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Re-evaluation Note   REV2009-08

Lindane Risk Assessment

Canada

Foreword

On March 15, 1999, Health Canada's Pest Management Regulatory Agency (PMRA) announced the special review of agricultural products containing lindane, an insecticide consisting primarily of the gamma isomer of hexachlorocyclohexane (SRA99-01). At the time, lindane was used predominantly in agriculture as a seed or soil treatment to protect crops.

The PMRA completed its assessment of occupational risk in October 2001, concluding that lindane poses unacceptable risk to the health of workers exposed to it during seed treatment and planting. In accordance with that assessment, a phase-out of lindane use was proposed to registrants and they provided comments. On April 5, 2002, the PMRA published an *Update on the Special Review of Lindane and the Status of Lindane Registrations* (REV2002-02). The registrants were given the option of choosing one of the two methods by which a product registration could be phased out, that is, voluntary discontinuation of sales or suspension of the registration. All registrants of lindane seed treatment products, except Crompton Corporation (Crompton), chose to voluntarily discontinue sales of their products and the registrations expired by the end of 2004. The Crompton registrations were suspended. Sale and use of the Crompton products that were in the marketplace prior to the suspension were permitted to continue.

Crompton requested a hearing by a board of review to examine the PMRA's decision with respect to its lindane products. On August 18, 2005, the Board submitted a report of its findings and recommendations to Crompton and the Minister of Health. The Board recommended that the Minister of Health direct the PMRA to reconsider aspects of the occupational health risk assessment and to consult with Crompton concerning measures that might mitigate the PMRA's health concerns relating to those risks.

To address the issues raised by the Board in the case of lindane, the PMRA initiated communication with all affected former registrants of lindane products and other interested parties to seek input into the risk assessment and to explore possible measures that would address health-related concerns for workers.

On April 26, 2006, the PMRA published an Information Note updating the public on the status of the follow-up special review of lindane and indicated that the target completion date of the review was the end of 2006. To ensure that the risk management decision would be made with a clear understanding of all risks, the PMRA undertook the human health risk assessment of areas not completed in the previous evaluation and considered data received from Crompton[1] in 2006 and 2007. These included special consideration of carcinogenicity and the evidence supporting the contention that young animals were more sensitive to lindane toxicity. The PMRA also finalized the environmental risk assessment.

On December 22, 2006, the PMRA published an Information Note updating the public that the target completion of this follow-up review would be delayed at the request of Crompton to allow time for submission of a new occupational exposure study. The study was provided by Chemtura in March 2007 and reviewed by the PMRA.

This document represents the comprehensive review by the PMRA, taking into account potential measures for mitigation. The document was reviewed by former registrants in May 2008 and revised following extensive consultation with Chemtura on numerous aspects of the risk assessment.

The PMRA will accept written comments on this document up to 60 days from the date of publication. Please forward all comments to Publications.

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Overview

Results of the Lindane Risk Assessment

After a thorough assessment, Health Canada's Pest Management Regulatory Agency (PMRA) finds that the pesticide lindane poses unacceptable risks of harm to human health and the environment. This assessment confirms an earlier decision by the PMRA, under the authority of the *Pest Control Products Act*, to withdraw all pest control products containing lindane from use in Canada.

Health Canada's pesticide re-evaluation program considers potential risks to ensure that registered products meet modern standards established to protect human health and the environment. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available. In the case of lindane, an evaluation of available scientific information found that, under the proposed conditions of use:

- the risks to human health and the environment do not meet current standards and cannot be mitigated to render them acceptable.

This Re-evaluation Note presents the science evaluation of lindane with respect to pest control products that were registered in Canada as of 2001, taking into account new data and proposals from some former registrants for mitigative measures relative to the application directions of former seed treatment products. The PMRA requested comments from former registrants on the April 2008 draft of the document. Chemtura provided additional information on a manufacturing process for technical lindane and alternative perspectives on the toxicity and exposure studies on which the health risk assessment is based. The PMRA has taken Chemtura's comments into account and is publishing this Lindane Risk Assessment for public comment with a 60-day comment period.

The information is presented in two parts. This Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health and environmental assessment of lindane.

What is Lindane?

Lindane is an organochlorine insecticide that was used to control a broad spectrum of insect pests on a wide variety of sites. Under international scrutiny, and as a result of its widespread occurrence and persistence in the environment, most uses of lindane were discontinued in Canada by 2002, including use on greenhouse ornamentals, livestock, terrestrial food and feed crops, structures, outdoor ornamentals and turf.

The PMRA's assessment of the occupational risk of lindane addressed the seed treatment uses of lindane registered as of 2001. At the time, seeds were coated with lindane using dry and liquid seed treatment equipment by farmers and farm workers on-farm and by applicators at commercial seed treatment facilities.

This current risk assessment considers uses that continue to be supported by some former registrants, including:

- wireworms on cereal crops (barley, oats, rye and wheat);
- flea beetles on oilseed crops (canola and mustard); and
- root maggots, seedcorn maggots and wireworms on field crops (corn, beans, soybean and peas).

This risk assessment also takes into account a new, more restricted use pattern, including application in closed systems, as proposed by former registrants. The PMRA reconsidered the original data, completed the human health risk assessment in areas not finalized in the previous evaluation (e.g. carcinogenicity) and finalized the environmental risk assessment.

Health Considerations

Exposure to lindane may occur through diet (food and water) and when treating seeds or handling treated seeds. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population, such as children and nursing mothers. Only those uses for which exposure is well below levels that cause no effects in animal testing are considered acceptable for continued registration.

An acute overexposure to lindane can produce a variety of symptoms in animals and humans. Symptoms may include nausea, exhaustion, convulsions or seizures. Health effects in animals exposed daily to lindane over long periods of time included effects on the liver, lung, kidney, spleen, thymus and testes. There is suggestive evidence that lindane is genotoxic and causes cancer in animals. There were also indications that lindane caused damage to the central nervous system and altered hormone levels in developing animals at doses that were not toxic to the mother, indicating that the young are more sensitive to lindane than the adult animal. The risk assessment is conducted to ensure that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests. Only uses for which exposure is well below levels that cause no effects in animal testing would be considered acceptable for registration.

Residues in Water and Food

This analysis is an estimate of the dietary burden to humans resulting from past seed treatment use of lindane in Canada. It does not account for existing amounts in human body tissues.

Dietary risk affects two distinct populations in Canada: the general population and the Northern, aboriginal peoples. The general population would be exposed to lindane residues from treated crops and livestock that constitute market foods, and from drinking water. The Northern communities, however, would be exposed to lindane through market food and traditional food (hunting and fishing), with little exposure from drinking water.

In the general population, chronic and cancer exposure estimates are unacceptable from both drinking water and food consumption. In addition, the children of the general population are subject to acute risk from drinking water. Northern communities also have unacceptable cancer risk from their consumption of market food.

