in water to air. For example, the estimated ratio of α-HCH concentration in seawater to that in air is 3000 at 25°C, but 22,000 at 0°C. For this reason, the world's oceans, particularly in Arctic region, are major reservoirs for HCHs. The highest levels of HCH in the world's oceans are found in Arctic oceans, especially in the Beaford Sea and the Canadian Archipelago. There is an increase in ∑HCH concentration in the ocean water column with an increase in latitude from the tropical western Pacific Ocean to the Arctic Ocean. Wania and Mackay (1996) have suggested that this is evidence of the "cold-condensation" (grasshopper) effect.

HCH isomers are not uniformly distributed throughout the Arctic Ocean. It is estimated that approximately 20 per cent of the HCH present in the environment is held in the first 75-200 meters of the oceans' surface layer. (Iwata *et al.,* 1998). Also, HCH concentrations in the surface water of the Canadian Basin is elevated by a factor of two or more in comparison with other regions of the Arctic Ocean, or other oceans (CACAR, 1997). A mass balance analysis of total HCHs for two Arctic domains (i.e. North American Arctic Ocean including the Canadian Basin and the Archipelago and the Eurasian Arctic Ocean including the Eurasian Basin and regional seas) estimated a total standing stock of HCHs at 8100 tonnes in the upper surface layers of the ocean, with a residence time of 20 to 30 years (Barrie *et al.,* 1992). A more recent mass balance study estimated the current total HCHs (both α and γ isomers) in the upper 200 m of the water column in the Arctic oceans as 5200-6100 tonnes. In this study, major HCH inputs are assumed to be from ocean currents, atmospheric deposition and rivers contributing 76%, 22% and 2%, respectively. The removal pathways are the output via ocean currents, loss to the atmosphere, chemical destruction and ice export, accounting for 69%, 16%, 14%, and 2%, respectively (CACAR, 1997).

HCH is also one of the most abundant organochlorines (OCs) found in Arctic air based on air sampling measurements conducted in various places. HCH isomers, as well as other organic pollutants, have been measured in Arctic air in four locations in Canada and Norway and one location in Russia on a weekly basis since 1992. As well, a limited number of air/water samples were collected in the Bering/Chukchi Seas and in Heimaey Island in Iceland. At all locations α-HCH was the most predominant OC present. A summary of these studies is presented in Table 15.

Seasonal variation of HCH isomer concentrations in air was observed in Alert and Heimaey Island in Iceland, with a summer minimum. However, the seasonal variation was not as pronounced in other locations (see AMAP for full descriptions of seasonal variation of HCH isomers in the Arctic).

Table 15: Mean and range of concentrations of HCH isomers in Arctic air (1992-1994)

LOCATION/YEAR	α-HCH (range) pg/m^3	γ-HCH (range) pg/m^3	REFERENCE
Svanvik, Norway 1992 (Mar-May)	97 (39-205)	46 (11-194)	Oehme *et al*., 1995d
Ny-Ålesund, Norway 1992 (Mar-May) 1993 1994	 144 (68-338) 78 (6.8-203) 61 (16-112)	 32 (13-99) 14 (3.3-38) 16 (5.3-62)	 Oehme *et al*., 1995d Oehme *et al*., 1995 Hagen (unpublished data)
Alert, Canada 1992 (Mar-May) 1993	 57 (1.1-116) 61 (13-116)	 11 (0.03-37) 10 (1.9-29)	 Fellin *et al*., 1996 Barrie *et al*., unpublished data (cited in AMAP, 1998)
Tagish, Canada 1993	79 (24-160)	11 (3.3-25)	Barrie *et al*., unpublished data (cited in AMAP, 1998)
Dunai Island, Russia 1993	40 (0.63-77)	9.8 (<0.05-23)	Barrie *et al*., unpublished data (cited in AMAP, 1998)
Heimaey Island, Iceland 1995	19 (7.8-46)	15 (<0.1-50)	Thorlacius, 1996 (cited in AMAP, 1998)
Bering-Chukchi Seas 1993	91 (60-114)	23 (12-37)	Jantunen and Bidleman, 1995
Resolute, Canada 1992 (May-Sept)	114	9.8	Bidleman *et al*., 1995b

(AMAP, 1998)

Concentrations of total HCH in Arctic air have fallen over the last 15 years, from 800 pg/m^3 in the early 1980s to less than 100 pg/m^3 in 1992-1994. This is attributed to a decrease in the use of technical HCH in Asian countries, especially India and China, and its complete ban in North America resulting in over a nine-fold decline (Bidleman *et al.,* 1995; Jantunen and Bidleman, 1995, 1996). The concentration of α-HCH in air in the Norwegian Arctic also decreased in 1992 as compared to values obtained in 1984. In 1992, mean levels of α-HCH ranged from 72 to 144 pg/m^3, whereas the mean concentrations measured for α-HCH in 1984 ranged from 279 to 471 pg/m^3, resulting in a three- to four-fold decline. On the other hand, mean levels of lindane at the same monitoring stations ranged from 32 to 137 pg/m^3 in 1992 and from 29 to 46 pg/m^3 in 1984, showing an increase of one- to two-fold over seven years (Oehme *et al*., 1991; Oehme *et al.,* 1995). This reflects the increase in lindane use in European countries, after the ban imposed on technical HCH use.

Examples of HCH presence in various compartments of the Arctic environment are presented in Table 16.

Table 16: Concentration of α- and γ-HCH in various compartments of the Arctic Ocean

SAMPLE TYPE	α-HCH	γ-HCH
Air vapour (pg/m^3)	352	44
Snow melt (ppq)	1,335	428
Ice (ppq)	1,320	186
Seawater (ppq)	4,465	610
Sediment (ppt sediment)	240	15

(CACAR, 1997)

3.4.2 Residue in Arctic Wildlife

Although HCH isomers are not as bioaccumulative as other OCs, they have been detected in all trophic levels of the Arctic food web, including terrestrial, fresh water and marine food chains, with increasing concentrations. For example, Elkin (1994), examining the transfer of OCs through the lichen, caribou and wolf food chain in three herds in Nunavut, found that HCH levels increased at the higher trophic levels. Elkin and Bethke (1995), examining the OCs in caribou herds of the Canadian Arctic, found that in fact HCHs are one the most predominantly found OCs in caribou liver. In general, they found a significant west to east trend in concentrations of total HCHs (consists almost entirely of α-HCH), ranging from 3.3 ppb per lipid weight (ng/g lipid weight) in Inuvik herds to 40 ppb per lipid weight (ng/g lipid weight) in Cape Dorset.

HCH isomers have been found in relatively high concentrations in marine food chains throughout the Arctic region. HCH isomers have been found in the tissue of ringed seals from the Kara Sea in the Russian Arctic and in Larga seals from the Sea of Okhotsk (Nakata *et al.,* 1998) at concentrations similar to those in sea mammals from the Canadian and Norwegian Arctic (Muir *et al.,* 1992; Oehme *et al.,* 1988). Mean levels of HCH isomers found in seal tissues are shown in Table 17.