The dietary risk estimates could be refined with livestock feeding studies, along with better estimates of drinking water concentrations. However, both occupational and environmental risks are presently unacceptable and seem unlikely to be mitigated. A review of additional dietary data would not result in an overall conclusion of acceptability.

Occupational Risks From Handling Lindane

Occupational risk assessments considered exposures to workers treating seed both in commercial facilities and on-farm, as well as to workers handling and planting treated seed. Exposure scenarios were highly refined using chemical-specific and use-specific information. Maximum personal protective equipment (PPE), by way of protection factors for dermal and inhalation mitigation, were also applied to the risk assessment where appropriate. Further mitigation measures such as the use of polymeric coatings on treated seeds and closed cabs for planting treated seeds were also included in the planting assessment.

Even with these refinements and mitigation, risk to workers treating or planting treated seed is unacceptable.

Environmental Considerations

What Happens When Lindane is Introduced Into the Environment?

Lindane accumulates in the environment

When lindane is applied as a seed treatment for the control of insect pests in crops, a large quantity of it finds its way into soil, air and water after the seeds are planted. The chemical is expected to persist in soil and water as it is not broken down rapidly by soil microbes or by chemical reaction in water. Lindane has low mobility in soil; however, field studies have shown that lindane can contaminate groundwater. Water runoff on the soil surface can move residues into nearby bodies of water, such as ponds and rivers. Lindane is released readily as a gas via the soil from crops such as canola and cereal seed. It enters the atmosphere in large amounts compared to the amount that is applied to seeds. By taking the total acreage of treated canola in a given year, an estimate of 28 to 191 tonnes of lindane would be released from the Canadian Prairies annually.

Once in the air, lindane is persistent and moves through the atmosphere to regions that are far removed from its area of use. Lindane moves from the Canadian Prairies to the Great Lakes region and the Canadian Arctic, where it is deposited through the process of condensation. As a result, lindane is detected not only in the air, but also in precipitation, oceans and rivers, in wildlife such as birds, fish, whales, seals, wolves and caribou and in humans. Concentrations of lindane in lakes and rivers are higher in western Canada than in eastern Canada, which is explained by the use of lindane on canola in the Prairies.

Lindane accumulates in wildlife to levels that are cause for concern. Not only does lindane bioconcentrate and bioaccumulate to high levels, particularly in fish, but it also biomagnifies in some animals such as lake trout, seals and whales.

Lindane was never manufactured in Canada. In other countries, its manufacture produced large quantities of waste chemicals that have similar chemical properties to lindane. Improper storage and disposition of this waste allows for its release into the atmosphere and global waters and entry into the Canadian environment. For every tonne of lindane produced, there are six to nine tonnes of waste chemicals that must be disposed of or otherwise managed. One management option reported by industry is to transform the waste isomers into trichlorobenzene and hydrochloric acid. However, the PMRA can neither confirm nor ensure that this process is being used to manufacture lindane outside of Canada. The use of lindane in Canada could contribute to the production of these waste chemicals. As with lindane, these waste chemicals are persistent and are found not only in the air, but also in precipitation, oceans and rivers, wildlife such as birds, fish, whales, seals, wolves and caribou, and in humans. Given the toxicity and environmental levels of the waste chemicals and their potential for long-range transport, the PMRA remains concerned that the production of lindane overseas would result in further contamination of the Canadian Arctic.

Lindane is considered as arising from anthropogenic sources and is also considered to be "CEPA-toxic Equivalent" under the *Canadian Environmental Protection Act* because it is entering the environment at levels that pose a risk to terrestrial and aquatic organisms. Lindane also meets the Government of Canada's Toxic Substances Management Policy (TSMP) Track 1 criteria for persistence in the environment. Lindane does not technically meet the TSMP Track 1 substance criteria for bioaccumulation. However, based on the strong evidence for biomagnification, particularly in organisms at the top of the food webs, the PMRA has serious concerns about the contamination of food webs.

The α- and β-isomers of hexachlorocyclohexane (HCH) are waste chemicals that result from the manufacture of lindane. Both meet the TSMP Track 1 criteria for persistence in the environment. The bioaccumulation of the β-isomer in fish meets the TSMP Track 1 criteria for bioaccumulation.

Lindane poses a potential risk to terrestrial and aquatic organisms
Terrestrial organisms such as birds and small mammals are at risk from feeding on lindane-treated seeds in agricultural fields (e.g. in fields planted with canola seed). Birds and small mammals can be killed after consuming a small number of lindane-treated seeds, especially canola seed. Lindane also has the potential to affect reproduction in birds and small mammals. Soil invertebrates such as earthworms are also potentially at risk.

For aquatic organisms, water monitoring and model estimations of concentrations in bodies of water (rivers and wetlands) have revealed lindane concentrations above the level of concern. In freshwater fish, lindane can pose an acute risk in some species. For marine invertebrates in shallow estuarine/marine habitats, lindane poses an acute risk and possible fertility problems.

Measures to Minimize Risk

Risk-reduction measures to address some of the potential risks from lindane use are identified in this assessment but are not proposed for implementation. It is not feasible to reduce risks sufficiently to address the levels of concern that have been identified for the following:

Human Health
Even with maximum personal protection equipment and engineering controls, risks to workers handling lindane and lindane-treated seed were unacceptable.

Environment
As a seed treatment, there are no effective measures from an environmental perspective to mitigate the volatilization, atmospheric transport, bioaccumulation and toxicity of lindane.

Science Evaluation

1.0   Introduction

1.1   Re-evaluation of Lindane in Canada

Lindane is a broad spectrum insecticide from resistance management Mode of Action (MoA) group 2A, which is a gamma-aminobutyric acid (GABA) chloride channel antagonist. It works by contact, ingestion and vapour action.

Lindane is one of the pesticides subject to re-evaluation in Canada as announced in the re-evaluation documents SRA99-01, *Special Review of Pest Control Products Containing Lindane,* and REV2002-02, *Update on the Special Review of Lindane and the Status of Lindane Registrations*. Lindane seed treatments were considered in the special review.

Following the independent Lindane Board of Review of 2005, some former technical registrants and primary data providers in Canada indicated that they continue to support some seed treatment uses included on the labels of products registered as of 2001, specifically, use for:

- wireworms on cereal crops (barley, oats, rye and wheat);
- flea beetles on oilseed crops (canola and mustard); and
- root maggots, seedcorn maggots and wireworms on field crops (corn, beans, soybean and peas).

In addition, one registrant proposed to limit treatment of canola and mustard seed to closed systems in commercial seed treatment facilities.