Table 17: Mean HCH Residues in Aquatic Organisms from the Arctic Seas

SPECIES	LOCATION	α-HCH (ppb lipid weight)	β-HCH (ppb lipid weight)	γ-HCH (ppb lipid weight)	ΣHCH (ppb lipid weight)
Ringed seal, male	Kara Sea	90	84	8.5	180
Ringed seal, female		65	49	6.5	120
Ringed seal, stomach contents		33	15	15	63
Larga seal, male	Sea of Okhotsk	75	250	4.6	330
Larga seal, female		110	170	5.7	280
Fish diet		36	16	6.3	59

(Nataka *et al.,*1998)

Table 18 is a summary of HCH concentrations in various trophic levels of the Canadian Arctic ecosystem. Muir *et al.* (1992) also found that the concentration of HCH in beluga whales from the St. Lawrence River were similar to those in the Canadian Arctic. Nataka *et al.* (1998) suggest this is due to the long range transport of HCH to the Arctic in a fairly homogeneous manner. HCH has also been found in the tissue of northern fur seals (Tanabe *et al.,* 1994).

TABLE 18: ∑HCH concentrations in various trophic levels of the Canadian Arctic

SPECIES	LOCATION	∑HCH CONCENTRATION ppb lipid (ng/g lipid)	REFERENCE
Amphipods (Pelagic) Amphipods (Anonyx)	Barrow Strait, Cornwallis Island	79-90 430-6,300	Hargrave, unpublished (AMAP, 1998)
Zooplankton(>500µm)	Barrow Strait, Canada archipelago	100-180	Hargrave, unpublished (AMAP, 1998)
Black guillemot, egg	Eastern low Arctic, High Arctic Canada	18.2* 19.7*	Hargrave, unpublished (AMAP, 1998)
Glaucous gull, egg	Western low Arctic, High Arctic Canada	21.0* 67.7*	Hargrave, unpublished (AMAP, 1998)
Thick-billed murre, egg	Eastern low Arctic, High Arctic Canada	20.3* 19.1*	Hargrave, unpublished (AMAP, 1998)
Arctic char, muscle and skin	Somerset Island Pond Inlet Spence Bay	83 69 87	Hargrave, unpublished (AMAP, 1998)
Ringed seal, blubber	Cumberland South Sanikiluaq (1989) (1991) Arctic Bay (1993) Barrow Strait (1993)	F:179* M: 210* F&M: 434* F: 69.4* M: 68.3* M: 201* F: 250* M: 310* F: 382*	Muir, 1994, 1996 Cameron and Weis, 1993 Cameron *et al*., 1997 Muir, 1994, 1996 Muir, 1994, 1996
Narwhal, blubber	Creswell Bay (1991)	M: 85*	Muir *et al*., 1995
Walrus, blubber	Inukjuak (1989) Akulivik (1989)	M: 267* M: 116*	Muir *et al*., 1995
Polar bear, fat	Baffin Bay north (1989-1990) Baffin Bay south(1989-90) Foxe Basin & Hudson Strait (1989-90) Eastern Hudson Bay (1990-91) David Strait (1989-90)	M: 212 M: 321 M: 241 M:259 M:272	Norstrom *et al*., 1997

3.4.3 Arctic Diet

An analysis of HCH in the diet of two communities in the Canadian Arctic (Kuhnlein *et al.,* 1995) is summarized in Table 19. The study showed that the Baffin Island Inuit in the eastern Arctic

consumed higher amounts of HCH due to the dietary habit of eating sea mammals, which are higher on the food chain than the diet of fish generally consumed by the Sahtu Dene/Metis of the western Arctic. The mean daily intake of HCH (α-, β-, and γ-isomers) for Baffin Inuit was 6.65 to 7.1 μg/day, depending on the age group, while the mean intake for Sahtu Dene/Metis was 0.55 to 1.07 μg/day (Kuhnlein *et al.,* 1995). The average intakes for both groups were less than the tolerable daily intake (TDI), of 0.3 ppb bw/day, established by Health Canada for HCH in 1996.

Table 19: ∑HCH concentrations in some foods consumed in the Canadian Arctic

FOOD	∑HCH CONCENTRATION (μg/100g, wet weight)
Baffin Inuit:	
Narwhal blubber (aged)	16.28
R. seal blubber (boiled)	15.43
B. seal blubber (raw)	14.92
Walrus blubber (aged)	14.48
Polar bear fat (boiled)	14.38
Sahtu Dene/Metis:	
Loche liver (baked)	1.18
Whitefish flesh (smoked/dried)	0.92
Whitefish eggs (raw)	0.57
Inconnu flesh (smoked, dried)	0.46
Caribou liver (baked)	0.34

(Kuhnlein *et al.,* 1995)

4.0 TOXICOLOGICAL PROFILE

4.1 Acute Toxicity

Lindane is considered to be moderately toxic to birds. Acute exposure to sublethal oral doses which cause 50 per cent mortality (LD_{50} is the dose of the compound that will produce death in 50 per cent of the animals) in birds range from 425 to more than 5,000 ppm (EXTOXNET, 1996). In birds, exposure to high concentrations of lindane has been shown to result in liver toxicity however, the effects may be dependent on the age of the birds when they are exposed (Samanta and Chainy, 1997a).

Lindane is highly toxic to aquatic organisms. Variable toxicity has been reported in different species of fish, which may be due to a number of reasons. For example, fish with higher lipid content appear to be more resistant due to increased deposition of lindane in lipids, with less available to target organs (Geyer *et al.,* 1993; Oliveira-Filho and Paumgartten, 1997). Additionally, the acute toxicity of lindane may be affected by the temperature of the water and physicochemical conditions (Ferrando *et al.,* 1987; Maund *et al.,* 1992). The acute toxicity of lindane and other HCH isomers in aquatic organisms, measured by the median lethal concentration (LC_{50}), is shown in Table 20. The LC_{50} is the concentration that causes 50 per cent of fish mortality in a specified time interval. The presence of elevated concentrations of lindane in sediment is also toxic to aquatic organisms. A 10-day LC_{50} of 60.5 ppb dry weight sediment was reported for the burrowing amphipod *Gammarus locusta* (Costa *et al.,* 1998).