1.2   International Regulatory Status of Lindane

1.2.1   North America

Under the North American Commission for Environmental Cooperation (CEC), Canada, Mexico, and the United States (the Parties) have recognized that the organochlorine pesticide lindane and other isomers of hexachlorocyclohexane (HCH) may constitute a risk to human health and the environment. The Parties also recognize that lindane and other isomers of HCH meet several internationally accepted criteria for persistence, bioaccumulation and toxicity. While lindane is no longer produced in North America, it continues to be used for varying applications and in different quantities in the three countries. The Parties are implementing a North American Regional Action Plan to reduce or eliminate the uses of lindane and other HCH isomers. They also participate in other international initiatives to promote emissions reductions from other global sources of lindane.

Canada: As of January 1, 2005, there are no registered agricultural or veterinary uses of lindane in Canada. Canada has agreed to assess and manage risks from its sole remaining use of lindane as a pharmaceutical drug to control head lice.

United States: Prior to 2002, all pesticide uses of lindane were cancelled in the United States, with the exception of uses on six crops.[2] In 2006, the United States announced the cancellation of the remaining agricultural uses of lindane, effective July 1, 2007, with the date of last use set to October 1, 2009.

Mexico: Lindane is currently used in Mexico for ectoparasite control on livestock and domestic animals, as well as for pharmaceutical purposes. It is also registered for use as a seed treatment on six crops (oats, barley, beans, corn, sorghum and wheat), and as a soil treatment for corn and sorghum. The use of lindane is being phased out due to risk concerns.

1.2.2 Global Status

Lindane and other HCH isomers are of concern to human health and the environment beyond North America, and are the subject of regulations and international agreements.

Lindane is banned for use in 52 countries, restricted or severely restricted in 33 countries, not registered in 10 countries, and registered in 17 countries (Table 1.2.2). Currently, the major globally reported uses of lindane are for head lice and as a veterinary topical insecticide.

A summary of action taken by different countries to regulate the use of lindane products is presented in Annex B of "The North American Regional Action Plan (NARAP) on Lindane and other Hexachlorocyclohexane (HCH) Isomers" found at: www.cec.org/programs_projects/pollutants_health/smoc/lindane.cfm

Table 1.2.2 Summary List of International Lindane Registration Status by Country

Banned	Russia	Spain
	Singapore	Sri Lanka
Argentina	Slovakia	Sudan
Armenia	South Africa	Switzerland
Bangladesh	St Lucia	Trinidad/Tobago
Barbados	Sweden	United Kingdom
Belgium	Taiwan	United States of America
Bulgaria	Thailand	Venezuela
Burundi	Tonga	Yugoslavia
Costa Rica	Turkey	
Croatia	Uruguay	**Not registered**
Cyprus	Vietnam	
Czech Republic	Yemen	Estonia
Denmark		Guinea-Bissau
Dominican Republic	**Restricted/Severely Restricted**	Indonesia
Ecuador		Monaco
Egypt	Algeria	Mongolia
El Salvador	Australia	Niger
Finland	Austria	Rwanda
Gambia	Belize	Slovenia
Georgia	Brazil	Uganda
Guatemala	Canada	Vanuatu
Honduras	China	
Hong Kong	Columbia	**Registered**
Hungary	Cuba	
Jamaica	European Community	Bolivia
Japan	Fiji	Burkina Faso

Kazakhstan	France	Cameroon
Korea, Dem. Rep	Germany	Cape Verde
Korea, Rep	Iceland	Chad
Latvia	Ireland	India
Liechtenstein	Israel	Kenya
Lithuania	Italy	Malaysia
Mozambique	Madagascar	Mali
Netherlands	Moldova	Mauritania
New Zealand	Morocco	Mexico
Nicaragua	Nigeria	Papua New Guinea
Norway	Philippines	Portugal
Paraguay	Samoa	Syria
Peru	Senegal	Tanzania
Poland		Togo
		Zimbabwe

Notes: Information for this table is from Annex B of "The North American Regional Action Plan (NARAP) on Lindane and other Hexachlorocyclohexane (HCH) Isomers", 2006, found at:
www.cec.org/programs_projects/pollutants_health/smoc/lindane.cfm.

1.2.3   International Agreements and Treaties

The importance of Canada's international agreements is reflected in section 27 of the *Pest Control Products Act*: "The Governor in Council may, by order, cancel or amend the registration of a pest control product or a class of pest control products if the Governor in Council considers it necessary to do so to implement an international agreement."
The Great Lakes Binational Toxics Strategy (between Canada and United States) for the virtual elimination of persistent toxic substances in the Great Lakes lists HCH (including lindane) as a Level II substance, which means that one of the two countries has grounds for concern respecting persistence, bioaccumulation and toxicity. Stakeholders are encouraged to conform with the laws and policies of each country with respect to those substances.

Canada has negotiated and ratified the United Nations Economic Commission for Europe (UNECE) Persistent Organic Pollutants (POPs) Protocol of the Convention on Long Range Transboundary Air Pollution. The POPs Protocol establishes obligations including a commitment to restrict expansion of the uses of lindane and to conduct a reassessment of all remaining uses.

In June 2005, Mexico submitted a proposal to the Stockholm Convention to add lindane to the list for elimination. At its third meeting in Geneva, November 19–23 2007, the POP Review Committee concluded that lindane is likely, as a result of long-range environmental transport, to lead to significant adverse effects on human health and/or the environment, and unanimously recommended that the Conference of Parties consider listing lindane in Annex A (elimination) of the Convention.

Lindane is included under the Rotterdam Convention on the Prior Informed Consent (PIC) Procedure for Certain Hazardous Chemicals and Pesticides in International Trade. As of December 2005, 34 countries have banned all imports of lindane and 38 have restricted or severely restricted the conditions under which it may be imported. There are currently 116 Parties to this Convention. In Canada, there is limited use for control of head lice.

HCH isomers, including lindane, are also included in the List of Chemicals for Priority Action (Updated 2005) under the (Oslo and Paris) OSPAR Commission for the Protection of the Marine Environment of the Northeast Atlantic. Under this initiative, the Hazardous Substance Strategy sets the objective of preventing pollution of the maritime area by continuously reducing discharges, emissions and losses of hazardous substances, with the ultimate aim of achieving concentrations in the marine environment near background values for naturally occurring substances and close to zero for man-made synthetic substances.

1.3   Potential Impact on Canadian Agriculture

Historically, lindane was a major insecticide used for seed treatment in Canada to control:

- wireworms on cereal crops (barley, oats, rye and wheat) and flax;
- flea beetles on oilseed crops (canola and mustard) and cole crops; and
- root maggots, seedcorn maggots and wireworms in field crops (corn, beans, soybean and peas).

Of the crops for which some former registrants support reinstatement of lindane seed treatment, several are grown primarily for export: canola, mustard, wheat, oats, dry beans, soybeans, dry peas. However, the export market for lindane-treated crops has become increasingly limited as countries have introduced restrictions or bans on lindane use and lindane residues in food. For example, in 2006, the United States revoked all tolerances for lindane residues (except for livestock fat which will be revoked October 2, 2009) following a determination that remaining uses of lindane were ineligible for reregistration and the registrants' request that American registrations of lindane products be cancelled. The United States is the major export market for canola, mustard, wheat flour, oats and dry beans.