Table 20: Acute toxicity values for HCH isomers in aquatic organisms

SPECIES	96-HOUR LC_{50} (ppm)	REFERENCE
γ-HCH/lindane		
Guppy	0.36	Oliveira-Filho and Paumgartten, 1997
Guppy	0.14[a]	Di Domenico *et al.,* 1988
Zebra fish	0.16	Oliveira-Filho and Paumgartten, 1997
Zebra fish	0.09[a]	Di Domenico *et al.,* 1988
Golden orfe	0.076-0.127[a]	Geyer *et al.,* 1993
Goldfish	0.12-0.23[a]	Bruggeman *et al.,* 1981; Geyer *et al.,* 1993
Carp	0.094-0.28[a]	Parthier, 1981; Geyer *et al.,* 1993
Neon fish	0.14	Oliveira-Filho and Paumgartten, 1997
Rainbow trout	0.04[a]	Katz, 1961; Parthier, 1981
Brown trout	0.038[a]	Geyer *et al.,* 1993
Chinook salmon	0.042[a]	Geyer *et al.,* 1993
Coho salmon	0.056[a]	Veith, 1981
Sheepshead minnow	0.104	Schimmel *et al.,* 1977
Bluegill sunfish	0.077[a]	Veith, 1981
Mosquito fish	0.074[a]	Fabacher and Chambers, 1971
Pinfish	0.0306	Schimmel *et al.,* 1977
Gudgeon	0.0743	Marcelle and Thorne, 1983
Tilapia	0.022[a]	Reichenbach-Klinke, 1974
Daphnia magna	1.19[a]	Zou and Fingerman, 1997
Daphnia magna	1.64[b]	Ferrando *et al.,* 1995
Chironomus riparius	2.0-6.5[c]	Maund *et al.,* 1992
Chaoborus flavicans	4.0	Maund *et al.,* 1992
Sigara striata	3.9	Maund *et al.,* 1992
Mysid	0.0063	Schimmel *et al.,* 1977
Pink shrimp	0.00017	Schimmel *et al.,* 1977
Grass shrimp	0.0044	Schimmel *et al.,* 1977
Eel	0.32-0.67	Ferrando *et al.,* 1987
American eel	0.07[a]	Tesch, 1983
European eel	0.67-0.9[a]	Geyer *et al.,* 1993
α-HCH		
Guppy fish	1.49	Oliveira-Filho and Paumgartten, 1997
Guppy fish	0.8-1.38	Canton *et al.,* 1978
Zebra fish	1.11	Oliveira-Filho and Paumgartten, 1997
Neon fish	1.52	Oliveira-Filho and Paumgartten, 1997
β-HCH		
Guppy fish	1.66	Oliveira-Filho and Paumgartten, 1997
Guppy fish	0.9[a]	WHO, 1992
Zebra fish	1.52	Oliveira-Filho and Paumgartten, 1997
Neon fish	1.10	Oliveira-Filho and Paumgartten, 1997
δ-HCH		
Guppy fish	2.83	Oliveira-Filho and Paumgartten, 1997
Zebra fish	1.58	Oliveira-Filho and Paumgartten, 1997
Neon fish	0.84	Oliveira-Filho and Paumgartten, 1997
Total HCH		
Pink shrimp	0.00034	Schimmel *et al.,* 1977
Pinfish	0.0864	Schimmel *et al.,* 1977

a = 48-hour LC_{50}; b = 24-hour LC_{50}; c = 240-hour LC_{50}

Acute exposure of fish to a sublethal concentration of lindane (0.05 ppm) resulted in biochemical changes in liver and brain tissue, as well as hyperglycemia (Soengas *et al.,* 1997). Effects such as decreased feeding activity were seen in the amphipod, *Gammarus pulex,* exposed to lindane at levels as low as 8.4 ppb, although no effects were seen at 4.1 ppb (Pascoe *et al.,* 1994; Blockwell *et al.,* 1998). Additionally, the exposure of two aquatic species, *G. pulex* and *Artemia aquaticus* to lindane concentrations of up to 6 ppb at the same time resulted in competitive exclusion. There was decreased survival in the less aggressive species (*A. aquaticus*) at the two high doses (Blockwell *et al.,* 1998). If this were to occur in nature, it could lead to decreased biodiversity.

Lindane is moderately toxic in mammals, although toxicity varies depending on the route of exposure and the species type. Most of the acute effects of lindane in mammals are on the liver, kidney, immune system and nervous system (US EPA, 1998a). Some LD_{50}s in mammals are shown in Table 21.

Table 21: Acute toxicity values for lindane in mammals

SPECIES	ROUTE OF EXPOSURE	LD_{50} (ppm)	REFERENCE
rat	intraperitoneal	35.85	Spector, 1956
rat	oral	76-270	EXTOXNET, 1996; NTP, 1998
rat	dermal	35	NTP, 1998
mouse	intraperitoneal	125	NTP, 1998
mouse	oral	44-246	EXTOXNET, 1993; NTP, 1998
cat	oral	25	NTP, 1998
dog	oral	40	NTP, 1998
rabbit	oral	60	EXTOXNET, 1996
rabbit	dermal	50	NTP, 1998
guinea pig	oral	127	NTP, 1998
hamster	oral	360	NTP, 1998

Acute oral exposure of people to high doses of lindane has been shown to affect the gastrointestinal, cardiovascular and musculoskeletal systems, as well as the nervous system, causing dizziness, headaches and seizures (Starr and Clifford, 1972; ATSDR, 1995; US EPA, 1998a). Other effects following inhalation of lindane include nose and throat irritation, anemia, and itchy skin (US EPA, 1998a).

4.2 Chronic toxicity

4.2.1 Reproductive Toxicity/Endocrine Effects

Mixed results have been found with regards to the endocrine effects of lindane in aquatic organisms and mammals. Estrogenic effects were found in some studies, but not others. The variability of response may be a result of different durations of exposure, time of exposure and route of administration. A summary of some studies relevant to this endpoint are discussed below.

The reproductive capacity of avian species is negatively affected by lindane. In the domestic duck, exposure to lindane (20 ppm bw/day) resulted in a reduction of eggs laid, increased time between

laying and thinner eggshell thickness than controls (Chakravorty and Lahiri, 1986). At this dose, vitellogenin levels decreased in the liver, plasma and ovaries; liver RNA levels were also reduced (Chakravorty *et al.,* 1986). The adverse effects on eggshell production and calcium homeostasis were likely due to estrogen deficiency. Estrogen is required for induction of vitellogenin synthesis in the liver. The decrease in liver synthesis of vitellogenin is reflected in decreased plasma and ovary levels. There was a delay in ovulation and histological effects in the ovaries which suggest an estrogen deficiency (Chakravorty *et al.,* 1986). It has been suggested that the reproductive effects of lindane may have implications in field situations, where exposure to lindane is lower (Chakavorty and Lahiri, 1986). An exposure level thought to produce no effects for this parameter was estimated in this study to be 2 ppm bw/day by dividing the lowest level to show effects (LOAEL) by a safety factor of 10 (Sample *et al.,* 1996).

Lindane may have either estrogenic or anti-estrogenic characteristics. Earlier studies have found lindane to have weak estrogenic activities (Raizada *et al.,* 1980; Lahiri *et al.*, 1985) although Beard and Rawlings (1998) indicated that "lindane has been shown to be anti-estrogenic in that it blocks the response of estrogen-dependent tissues to estradiol" (Chadwick *et al.,* 1988; Cooper *et al.,* 1989). In rats exposed to 40 ppm lindane, there were no effects on serum concentrations of estradiol, no effects on the functional response to estrogen and no change in estrogen receptor number (Laws *et al.,* 1994). Lindane treatment (15 ppm) resulted in reduced uterotropic action in the rat, leading to increased metabolism of the estrogen, with a resultant decrease in uterine activity, as well as decreased uterine weight (Welch *et al.,* 1971).

The thyroid gland is an important part of the endocrine system because of its potential for effects on hormone regulation. Effects on thyroid activity, which led to thyroid dysfunction, were found in a study with fish, *Oreochromis mossambicus*, exposed to 0.001 ppm technical HCH (Pandey and Bhattacharya, 1991). There was however, complete recovery from treatment-related effects after cessation of treatment. Lindane also had effects on the circulating thyroid hormone in female catfish exposed to more than 8 ppm lindane at different times during the reproductive cycle (Yadav and Singh, 1987). In the treated groups, significant increases or decreases were seen in plasma thyroid hormone levels (T_4 and T_3), depending on the phase of the reproductive cycle. Generally, levels of T_3 were inhibited, which may be due to either increased use of T_3 or inhibited conversion of T_4 to T_3.