2.0   The Active Substance, Its Properties and Uses

2.1   Identity of the Active Ingredient

2.1.1   Lindane

Common Name:	Lindane
CAS Chemical Name:	1α,2α,3β,4α,5α,6β-hexachlorocyclohexane
Other Name:	gamma-hexachlorocyclohexane (γ-HCH); {gamma-benzene hexachloride (γ-BHC) is not technically correct but is still widely used}

Trade names:	Agrocide, Aparasin, Arbitex, BBH, Ben-hex, Bentox, Celanex, Chloresene, Dvoran, Dol, Entomoxan, Exagamma, Forlin, Gallogama, Gamaphex, Gammalin, Gammex, Gammexane, Hexa, Hexachloran, Hexaverm, Hexicide, Isotos, Kwell, Lendine, Lentox, Linafor, Lindafor, Lindagam, Lindatox, Lintox, Lorexane, Nexit, Nocochloran, Novigam, Omnitox, Quellada, Silvanol, Tri-6, Vitron.

CAS Number: 58-89-9

Molecular Formula: $C_6H_6Cl_6$

Molecular Mass: 290.85

Physical State: Colourless crystalline solid

Melting Point: 112.5 - 113.5 °C

Boiling Point: 288°C

Structure:
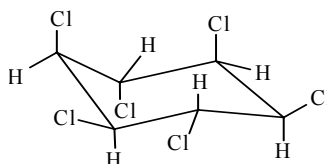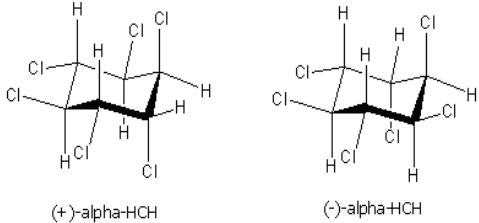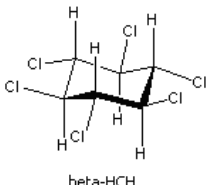
Structural code
(<u>A</u>xial/<u>E</u>quatorial): AAAEEE

Pesticide Class: Organochlorine insecticide

2.1.2 Alpha- and Beta-HCH

These isomers of lindane are waste byproducts resulting from the manufacture of lindane.

Table 1   Chemical Identity of Alpha- and Beta-HCH

Identifier	α-HCH	β-HCH
CAS#	319-84-6	319-85-7
CAS Chemical Name	1α,2α,3β,4α,5β,6β-hexachlorocyclohexane	1α,2β,3α,4β,5α,6β-hexachlorocyclohexane
Other Name	alpha-benzene hexachloride (α-BHC) is not technically correct but is still widely used	beta-benzene hexachloride (β-BHC) is not technically correct but is still widely used
Physical State	brownish to white crystalline solid	crystalline solid
Molecular Mass	290.85	290.85
Molecular Formula	$C_6H_6Cl_6$	$C_6H_6Cl_6$
Melting point (°C)	160[a]	310[a]
Structure[a]	(+)-alpha-HCH (-)-alpha-HCH	beta-HCH
Structural code (Axial/Equatorial)	AAEEEE	EEEEEE

[a]   Cited in Willett et al., 1998 - averaged value from reference, Mackay et al. (1997). Mackay, D., W.Y. Shiu and K.C. Ma. 1997. *Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals*. Vol. V. Pesticide Chemicals. Lewis Publishers: Boca Raton, FL.

2.2   Physical and Chemical Properties

The physical and chemical properties of lindane indicate it has low solubility in water (7.3 mg/L), and is volatile from soil and water (Henry's Law Constant = 4.9×10^{-7} - 3.7×10^{-6} atm·m^3/mole). In addition, it is not expected to phototransform on soil or in water and has the potential to bioaccumulate (log K_{ow} = 3.2-3.7). Compared to other organochlorines, HCH isomers are more water soluble and volatile, which accounts for their comparatively high detection frequency in bodies of water, air and animals.

Table 2   Summary of Physical/Chemical Properties of Lindane

Property	Value[a]	Interpretation
Solubility in water (25°C)	7.3 - 8.7 mg/L	Low solubility in water
Vapour pressure (20°C)	1.25 - 9.4 × 10-3 Pa	Intermediate to high volatility
Henry's Law Constant (20°C)[b]	4.9×10^{-7} - 3.7×10^{-6} atm·m^3/mole	Potential to volatilize from moist soil and water
n-Octanol/water partition coefficient (25°C)	log K_{ow} = 3.72	Potential for bioaccumulation
UV/Visible Absorption Spectrum	No absorption at wavelengths above 250 nm	Phototransformation is not expected as a route of transformation
Dissociation constant (pK$_a$)	No dissociable functionality	Dissociation not expected under environmental conditions

[a]   Cited in Xiao *et al.* (2004).
[b]   Calculated by the PMRA (using a water solubility of 7.3 mg/L).

The physical and chemical properties α- and β-HCH isomers are outlined in Table 3. Alpha-HCH has the highest volatility of the three isomers as indicated by its Henry's Law Constant (HLC) of 6.0×10^{-6} atm·m^3/mole. Beta-HCH is the least volatile as indicated by its HLC of 4.2×10^{-7} atm·m^3/mole, which indicates it has a low potential for volatilization. The Henry's Law constants indicate that lindane and α-HCH will be rapidly lost from moist soil or from surface waters to the air, and while β-HCH has a low potential for volatilization, it does indicate that some loss to the air may occur. Both α- and β-HCH have similar K_{ow}s to that of lindane, which indicates that all three isomers have the potential to bioaccumulate.

Table 3   Summary of Physical/Chemical Properties of α-HCH and β-HCH

Property	α-HCH[a]		β-HCH[a]	
	Value	Interpretation	Value	Interpretation
Solubility in water (20°C)	1.6 - 2.0 mg/L	Low solubility in water	0.20 - 0.70 mg/L	Sparingly soluble in water
Vapour pressure at (20°C)	3.33×10-3 Pa	Intermediate volatility	$2.9 - 3.7 \times 10$-5 Pa	Low volatility
Henry's Law Constant (atm·m3/mole)	6.0×10-6 atm·m3/mole[b]	Potential to volatilize from moist soil and water	4.2×10-7 atm·m3/mole[c]	Low potential for volatilization from moist soil and water
n-octanol/water partition coefficient (log Kow)	3.81	Potential for bioaccumulation	3.82	Potential for bioaccumulation

[a]   Cited in Xiao et al. (2004).
[b]   Calculated by the PMRA (using a water solubility of 1.6 mg/L).
[c]   Calculated by the PMRA (using a water solubility of 0.20 mg/L).