Effects of lindane exposure on circulating thyroid hormones, including decreased serum thyroxine (T_4) levels, have also been seen in mammals (Rawlings *et al.,* 1998). These were speculated to have been a result of an "enhanced metabolism of T_4," resulting from the induction of liver microsomal enzymes (Street and Chadwick, 1975; Schulte and Parzefall, 1980). Indirect stimulation of estradiol secretion in mammals was suspected to be due to increased insulin concentrations in serum (Rawlings *et al.,* 1998). Another study (Roche, 1996) also showed that insulin could affect estradiol production. The effects of lindane on estradiol were found in a study with sexually immature rats given lindane at 30 or 60 ppm bw. In this study, there was a decrease in cytosolic estrogen receptor binding in the uterus, indicating that lindane may bind to the estradiol receptor in competition with estradiol in rat uterus cytosol (Tezak *et al.,* 1992). Similar results were found *in vitro* in this study. However, the binding affinity of estrogen for the receptors was not affected by exposure to lindane. Estradiol binding to estrogen receptors in brain or uterine cells was not altered in the presence of lindane *in vitro* at concentrations from

10^{-8} to 10^{-5} M (Uphouse and Williams, 1989). The lack of interaction with the estradiol receptor suggests that lindane does not interfere with the intracellular steroid receptor, although other mechanisms of action remain speculative. As indicated above, another study found that the presence of lindane did not affect the number or affinity of estradiol receptors (Laws *et al.,* 1994). While lindane inhibited DNA synthesis in bovine reproductive tissue cells at levels above 1.45 µg/100 µL incubation volume, it did not have any effects on the binding of estradiol to bovine uterine endometrial explants. This latter result is consistent with findings from other studies in which lindane does not interfere with the estrogen receptor.

A hormonal imbalance, due to inhibited ovarian steroidogenesis, was reported in fish exposed to lindane at levels of more than 4 ppm, which included altered sex steroid metabolism and steroid regulation (Singh and Singh, 1992). In another study, 16 ppm lindane caused a decreased gonadosomatic index (which is indicative of decreased growth of gonads), histological effects on the ovary, inhibited ovarian growth and altered cholesterol levels in fish (Singh *et al.,* 1993). Additionally, there were effects on the levels of sex steroids and potentially an inhibition of steroidogenesis that may have been due to decreased ovarian concentrations of free cholesterol. In another study, there was also a reduction in steroidogenesis following exposure of male and female goldfish (*Carassius auraus*) to lindane at more than 0.01 ppm. At 0.01 ppm there were no behavioural effects in fish, but at 0.1 ppm there was increased locomotor activity in fish and increased mucus production (Singh *et al.,* 1994).

β-HCH has been shown to have estrogenic activity in freshwater fish due to the induction of vitellogenesis in guppies exposed to more than 0.1 ppm β-HCH (Wester *et al.,* 1986). Additionally, while no effects were seen at 0.032 ppm, exposure of fish to β-HCH at concentrations of more than 0.1 ppm resulted in histopathological effects in liver, kidney and heart tissue. No estrogenic effects were found in the water flea (*Daphnia magna*) following lindane treatment of up to 0.2 ppm (Zou and Fingerman, 1997). Lindane concentrations of more than or equal to 0.25 ppm cause significantly decreased growth, reproduction and survival of *D. magna* (Ferrando *et al.,* 1995). Reproductive effects included a significant decrease in the number of young produced by lindane-exposed females. The exposure of zebrafish to a mixture of lindane (0.04 ppm) and 3,4-dichloroaniline (0.1 ppm) had adverse effects on reproduction in a life-cycle test (Ensenbach and Nagel, 1997).

Lindane has been shown to have effects on estrogen activity *in vitro* as well as *in vivo*. For instance, human breast cells exposed to lindane had increased levels of 16α-hydroxyoestrone, an estrogen that may be associated with an increased risk of breast cancer (Bradlow *et al.,* 1995). Petit *et al.* (1997) studied the estrogenic effects of lindane in a yeast recombinant *in vivo* system which expresses rainbow trout estrogen receptors and also in an *in vitro* test with rainbow trout hepatocyte culture vitellogenin gene expression (which depends on estradiol). Lindane had effects on β-galactosidase activity in yeast, but was not "able to displace $[^3H]E_2$ bound to" the rainbow trout estrogen receptor in the yeast system at the highest concentration used. It had the ability to cause vitellogenin induction in hepatocyte culture. Exposure to lindane resulted in 47.75 per cent β-galactosidase activity and 127.6 per cent vitellogenin gene expression, which compared with 100 per cent for estradiol. It was concluded that lindane was estrogenic in these tests. In rainbow trout hepatocyte cultures, lindane was shown to have estrogenic effects due to increased expression of the estrogen receptor gene and the vitellogenin gene (Flouriot *et al.,* 1995). Lindane did not have any affinity for the estrogen receptor binding site. The effects seen on gene

expression were due to metabolites of lindane rather than the parent compound. In contrast to the above reports, no estrogenic or antiestrogenic activity was found with lindane in rooster liver cells on the estrogen-regulated mRNA stabilizing factor which is expressed following exposure to estrogen (Ratnasabapathy *et al.,* 1997). Similarly, lindane did not show estrogenic activity in the E-SCREEN system (Soto *et al.,* 1995).

Another *in vitro* test showed lindane to have some estrogenic activity on bovine cells (Tiemann *et al.,* 1996). It was also shown to have estrogenic activity in yeast that expresses the human progesterone receptor B-form (Jin *et al.,* 1997). Exposure to lindane resulted in significantly decreased progesterone activity at levels of 1.0 to 10 μM, but this was not due to inhibition of binding. Significant reductions in progesterone activity were not seen at 500 or 100 nM. Since lindane did not displace [^{3}H]progesterone from the human progesterone receptor, the authors suggest that the decrease in activity was due to the interaction of the chemicals with another site or via another mechanism. Similarly, β-HCH was shown to have estrogenic activity in the estrogen-sensitive human MCF-7 cells, since it was able to induce the cytosolic progesterone receptor, although it also was not able to bind to the estrogen receptor (Coosen and van Velsen, 1989). In a recent study, β-HCH (0.1 to 10 nM) was found to be a weak agonist or antagonist of the estrogen receptor in MCF-7 cells (Enan and Matsumura, 1998). β-HCH has weak estrogenic activity, but the mode of action of β-HCH is different than other estrogens since it does not compete for binding of the estrogen receptor (Bigsby *et al.,* 1997).

β-HCH produced estrogenic effects *in vivo,* when released from the fat of adult ovarectomized mice during fasting (Bigsby *et al.,* 1997). Mice exposed to 100 ppm bw β-HCH had increased uterus weights, as well as a higher number of cells in the uterus (luminal epithelial cells) than in controls; this is an indicator of estrogen stimulation. These effects were not seen in mice exposed to 10 ppm bw β-HCH. In an earlier study, rats exposed to 2 to 250 ppm bw/day β-HCH, had effects ranging from the induction of liver enzymes at the low dose, to effects on organ weights and histopathology and severe central nervous system depression at the high dose (van Velsen *et al.,* 1986). Lymphoid and endocrine organs were also affected.

In ewes, lindane has been shown to affect serum hormone levels important in reproduction and metabolism at a level of 2.5 ppm lindane, which is suggestive of endocrine changes although there were no effects on clinical toxicity, body weight or tissue histopathology (Rawlings *et al.,* 1998). Endocrine changes in serum included increased insulin and estradiol, and decreased thyroxine and basal luteinizing hormone levels. Lindane did not show estrogenic nor antiestrogenic activity at this level of exposure which is higher than would be expected for wild or domestic animals (Rawlings *et al.,* 1998).

Lindane treatment (33 to 75 ppm) resulted in decreased sexual behaviour of female rats (Uphouse, 1987; Uphouse and Williams, 1989). Additionally, lindane interfered with the reproductive cycle of female rats, and had effects on the central nervous system including convulsions and death. The authors suggested that the decrease in sexual behavior was likely due to the disruption of the estrus cycle. Effects on estrus cycles were also seen in female rats at 5 to 40 ppm lindane (Cooper *et al.,* 1989; Lahiri *et al.,* 1985) which may have been due to the estrogenic activity of lindane. Additionally, there was evidence of increased body weights, decreased uterine weights, and decreased serum pituitary luteinizing hormone (LH) and prolactin concentrations at 20 and 40 ppm (Cooper *et al.,* 1989). At these levels, pituitary LH was lower

while pituitary follicle stimulating hormone was higher than in controls. Serum estradiol concentrations were lower in the high dose group. Mice fed 0.03 mg lindane/day had decreased gonadal hormone levels (e.g., progesterone), which can cause problems with reproduction; this may be a result of the decreased rate of steroid production in the ovaries (Sircar and Lahiri, 1990). Reproductive effects, decreased rate of ovulation, were seen in rabbits at 0.8 ppm bw lindane; however, there were few effects on reproductive organs and no overt toxicity (Lindenau *et al.,* 1994).

In addition to effects on the female reproductive system, biochemical and histological effects were seen in the testis of rats and mice following oral treatment with lindane or HCH (Dikshith *et al.,* 1978; Nigam *et al.,* 1979; Srinivasan *et al.,* 1988). Significant histological effects were seen in testes and decreased body weight and testes weight were found in male rats exposed to either 4 or 8 ppm lindane (Chowdhury *et al.,* 1987). Histological effects were also seen in the testes of rats injected with 0.2 to 5 mg lindane in each testis (Dikshith and Datta, 1972). In another study, male rats exposed to lindane (17.6 ppm) had histological changes in both the liver and testes, and effects on enzyme activity in liver, testes, blood and brain although there were no clinical signs of toxicity or gross pathological lesions in treated animals (Dikshith *et al.,* 1978). An increased number of dead and damaged spermatozoa were seen in rats treated with technical HCH, (10 and 20 mg), although there were no significant histological changes in the testis (Samanta and Chainy, 1997b). Lindane (60 ppm bw/day) also had reversible effects on the prostate of male rats (Simic *et al.,* 1991). Mice fed 500 ppm technical HCH caused increased testicular weight and degeneration of testicular tissue (Nigam *et al.,* 1979).

There were no adverse reproductive effects found in rats exposed to up to 100 ppm lindane in the diet (approximately 8 ppm bw/day) in a three-generation study (Palmer *et al.,* 1978; Sample *et al.,* 1996). Palmer *et al*. (1978) found an increase in liver weights of treated animals in the third generation, as well as enlarged hepatocytes in these animals; however, they indicated that these findings were “of doubtful importance.” Mink appear to be more sensitive to the reproductive effects of lindane than rats, with effects on reproductive efficiency at levels as low as 1 ppm bw/day (Beard *et al.,* 1997; Beard and Rawlings, 1998). Thyroid hormone (thyroxine) levels were significantly decreased in treated second generation males. Additionally, there was a decrease in mated mink that whelped and in litter size. In the third generation, there was also a decrease in testis size. Therefore, effects are seen in mink at lower levels than in rats. It is suggested that mink in the wild would be exposed to lower concentrations of lindane than 1 ppm bw/day (Beard *et al.,* 1997).

Beard and Rawlings (1998) suggest that effects of lindane exposure *in utero* may not manifest until later in life. Rats exposed to 1 to 5 ppm lindane *in utero* showed effects in brain tissue, suggesting that lindane may “negatively regulate expression of $GABA_A$ receptors in fetal brainstem,” and potentially result in postnatal behavioural effects (Brannen *et al.,* 1998). Exposure of rats *in utero* to 30 ppm bw lindane had effects on male reproductive function in adults, including a reduction in the number of spermatids, decreased serum testosterone levels and a transitory lack of libido (Dalsenter *et al.,* 1996, 1997a,b). However, following mating, there were no effects on pregnancy rates, resorption rates, number of implantations or number of viable and dead fetuses. In another study, male rats exposed to 1 or 6 ppm bw during lactation had significantly decreased testicular weight, decreased testosterone levels, histological effects in

testes and a decreased number of sperm and spermatids, although no effects were seen with mating, pregnancy or the fertility index (Dalsenter *et al.,* 1997b).

Administration of lindane to rats during gestation and/or lactation, at up to 400 ppm in the diet, did not have significant effects on survival, body weight, pregnancy rate, litter size, or pup survival (Srinivasan *et al.,* 1991); however, in the litters exposed to lindane, there was an increase in liver weight and a decrease in kidney weight. Effects were seen in litters of rats exposed to β-HCH at levels of 400 ppm in the diet, with reduced numbers of litters and decreased survival of pups, and increased liver weights at 50 ppm β-HCH (Srinivasan *et al.,* 1991).

Fetotoxicity and a decrease in steroid hormones were seen following exposure of pregnant mice to 0.09 to 0.26 mg lindane/day during early, mid or late pregnancy (Sircar and Lahiri, 1989). In a later study with mice, administration of a single oral dose of lindane at 30 ppm bw during gestation was fetotoxic (Hassoun *et al.,* 1996). Technical HCH (25 and 50 ppm bw/day) administered to mice during gestation was also fetotoxic, but not teratogenic (Srivastava and Raizada, 1993). Maternal liver enzymes were altered in the treated groups. Therefore, lindane is not considered a teratogen.

Men exposed to lindane occupationally have non-significantly increased levels of follicle stimulating hormone and decreased levels of testosterone (US EPA, 1998a). None of the studies available in the literature reviewed for this report suggest that lindane exposure results in reproductive or teratogenic effects in humans.

4.3 Neurotoxicity

Effects on the nervous system, including behavioural effects, have been seen in mammals following exposure to lindane (Fishman and Gianutsos, 1988; Rivera *et al.,* 1991; 1998; Anand *et al.,* 1998). The possible mechanisms of lindane-associated neurotoxicity were evaluated in a number of *in vitro* studies using cultured neuronal cells (Ogata *et al.,* 1988; Pomes *et al.,* 1994; Huang and Casida, 1996; Rosa *et al.,* 1996). In primary cultures of rat cerebellar granule cells, lindane exposure was associated with increased intracellular free calcium concentrations and increased mitochondrial transmembrane potential (i.e. mitochondrial activity) (Rosa *et al.,* 1996). The effect of lindane on the activity of GABA-activated chloride channels of neuronal cells was also evaluated (Ogata *et al.,* 1988; Pomes *et al.,* 1994; Huang and Casida, 1996). GABA (gamma-aminobutyric acid) is the major inhibitory neurotransmitter in the central nervous system of vertebrates. GABA binds to two classes of receptors known as $GABA_A$ and $GABA_B$ receptors. The $GABA_A$ receptor is a postsynaptic chloride-selective ion channel. In the nervous system, GABA binds to the $GABA_A$ receptor, which induces the opening of the chloride ion channels, resulting in an influx of chloride ions into the neuronal cell through an electrochemical gradient. This produces hyperpolarization of the cell membrane and inhibits cell firing or action potentials. Lindane has been reported to inhibit GABA-stimulated chloride ion influx in primary cultures of rat cerebellar granule cells, rat dorsal root ganglia or mouse neocortical neurons, by most likely interacting with the non-competitive blocker site of the $GABA_A$ receptor (Ogata *et al.,* 1988; Pomes *et al.,* 1994; Huang and Casida, 1996). This suggests that lindane inhibits GABA-dependent chloride flux in neurons resulting in the stimulation of the nervous system.