2.3   Description of Registered Lindane Uses

Currently there are no lindane products registered under the authority of the Pest Control Products Act. Appendix I lists the lindane products that were registered for seed treatment use as of 2001. Appendix II lists the various seed treatment uses that appeared on the labels of these products and indicates which uses former registrants would like to re-instate. Uses proposed by some former registrants for re-instatement were considered in this health and environmental risk assessment of lindane.

Uses of lindane considered in this assessment belong to the following Use-site Category: seed treatments.

3.0   Impact on Human and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels at which no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species.

3.1   Toxicological Summary

Lindane is the γ-isomer of hexachlorohexane (HCH). It is the most insecticidally active isomer of HCH, largely the result of its binding affinity towards GABA receptors (picrotoxin binding site), leading to unchecked excitation in the insect nervous system. There is a sizable toxicology

database for lindane; however, many of the available studies were considered to be of low quality due to limited reporting and issues regarding test material purity. The present review of lindane has been supplemented with studies reported in the public literature as well as studies conducted with other HCH isomers (α, β, or δ-HCH). As noted below, the studies conducted with a variety of HCH isomers were considered valid for characterizing the toxicological profile for lindane as many of the toxicological modes of action are considered equivalent amongst the HCH isomers.

While γ- HCH, or lindane, is known to be the most potent of the HCH isomers in inhibiting the GABA receptor, several other possible mechanisms of toxicity have been investigated. Enzyme changes in the liver (increased monooxygenase and decreased epoxide hydrolase) resulting from lindane ingestion may cause cytotoxicity via increased production of epoxide and superoxide radicals, leading to oxidative stress and lipid peroxidation. Cytotoxicity may also be induced by Na^+ - K^+ - ATPase inhibition, Ca^{2+} channel (intracellular inositol triphosphate mediated and membrane bound voltage gated) modulation, or gap junction inhibition. This mechanism of toxicity has been attributed to γ-HCH, α-HCH and technical grade HCH, suggesting that the effect is common to isomers of HCH. Several HCH isomers (α, β and γ) have been shown to disrupt steroid metabolism by inhibiting steroidogenic acute regulatory (StAR) protein in cells from steroid hormone generating tissues, including the gonads, adrenal gland, brain (neuro-steroids) and placenta. It is not possible to predict with certainty the toxicity outcomes following lindane exposure; however, on the basis of these mechanisms of toxicity, the available mechanism of action information predicts endocrine modulation, carcinogenicity and neurotoxicity as likely manifestations of toxicity. Direct binding to the GABA receptor can produce a toxicological response of rapid onset and resolution. The other mechanisms of lindane toxicity, however, would be expected to produce toxicity that would progress in severity with duration of exposure.

In rats, oral absorption has been reported to be greater than 90% for all isomers of HCH. Oral and inhalation absorption have not been characterized in humans. Dermal absorption has been measured between 9% and 100% depending on the vehicle and level of occlusion in humans, with up to a 20-fold variation in dermal absorption reported for children. While variability in human dermal absorption of lindane has been documented, the difference in human lindane absorption as compared to other insecticides is equally surprising. In humans, the absorption of a lindane cream was found to be 20-fold greater than a pyrethroid-based cream, whereas absorption was similar for the two products in guinea pigs, thus demonstrating an unexpected interspecies difference in dermal bioavailability.

Strain and species differences in distribution and metabolism were noted. Literature information reports high variability in lindane concentrations in the brain and other organs. For example, D2 mice had 78% higher brain lindane concentrations than similarly dosed B6 mice. Rats did not show elevations in brain lindane content following dosing and, unlike mice, the tissue concentrations plateaued within two weeks of dosing. In mice, the highest tissue concentrations were noted in fat, brain, kidney, muscle, liver, adrenal and ovary. In rats, organ sequestration was noted; however, accumulation of residues was mainly restricted to adipose tissues. Rats gavaged with lindane on lactation days 9 or 14 were noted to have higher concentrations of lindane in milk than plasma, suggesting the potential for substantial transfer of residues to

offspring. In humans, several more recent studies have noted dramatically higher (as much as 100-fold) concentrations of lindane in milk than in maternal serum. Cord blood levels of lindane were similar to maternal sera concentrations in some studies, while in other studies, cord blood levels were up to 25-fold higher. These studies suggest that developing humans will be exposed to much higher concentrations of lindane than their mothers. Although these studies were not conducted in Canadian women, the physiological principles are relevant to the Canadian scenario. Given the lipophilic nature of lindane and its ability to bioaccumulate, it is expected that lindane will concentrate in milk. The longer life span (in which to accumulate lindane in fatty tissue) and duration of gestation and lactation in humans (greater time period to express lindane across the placenta and in breast milk) would predict a greater degree of exposure of the developing human than that noted in rodent studies.

The metabolism of lindane in humans is considered to be extensive, highly variable within the population and not fully characterized. For example, age and diet have been shown to impact the expression of lindane across the placenta as well as through milk. Body burden cannot be predicted on the sole basis of adipose content in humans, as other factors influence the accumulation of lindane in humans. In one study, younger women and vegetarians demonstrated less serum lindane than older women or women who ate meat. In a more recent study, premenopausal women had higher serum concentrations of lindane than postmenopausal women. Women in their first pregnancy expressed more lindane in milk than women who had previously given birth. These indications of metabolic diversity within humans suggest that there will be subpopulations of sensitivity to lindane toxicity. Also, it has been demonstrated that children metabolize and excrete lindane more slowly than adults. Although lindane is highly lipophilic, humans with lower body fat levels paradoxically accumulated greater concentrations of lindane. The variability within the human population was notable with reports of several fold differences in maternal serum and milk concentrations in women of similar age, BMI, and city of habitation. Even the number of children previously born impacted on the body burden of the mothers.

Accumulation of lindane and its metabolites is noted in developing rodents and may be attributed to the sequestration of lindane in the lipid-rich myelin sheath surrounding neurons of the nervous system; a similar mechanism would be postulated to occur in humans. Mice had increased monooxygenase activity and reduced epoxide hydrolase activity, resulting in the generation of reactive epoxides during metabolism. In vitro experiments in rats have confirmed the generation of reactive epoxides, which may be indicative of similar processes in other mammals and humans. Tissue-specific metabolite sequestration was evident, with gamma-pentachlorocyclohexene identified as the predominant metabolite in kidneys and brain of rats, pentachlorophenol the most notable in the spleen, and 2,3,4,6-tetrachlorophenol, gamma-pentachlorocyclohexene and 2,4,6-trichlorophenol (a known carcinogen) most commonly found in the heart. Differences in the metabolites of interest exist between the strain and species of animals tested. However, all test systems have demonstrated that lindane is extensively metabolized following oral dosing and excreted primarily in the urine, and that the di-, tri-, and tetrachlorphenols are the primary metabolites in humans, rats, and mice. In rodents, 2,4,6-trichlorophenol, a metabolite of either lindane or the α and β isomers of HCH, accounts for 10-20% of urinary excretion. When administered in the diet, 2,4,6-trichlorophenol induced leukemias and lymphomas in male rats and hepatocellular carcinomas and adenomas in mice of both sexes. It has been associated with Non-Hodgkin's lymphoma and soft tissue sarcomas in

humans. In human bio-monitoring studies, 2,4,6-trichlorophenol was one of three major metabolites noted in excreta of lindane production workers. Lindane is metabolized by five major pathways in mammals. The differences in strain, species, and developmental age result in the identification of more than 80 metabolites of lindane in laboratory animals and humans. Given the derivations of lindane metabolism, it is difficult to predict toxicity with the available ADME information. However, based on the proposed mechanisms of toxicity, insult to the central nervous system, endocrine system and cellular genetic material would be expected outcomes of lindane exposure.