Lindane exposure (80 ppm) increased drug-induced seizure activity but had no effect on locomotor activity of mice (Fishman and Gianutsos, 1988). Developing rats exposed to lindane

(20 ppm) also showed effects on behaviour, motor activity and chemical levels in the brain (Rivera *et al.,* 1991, 1998). High doses of lindane have been reported to induce convulsions as the main neurotoxic effect, and seizures have been seen in rats at 10 ppm bw (Gilbert, 1995; Gilbert and Mack, 1995). In another study, 10 ppm lindane did not cause seizures, tremors, or weight loss but did cause chemical changes in the brain of rats (Rivera *et al.,* 1998). Lindane neurotoxic activity also involved a decrease in spontaneous locomotor activity at 2 ppm and increased GABA levels in the cerebellar region in rats at 3 ppm (Anand *et al.,* 1998). It was concluded that "low dose chronic exposure of lindane causes neurobehavioural, neurochemical and electrophysiological effects involving GABA mechanism(s)" (Anand *et al.,* 1998).

4.4 Immunotoxicity

Lindane exposure has been shown to have adverse effects on the immune system of fish, including immunosuppression, at sublethal concentrations of lindane (10 or 15 ppm) (Dunier *et al.,* 1995). Additionally, stress effects and adverse effects on the immune system were seen in birds exposed to 5 ppm bw lindane (Mandal *et al.,* 1986).

Effects on the immune system were seen in mice fed 150 ppm lindane (Andre *et al.,* 1983) and in rabbits exposed to 500 ppm lindane in drinking water (Wasserman *et al.,* 1972). Additionally, β-HCH has also been shown to have adverse effects on the immune system of mice fed 100 or 300 ppm β-HCH (Cornacoff *et al.,* 1988). Cornacoff *et al*. (1988) suggested that the immunological effects in mice were not due to estrogenic activity since there were no adverse effects on histology of ovaries and the endometrial epithelium.

In mammals, the intermediate minimal risk level established by the Agency for Toxic Substances and Disease Registry (ATSDR) for oral exposure to lindane is 0.01 ppb bw/day, based on immunological effects (ATSDR, 1997a). The intermediate minimum risk levels for α-HCH and β-HCH are 0.01 and 0.0006 ppm bw/day respectively, based on effects on the liver (ATSDR, 1997a). No levels were set for chronic exposure to any of the compounds.

Lindane has been shown to have adverse effects on the hematological system (e.g. blood) of birds, with anemia and decreased hemoglobin concentrations found following exposure to 5 ppm bw twice in one week (Mandal *et al.,* 1986). There were no overt signs of toxicity in these birds and the authors suggested that monitoring of hematological effects may be an indicator of pesticide toxicity. The level used in this study was thought to be a reasonable level for short-term environmental exposure to birds.

Lindane is toxic to the kidneys and has been shown to affect calcium metabolism and bone morphometry in rats exposed to lindane at levels of 10 or 20 ppm bw/day (Andrews and Gray, 1990). Additionally, there were increased kidney weights and histopathological effects in kidney tissue. In serum, cholesterol levels were increased and triglyceride levels were decreased. No effects were seen in serum parathyroid hormone levels (which control urinary calcium concentrations), although, urinary enzyme concentrations were affected.

Liver toxicity, including effects on liver enzyme levels and morphological effects, has also been seen in mammals exposed to lindane at levels of 20 or 60 ppm (Junqueira *et al.,* 1997; Videla *et al.,* 1997). Lindane has also been shown to have adverse effects on the adrenal gland and

adrenocortical function at levels as low as 1.02 mg for two weeks (Lahiri and Sircar, 1991). Effects included decreased adrenal weights and histopathological effects as well as increased cholesterol and decreased ascorbic acid in adrenal glands. Toxic effects in rabbits treated with 4.21 ppm bw/day lindane included effects on plasma enzyme activity, decreased feed intake and body weight gain (Ceron *et al.,* 1995).

The US EPA (1988b) provides an oral reference dose (RfD) for humans exposed orally to lindane based on the results from a subchronic feeding study in rats (Zoecon Corp., 1983). A RfD is a value which is considered to be an "acceptable" exposure level to a non-carcinogenic chemical. The RfD is based on a toxicological study from which no effects (NOAEL) have been reported for health effects. Histopathological effects were seen in the liver and kidney tissue in rats given 20 and 100 ppm lindane in the diet. No effects were seen at 4 ppm lindane in the diet. The US EPA derived an oral RfD of $3x10^{-4}$ ppm bw/day based on the no effects level of 4 ppm diet (0.33 ppm bw/day) from this study. A safety factor of 1000 was applied to the NOAEL for extrapolation from an animal study to humans (with a factor of 10 for interspecies extrapolation, 10 to account for subchronic to chronic exposure and 10 for protection of sensitive individuals). In summary, the main chronic effects of lindane exposure in mammals are effects on the nervous system, musculoskeletal system, immune system, liver and kidneys (US EPA, 1998a). The adverse renal effects of lindane in rat studies are considered to be species-specific and are not considered to be relevant to human exposure (US EPA, 1998c).

Most people are not exposed to lindane at concentrations that cause adverse health effects, although a few cases of poisoning occurred from topical lindane treatment for scabies, but these were due to overuse or inappropriate use of the product (Franz *et al.,* 1996; Meinking and Taplin, 1996; Downs, 1997). Occupationally exposed people may receive exposures that can result in toxicity, and people exposed to lindane occupationally via inhalation have been shown to have effects on the blood, liver, nervous system, cardiovascular system, immune system and levels of sex hormones (ATSDR, 1995; US EPA, 1998a). Lindane was cytotoxic in human leukemia cells *in vitro* (Kang *et al.,* 1998). This is of interest since effects of blood have been seen in people with high levels of long-term lindane exposure.

4.5 General Toxicity

Exposure of the juvenile amphipod *G. Pulex* to lindane resulted in reduced growth, with effects observed at 6.1 ppb but not at 2.7 ppb (Blockwell *et al.,* 1996). Effects of lindane on emergence and growth was observed in insect larvae, *Chironomus riparius* (Meigen), *Chaoborus flavicans* (Meigen), and *Sigara striata* (L.), in an experimental pond system at lindane levels as low as 1.0 ppb (Maund *et al.,* 1992). However, no effects on growth were found with *C. riparius* in another study at 0.09 ppb (Taylor *et al.,* 1991).

4.6 Carcinogenicity

The US EPA (1993a) IRIS database did not provide a carcinogenicity assessment for lindane due to a lack of data. However, a US EPA (1998a) fact sheet for lindane indicates that lindane is classified as a possible human carcinogen of low to medium carcinogenic hazard (Group B2/C). The conclusion was based on oral studies with laboratory animals in which lindane had carcinogenic effects on the liver. Liver carcinogenicity was reported in both rats and mice exposed

to lindane. The International Agency for Research on Cancer (IARC) also classifies lindane as a possible human carcinogen (Group 2B) (NTP, 1998).

Technical grade HCH has been classified as a probable human carcinogen (B2) by the US EPA (1993b). The classification for technical grade HCH is based on positive results in carcinogenicity studies with dietary exposure to mice. Inadequate data were available from humans exposed to technical grade HCH. Additionally, β-HCH was shown to be increased in the breast fat of breast cancer patients when compared with subjects without breast cancer (Mussalo-Rauhamaa *et al.,* 1990). The authors suggested that the increased concentrations of β-HCH may be due to a greater fat intake, which is a risk factor for breast cancer.

4.7 Mutagenicity

Lindane was negative for mutagenicity and genotoxicity in a number of *in vitro* and *in vivo* studies (Morita *et al.,* 1997; Zeiger *et al.,* 1992; Suzuki *et al.,* 1994; Sasaki *et al.,* 1997; IARC, 1987a,b; Glatt and Oesch, 1987; WHO, 1991a). Lindane did not induce micronucleated polychromatic erythrocyte in mice *in vivo* following exposure to by gavage (Morita *et al.,* 1997). In another study, negative results were obtained for HCH in the *in vivo* alkaline single-cell gel electrophoresis assay with mouse liver, lung, kidney, spleen and bone marrow cells (Sasaki *et al.,* 1997). Metabolites of lindane have also been shown to have negative mutagenic activity. Fitzloff and Pan (1984) found no mutagenic activity with β-PCCH, an epoxide metabolite of lindane, in a forward mutation assay with *Salmonella typhimurium*. Glatt and Oesch (1987) reported weak chromosomal aberrations in plants exposed to lindane. Also, weak but significant increases were found with microsomal epoxide hydrolase activity at high doses (Oesch *et al.,* 1982).

5.0 REGULATORY STATUS

Lindane has been listed as one of the *Dirty Dozen Pesticides* by the Pesticide Action Network North America (PANNA) which have been banned or severely restricted in a number of countries. Lindane is banned from use in 28 countries, severely restricted in 18 and deregistered in one; it is not however, restricted for use in Canada (PANNA, 1998). Additionally, use of HCH is banned from 52 countries, restricted in 8 and deregistered in 10 (including Canada) (PANNA, 1998).

5.1 North and South America

In Canada, lindane is neither restricted nor banned from use, while HCH is deregistered (PANNA, 1998). In North and South America, lindane is no longer produced, although it is imported into the US and is regulated by the Toxic Substances Control Act (TSCA), Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), RCRA, and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) (ATSDR, 1995, 1997b). The use of lindane is restricted in the US and it cannot be applied agriculturally by air (ATSDR, 1995; US EPA, 1998a).

Lindane, like other pesticides in Canada, is regulated by Pest Management Regulatory Agency (PMRA). Due to many international treaties as well as the global POPs negotiations headed by the United Nations (which is asking member countries to severely restrict the use of products

containing lindane) the PMRA, is conducting a Special Review which obligates the registrants to provide the needed data for risk assessment analyses. After the data is collected, the PMRA will conduct a risk assessment review, to determine if human exposure is at the acceptable level.

In Canada, lindane concentrations are allowed to be present in foods up to a certain limit. The maximum residue limits for lindane in Canadian foods are shown in Table 22 (Health Canada, Food & Drug Regulation, 1996)

Table 22: Maximum residue limits on foods in Canada

FOOD	MAXIMUM RESIDUE LIMIT (ppm)
Apples, apricots, asparagus, avocados, broccoli, Brussels sprouts, cabbage, cauliflower, celery, cherries, collards, cucumbers, eggplant, grapes, guavas, kale, kohlrabi, lettuce, mangoes, melons, mushrooms, mustard greens, okra, onions, peaches, pears, peppers, pineapple, plums, pumpkins, quinces, spinach, squashes, strawberries, Swiss chard, tomatoes	3.0
Meat, meat by-products and fat of cattle, goats, hogs and sheep	2.0*
Meat and meat by-products of poultry	0.7*
Butter, cheese, milk and other dairy products	0.2*

* the MRLs for these items are calculated on the basis of fat content
(Health Canada)

In South and Central America, lindane has been banned from use in a number of countries, including Bolivia, Brazil, Dominican Republic, Ecuador, Guatemala, Honduras, Nicaragua, Paraguay and Santa Lucia. Lindane use is restricted in Argentina, Belize, Columbia, Dominica, Jamaica and Venezuela (PANNA, 1998).

Technical HCH has also been banned in Argentina, Bolivia, Canada, Columbia, Cuba, Dominican Republic Ecuador, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru and the United States. Its use also is restricted in Belize, Brazil and Uruguay (PANNA, 1998).

In the US, the oral reference dose (RfD) for humans exposed orally to lindane is $3x10^{-4}$ ppm body weight/day (0.3 ppb bw/day). This level is based on a no effect level of 0.33 ppm bw/day from a subchronic feeding study in rats with an applied safety factor of 1000 (US EPA, 1988b; Zoecon Corp., 1983), as discussed in Section 4. Some acceptable levels of lindane in the US are shown in Table 23.

Table 23: Some limits for lindane in the United States

PARAMETER	LEVEL	REFERENCE
Apples, apricots, asparagus, avocados, broccoli, Brussels sprouts, cabbage, cauliflower, celery, cherries, collards, eggplants, kale, kohlrabi, mangoes, quinces, spinach, strawberries	1.0ppm	EPA 1996 (40CFR 180.133)
squash, squash (summer), tomatoes, melons, mushrooms, cucumbers	3.0ppm	EPA 1996 (40CFR 180.133)
pecans	0.1ppm	EPA 1996 (40CFR 180.133)
fat of meat (cattle, horses, sheep)	7.0ppm	EPA 1996 (40CFR 180.133)
fat of meat (hogs),	4.0ppm	EPA 1996 (40CFR 180.133)
Edible fish and shellfish	0.3 ppm	US FDA, 1973
Drinking water	0.2 ppb	US EPA, 1998b
Reference dose (RfD)	0.3 ppb bw/day	US EPA, 1988b

Schimmel *et al.* (1977) suggested that, based on the bioconcentration seen in laboratory studies, it would be improbable for fish and shellfish to accumulate lindane to the allowable US concentration of 0.3 ppm unless the environment was very contaminated.

For occupational exposure to lindane, the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH) recommend that lindane levels in air not exceed 0.5 mg/m^3 for an eight-hour workday (ATSDR, 1995).

5.2 Europe and the Middle East

Most countries in Europe and the Middle East have banned or severely restricted the use of either lindane or HCH or both (PANNA, 1998), as shown in Table 24.