Lindane is highly acutely toxic by the oral route and slightly to moderately acutely toxic by the inhalation and dermal routes, respectively. Lindane is not irritating to the skin or eyes and is not considered to be a dermal sensitizer. Acute toxicity is characterized by effects on the central nervous system. Clinical signs of toxicity in humans following accidental poisonings are consistent with its acute neurotoxic effects in laboratory animals (i.e. nausea, exhaustion, convulsions, seizures).

The main effects noted in rodents following repeated oral dosing of lindane consisted of progressive liver toxicity including organ weight change, enzyme induction, hepatocellular hypertrophy, hyperplasia and necrosis, as well as the formation of areas of eosinophilic or fatty metamorphosis foci following more extended dosing duration. These liver effects progressed in severity with dose concentration and duration. In some cases, short to chronic duration of dosing produced Clara cell hyperplasia in the lung of mice, which is considered to be an irreversible change to the cellular architecture of the respiratory tract.

Following repeated dermal dosing, toxicity studies revealed adrenal, liver and kidney toxicity in rabbits and/or rats at doses as low as 60 mg/kg bw/day. Increased thymus weights were recorded in the rat study, suggesting a possible effect on the immune system via the dermal route of exposure. Repeat dose inhalation studies demonstrated kidney toxicity (weight change with histopathology) and decreased bone marrow lymphocyte content in the rat while mice demonstrated spleen and thymus weight changes and mortality at doses as low as 0.00104 mg/L (equivalent to 0.25 mg/kg bw/day). These studies demonstrated a different spectrum of effects from the oral route of exposure, suggesting route-specific toxicokinetics.

Other evidence suggested that lindane may be associated with effects on the immune system. In several short- to intermediate-duration studies, thymus and spleen weights were altered in rodents given lindane in the diet. Immune effects were critical effects at the LOAEL from the 13-week inhalation toxicity study, whereas similar effects were noted in the oral dosing rodent studies at doses higher than the LOAEL. Published articles provide evidence that lindane may affect certain immune responses in mice, rats and pigs that may be of clinical significance to humans. There were indications that the production of free radicals was responsible for the lindane-induced immunotoxicity, as co-administration of a free radical scavenger (ascorbic acid) attenuated the adverse effect on humoral immune function. Similarly, the insult on the immune system followed a distinct pattern of effect with initial immune system activation followed by immune suppression after prolonged dosing. The known cytotoxic action of lindane (increased production of epoxide and superoxide radicals, leading to oxidative stress and lipid peroxidation) would be expected to cause oxidative damage to lympho-reticular cells secondary to systemic

toxicity. Although the test material used in these studies varied (γ-HCH or technical grade HCH), the cytotoxicity responsible for the immunotoxic endpoints would be a common mechanism of the various isomers of HCH. While these endpoints are of relevance to humans, they are considered likely to represent a secondary response to generalized systemic cytotoxicity.

Lindane has been reported to cause convulsions, behavioural effects and changes to resting membrane potentials in excitable tissues. The neurotoxic effects of lindane have been linked to its ability to interact with the $GABA_A$ receptor in the brain, which can result in overstimulation of the central nervous system. Clinical signs of toxicity in humans begin within 30 minutes following accidental poisonings and are consistent with lindane's acute neurotoxic effects in laboratory animals (i.e. nausea, exhaustion, convulsions, hyper-excitability and seizures). Laboratory animals also demonstrated changes in grip strength and motor activity following acute exposure to lindane at doses as low as 20 mg/kg bw, while higher doses produced tremors and convulsions. A single oral dose of 20 mg/kg bw was noted to reduce neurotransmitter levels in suckling rats, while weanling rabbits demonstrated clinical signs of neurotoxicity and death after a single dermal dose of 60 mg/kg bw. Adult rabbits given a similar dose did not demonstrate toxicity. Following 90 days of exposure to γ-HCH, rats demonstrated clinical signs of toxicity (hypersensitivity to touch and hunched posture) at 28/30 mg/kg bw/day (in males and females respectively) while indications of alterations in motor activity and learning at doses as low as 2 mg/kg bw/day in rats have been reported in the literature. In a developmental neurotoxicity study, lindane exposure was noted to cause changes in motor activity and response to auditory stimulus at doses as low as 4.2 mg/kg bw/day in weanling rats. Suggestive evidence of a reduction in learning ability was noted in males, but a conclusion could not be rendered for this endpoint due to the variability of the data. Despite this limitation, the developmental neurotoxicity study was considered to be acceptable for regulatory purposes. It is important to note that the neurological effects in young rats occurred at dose levels that were non-toxic to the maternal animals. As well, while the alterations in neurological function were detected in weanling animals, it is not known how many chemical insults were required to precipitate the pathology. Changes in motor activity and auditory startle may occur following a direct acute insult of a neurotoxicant to the central nervous system. However, lindane has several mechanisms of toxicity including the modulation of membrane ion pumps, induction of oxidative stress, and alteration of steroid hormone production. These mechanisms of toxicity are expected to result in more severe effects and, in all likelihood, occur at lower doses following repeated exposures.

Lindane was not teratogenic in either rats or rabbits. However, studies are available that provide evidence that the developing young appear to be more severely affected than adults at a comparable dose. In the rabbit developmental toxicity study, maternal toxicity was limited to slight reductions in body-weight gain at doses of 5 mg/kg bw/day and greater for the initial 4 days of treatment, which was resolved by the end of the dosing period. Developmental toxicity was manifested as decreased live fetuses per dam and fetal losses at doses of 5 mg/kg bw/day and greater. In a developmental neurotoxicity study in rats, toxicity in the young (decreased weight gain, increased motor activity and decreased auditory startle) was noted at a maternally non-toxic dose.

In the two-generation reproduction study, no adverse effects on reproductive performance were observed; however, sperm analysis was not conducted. Offspring were noted to be more severely affected than parental animals. In addition to decreased pup birth weights and a delayed maturation (tooth eruption), survival was reduced in F_1 pups at a maternally non-toxic dose. Maternal toxicity was less severe and was limited to decreased body-weight gain, liver and kidney effects at a dose 8-fold higher than the offspring lethal dose. Aspects of lindane's mode of toxicity play a role in the reduction in pup survival. Lindane has been reported to inhibit steroid metabolism, resulting in lowered neuro-steroid levels. After a period of repeated exposure, the generation of neuro-steroids could be greatly reduced. A key target of these steroids is the GABA receptor. A variety of chemical and physiological stressors may activate the expression of neuro-steroids including low oxygen or high levels of carbon dioxide in neuronal tissue. Parturition represents a time of low oxygen to the infant, whereby neuro-steroid release stimulates GABA-ergic neurons to initiate respiration in the newborn. The inhibition of GABA signalling (due to loss of neuro-steroid production secondary to lindane inhibition of the StAR protein) would be expected to manifest as difficulty in breathing acquisition in the newborn. Early failure to thrive would be an expected outcome following repeated maternal exposure to lindane during a critical developmental period. It is known that the fetal unit can sequester up to 3-fold higher concentrations of lindane than the maternal animal. Thus, with any given dose of lindane administered to a pregnant animal, the offspring would be considered to be more susceptible to toxicity due to the increase in anticipated dose to the fetal unit. This would represent an inherent sensitivity of the young to lindane toxicity by virtue of the fetal predisposition for lindane sequestration as a result of placental transfer. This placental transfer of lindane may account for the spectrum of offspring toxicity noted in the reproductive toxicity study at maternally non-toxic doses.

Other evidence of sensitivity to the young can be consolidated from the open literature. The mean brain concentration of lindane required to elicit convulsions in neonatal rats was lower (2.5 ppm) than in adults (4.5 ppm). Young animals were noted to demonstrate reduced neurotransmitter levels, display clinical signs of neurotoxicity and succumb to lindane exposure at doses below maternally toxic concentrations. Lindane can cross the placenta to produce fetal serum levels higher than maternal levels. Because lindane also accumulates in milk fat, lactational exposure results in higher doses to offspring than those of the maternal animals. These sources of exposure to the young animal are compounded by the inability of the developing young to metabolize and excrete many compounds due to under-developed liver enzymes and low renal clearance. In fact, the half-life of elimination in children may be much greater than the adult rate for a given compound. Because the young have lower adipose deposits, lindane, being lipophilic, may sequester to a greater extent in the lipid-rich myelin of the central nervous system, leading to greater neurotoxicity following repeated exposure. This supposition is based on a similar set of events identified in developing rodents. This central nervous system sequestration is a likely outcome in the developing young because the blood-brain barrier is immature and susceptible to disruption following lindane exposure. Young animals and children have been shown to absorb much greater quantities of lindane dermally than would be expected based on adult dermal absorption values. Sensitivity in the human population has also been suggested in epidemiological studies, in which higher lindane concentrations were noted in umbilical cord blood of mothers that delivered low birth weight babies, had still births or delivered prematurely. There was a high degree of variability within

measurements of lindane in human tissue. Milk, maternal sera and cord blood samples varied by as much as 100-fold among women within the same city.

Published studies have linked lindane exposure with reproductive and endocrine effects in laboratory animals. The spectrum of endocrine and reproductive toxicity was identified in adult animals and also in animals exposed during critical periods of development. Lindane administered to weanling rats as a single dose (6 mg/kg bw) or 5 consecutive doses (1 mg/kg bw/day) was noted to decrease spermatid counts, degenerate Sertoli cells and decrease testes weights in males once they reached adulthood. Toxicity of the male reproductive system was also noted in several other species including rams, mink and mice, often in the absence of systemic toxicity. Investigations into the cause of the testicular toxicity noted decreased luteinizing hormone, decreased testosterone and progesterone and even decreased estradiol in lindane-exposed animals. These changes in gonadal and pituitary hormones altered oestrus cycles and disrupted sexual maturation and reproductive performance. In vivo and in vitro studies suggest that these changes are possibly attributable to alterations in membrane potential, enzyme activities and receptor-binding, with inhibition of antioxidant defences and gap-junction disruption. The end result of the multi-faceted mechanism of HCH toxicity is the disruption of steroid hormone production, alteration of enzyme production and disruption of endocrine tissue architecture and function. Literature information identified that changes in testicular StAR protein, peroxide generation, androgen binding protein and induction of steroidogenic enzyme activities following an acute exposure of lindane were reversible after 72 hours, suggesting that toxicity could be dependent upon duration of exposure. In fact, in a rat study, the duration of exposure was noted to affect the generation of testicular toxicity,with 30 days of treatment producing a greater insult to sperm than that observed following a treatment regime of 7 days. Although a single dose group was not included in this study, it was evident that sperm toxicity did progress in severity with the duration of dosing. All of the reproductive and endocrine parameters reportedly affected in laboratory animals by lindane are of biological significance in humans and would be expected to progress in severity with prolonged exposure to lindane.

Studies in animals including rams, mink and mice also show that lindane has been found to accumulate in testes and sperm, while mice accumulated lindane in specific brain regions, indicating that it crosses the blood-testis and blood-brain barriers following oral and/or dermal administration. Effects on gonadal and endocrine function were noted in developing young. However, as many of the literature studies only examined the effects of a single dose level of lindane, NOAELs were not determined in many studies for these endpoints of concern. Robust assessments of sperm morphology and function were not available in the lindane database. Therefore, there is residual uncertainty in determining a point of departure for these endpoints of concern in the developing young.

A large number of genotoxicity studies have been conducted, although many of these studies provide limited information as a result of the protocols used, the purity of the test material or the degree of reporting of the results. Lindane has been assessed in many literature articles with both positive and negative results reported. The recent articles in the public domain indicate a genotoxic potential for lindane in human tissue. Repeated studies using the comet assay have indicated a potential for lindane to cause single and double strand breaks in human respiratory tract epithelial cells in vitro. The existing information suggests that the active ingredient should

be considered of genotoxic potential. The related HCH isomers (α and β) have been investigated in multiple genotoxicity studies. While a mixture of positive and negative results were identified for both of these isomers, α- and β-HCH were noted to bind to DNA, while DNA repair mechanisms were inhibited by α-HCH. The overall weight of evidence suggests that lindane and its related HCH isomers have some genotoxic potential.