Table 24: Countries in Europe and the Middle East that have banned or severely restricted lindane/HCH

COUNTRY	BANNED	SEVERELY RESTRICTED
Austria	HCH	
Belgium		lindane
Bulgaria	HCH, lindane	
Cyprus	HCH	lindane
Denmark	HCH, lindane	
European Community	HCH	
Finland	HCH, lindane	
France	HCH	
Germany	HCH	
Greece	HCH	
Hungary	HCH	lindane
Ireland	HCH	
Israel		lindane
Italy	HCH	lindane
Jordan	HCH	
Liechtenstein	HCH	
Luxembourg	HCH	
Moldova	HCH	lindane
Netherlands	HCH, lindane	
Portugal	HCH	
Spain	HCH	
Sweden	HCH, lindane	
Switzerland		lindane
Turkey		HCH
United Kingdom	HCH	
Yemen	lindane	

(PANNA, 1998)

Lindane is regulated in foods as well as in soil and water in many countries, including the Netherlands, as shown in Table 25.

Table 25: Environmental quality objectives and exposures standards for lindane in the Netherlands

PARAMETER	EXPOSURE STANDARDS
Soil	2.0 ppm
Surface water	0.01 ppb
Drinking water	0.1 ppb
Meat	0.25 ppm
Milk and milk products	0.008 ppm
Cheese	0.05 ppm
Fish, eggs and grain products	0.1 ppm
Potatoes	0.01 ppm
Vegetables	1.5 ppm
Legumes and fruit	1.0 ppm
Acceptable daily intake (ADI)	**1.0 ppb bw/day**

(Ragas and Huijbregts, 1998)

In England, the only supplier of ointment containing lindane for the treatment of scabies has voluntarily discontinued its supply (Downs, 1997).

5.3 Asia/Pacific

In Asia/Pacific, lindane has been banned in Bangladesh, Hong Kong, Indonesia, Japan, Korea, Singapore, Taiwan and Tonga. Lindane use is restricted in Australia, New Zealand, Philippines and Sri Lanka (PANNA, 1998).

Technical grade HCH has been banned in a number of Asia/Pacific countries, including Bangladesh, Fiji, Hong Kong, Japan, Korea, Philippines, Singapore, Taiwan and Thailand. HCH has restricted use in China and Sri Lanka (PANNA, 1998).

5.4 Others

In Africa, lindane has been banned in Chad, Egypt, Mauritania and Mozambique. Lindane has restricted use in Kenya and Madagascar (PANNA, 1998).

Technical grade HCH has been banned in a number of African countries, including Benin, Burkina Faso, Egypt, Ivory Coast, Kenya, Madagascar, Mauritania, and Mozambique. HCH has restricted use in South Africa (PANNA, 1998).

5.5 World Health Organization and Food and Agriculture Organization

The World Health Organization's (WHO) acceptable daily intake (ADI) for lindane was 0.008 ppm bw/day (8 ppb bw/day) (WHO, 1991a), based on a no effects observed (NOAEL) at a level of 10 ppm diet (0.75 ppm bw/day for rats and 1.6 ppm bw/day in dogs) (WHO, 1991a). However,

this ADI was recently reduced to a temporary ADI of 0.001 ppm bw/day during the 1997 meeting of the Food and Agricultural Organization (FAO) (FAO, 1998).

Table 26: World Health Organization maximum residue limits for lindane

PARAMETER	MRL (ppm)
Potatoes, rapeseed	0.05
Peas, sugar beets, eggs (shell-free)	0.1
Carrots	0.2
Apples, Brussels sprouts, cabbage, cauliflower, cereal grains, cherries, currants, grapes, pears, plums	0.5
Poultry (carcass fat)	0.7
Beans (dried), cocoa beans, cocoa butter, cocoa mass, kohlrabi, radishes	1
Endive, lettuce, spinach, tomatoes, fat of cattle carcass meat, pig carcass meat, sheep carcass meat	2
Cranberries, strawberries	3
Milk	0.01
Other Parameters	
Drinking water*	0.003
Temporary ADI**	1 ppb bw/day

* EXTOXNET, 1996
** FAO, 1998
(Codex Alimentarius Commission, 1986)

6.0 CONCLUSIONS

The pesticide lindane is a persistent organochlorine compound which is widely distributed in the environment. Long distance transport of lindane is evidenced by its presence in the Arctic, where is has never been used. Most of the lindane present in the environment is in water, although a significant amount is also found in the soil/sediment and some in air. Lindane has also been shown to bioaccumulate in the fatty tissue of organisms.

Lindane, the γ-HCH isomer, is extracted from technical HCH, which consists of 60-70% α-HCH, 5-12% β-HCH, 10-15% γ-HCH); it is the only isomer with pesticidal properties. Because of the ban in production and use of technical HCH by two major producing countries (Russia and China), the concentration of α-HCH in air, particularly in Arctic regions, is decreasing. However, the use of lindane has continued or intensified in most countries, increasing lindane levels by one- to two-fold in Canadian Arctic air. And, the global problem of α-HCH is far from over. Bidleman *et al*. (1995) suggest that because of the decline in atmospheric α-HCH and a relatively constant concentration in ocean surface water, the net direction of air-sea gas exchange of α-HCH has reversed to the point where some northern waters are degasing α-HCH to the atmosphere.

Lindane is considered to be highly toxic to aquatic organisms and moderately toxic to birds and mammals. Effects can be manifested in the central nervous system, liver and kidneys. Reproductive effects have been seen, as well as other endocrine system effects, in laboratory studies of aquatic organisms and mammals. These include effects on male and female reproductive organs, hormonal activity and sexual behaviour.

Immunotoxic effects have been found in mammals, fish and birds. Based on the effects seen in test animals, ATSDR has set an intermediate minimal risk level of 0.01 ppb bw/day. This level is lower than the reference dose of 0.3 ppb bw/day established by the US EPA for effects on liver and kidney tissue as well as Health Canada's ADI. It is also lower than the temporary ADI established by the WHO. Lindane is not considered to be a teratogen, neither was it shown to be mutagenic or genotoxic in a number of studies. Lindane and technical HCH are classified as possible and probable human carcinogens, respectively.

People are exposed to lindane mainly from ingestion of foods contaminated with this pesticide. Additional exposure may come from breathing air contaminated with lindane, dermal contact with contaminated soil or in drinking water. Some people, especially children, may also come into contact with lindane through the use of lotions for scabies or lice control. Infants are also exposed to lindane and other HCH isomers via their mother's milk.

In Canada, exposure of the general public to lindane is at levels considered to be "acceptable" by Health Canada. That is, intake levels are lower than levels known to cause adverse effects. However, this may not be the case in the Arctic, where HCH is the most abundant pesticide as a result of long-distance transportation from the temperate regions and deposition into Arctic oceans. Marine organisms in all trophic levels, including fish, seals and polar bears, contain significant body burdens of this pesticide. Although there are no data available on the daily intake of HCH by the Arctic population, consumption of country food by Inuit living in the Arctic leads to significantly higher exposure than people living in other parts of Canada. Similarly, Inuit infants

may be more exposed to HCH than infants living in southern Canada. In addition, farmers who use lindane, workers in HCH manufacturing facilities, and children because of their higher consumption to body weight ratio, are more exposed than the average Canadian.

Although the use of lindane and technical grade HCH has been banned and/or restricted in many countries, there are a number of developing countries that still use them. The use of technical HCH is banned in North America; however, lindane is still used in Canada. Currently, the PMRA is conducting a special review of lindane under the Pest Control Products Act.

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