The Department of Health and Human Services (DHHS), ATSDR, CALEPA and IARC have previously classified lindane as a possible human carcinogen based on an increased incidence of mouse liver tumours. The USEPA has classified lindane as a group 2B/C compound with "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." At doses of 80 ppm and higher, lindane was found to induce liver and/or lung tumours in rodents. The reproducibility of the mouse liver tumours across strain, time and in several labs is considered to be supportive evidence of a carcinogenic potential for lindane. Lung tumours were similarly noted in 2 studies in 3 strains of mice. These results, coupled with positive hepato-carcinogenicity findings of structurally-related compounds (α- and β-HCH) as well as a major lindane metabolite in rodents and humans (2,4,6-trichlorphenol) provide sufficient evidence to conclude that lindane has carcinogenic potential. Subsequently, a unit risk (denoted by Q_1*, representing the upper 95% confidence limit on the slope of the dose response curve in the low dose region) for lindane was calculated on the basis of the averaged risk for the lung tumours identified in mice. The decision to use the lung tumour data for cancer risk assessment was due to the fact that the lung tumour data was considered more robust than the liver tumour data. This unit risk of 6.73×10^{-2} (mg/kg bw/day)$^{-1}$ was applied to the risk assessment for dietary and worker exposure. The CALEPA used a linear (multistage) model for carcinogenicity based on liver tumours in mice and derived a human potency value of 1.1 (mg/kg bw/day)$^{-1}$.

In conclusion, the lindane toxicology database was considered to be adequate for characterizing general systemic toxicity despite some limitations with respect to the quality of individual studies. The absorption and metabolism of lindane in humans is considered to be extensive, highly variable within the population and not fully characterized. Differences in the metabolites of interest exist between the strain and species of animals tested. While lindane exposure may be associated with effects on the immune system, these endpoints are considered likely to represent a secondary response to generalized systemic cytotoxicity. Lindane was found to induce liver and lung tumours in rodents and is considered to be genotoxic. These results, coupled with positive hepato-carcinogenicity findings of structurally-related compounds (α- and β-HCH) as well as a major lindane metabolite in rodents and humans (2,4,6-trichlorphenol), provide sufficient evidence to conclude that lindane has carcinogenic potential. Lindane was not teratogenic in either rats or rabbits and did not adversely affect reproductive performance in a reproductive toxicity study. Young animals were noted to demonstrate reduced neurotransmitter levels, display clinical signs of neurotoxicity and succumb to lindane at doses below maternally toxic concentrations, suggesting that the young are more sensitive than the adult animal to lindane toxicity. Because lindane also accumulates in milk fat and can cross the placenta, offspring will be exposed to higher doses than those of the maternal animals during early development. Mobilization of lindane from maternal adipose tissue would increase the transfer of lindane to the developing young during early development. Lindane has been found to accumulate in testes and sperm, while mice accumulate lindane in specific brain regions,

indicating that it crosses the blood-testis and blood-brain barriers following oral and/or dermal administration. Lindane causes changes in gonadal and pituitary hormones (decreased luteinizing hormone, testosterone, progesterone and estradiol), which alters oestrus cycles and disrupts sexual maturation and reproductive performance. Although toxicological changes have been noted following a single exposure to lindane, the potential for accumulation in fatty tissue coupled with the multi-faceted mechanism of toxicity suggests that repeated exposures to lindane would magnify the spectrum and severity of toxicological outcomes. While several toxicological endpoints of concern have been identified in the lindane database, there remains some degree of uncertainty with regards to characterizing toxicological sequella of the developing nervous, endocrine and male reproductive systems. For this reason, extra protective measures are taken into consideration in the health risk assessment.

Pest Control Products Act Hazard Considerations
For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into the account completeness of the data with respect to the exposure of and toxicity to infants and children, as well as potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, extensive data were available on lindane including prenatal developmental toxicity studies in rats and rabbits, a multi-generation reproductive toxicity study, and a developmental neurotoxicity study. There were some limitations in the guideline studies; however, they were considered to be acceptable for regulatory purposes.

With respect to prenatal and postnatal toxicity, there is evidence of increased sensitivity in the young compared to parental animals. In the rabbit developmental toxicity study, decreases in live fetuses occurred at a dose that produced only slight body weight reductions in dams. In the rat reproductive toxicity study, decreased pup viability occurred in the absence of effects on the dams, while the parental male animals displayed organ weight changes. Decreased birth weights, survival and weight gain were noted along with delayed maturation, increased motor activity and decreased auditory startle at maternally non-toxic doses in the rat developmental neurotoxicity study. Young animals were noted to demonstrate reduced neurotransmitter levels, display clinical signs of neurotoxicity including convulsions and succumb to lindane exposure at doses below maternally toxic concentrations. Lindane accumulates in milk fat and can cross the placenta, suggesting that exposure during gestation and lactation results in higher doses to offspring than those of the maternal animals. An insult to the testes and sperm production has been demonstrated in young animals from several species. However, sperm assessments were only noted in papers extracted from the public literature and assessments of sperm toxicity were not conducted in guideline regulatory studies. Furthermore, age sensitivity for this adverse outcome of lindane exposure has not been fully characterised. Sensitivity in the human population has also been suggested in epidemiological studies in which higher lindane concentrations were noted in umbilical cord blood of mothers that delivered low birth weight babies, had still births or delivered prematurely.

It is possible that changes in neuronal function may be altered following acute exposure to lindane; however, given the potential for lindane to accumulate in fatty tissue (including the brain, as noted in mice), and keeping in mind the mechanisms of lindane toxicity, repeated exposures would be expected to induce greater neurotoxicity. Similarly, repeated exposure to the developing young would be expected to elicit changes in pup body weight, endocrine function, survival and developmental maturation. It is known that changes in testicular steroidogenic enzymes, StAR protein and hydrogen peroxide levels return to normal levels within three days of a single exposure to lindane. With repeated daily exposure, lindane residues would accumulate in testicular tissue and toxicological outcomes would progress in severity. The overall weight of evidence suggests that a single exposure to lindane may be expected to precipitate adverse sequella, while the presumed mode of toxicity of lindane suggests that the consequences of repeated exposure would exacerbate toxicity. For these reasons, a greater level of concern exists for repeated exposure to lindane. This is reflected in the selection of factors for risk assessment.

3.2   Occupational Risk Assessment

Occupational non-cancer risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating safety factors protective of the most sensitive subpopulation. MOEs greater than or equal to the target MOE do not require risk mitigation.

Occupational cancer risk is estimated by calculating the Lifetime Average Daily Dose (LADD) to which a person may be exposed assuming 40 years of exposure over a 75-year lifetime. This value is then multiplied by the cancer potency factor (Q_1*) to estimate lifetime cancer risk as a probability. The Q_1* is determined based on dose response data from an appropriate toxicity study. A lifetime cancer risk in the range of 1×10^{-4} to 1×10^{-6} in worker populations is generally considered acceptable.

3.2.1   Toxicological Endpoints

Short-term (1–2 weeks) and intermediate-term (60–90 days of exposure within a 5-month period) dermal toxicity endpoint—occupational:
The most relevant toxicological endpoint for these risk assessments is liver toxicity observed at a dose of 60 mg/kg bw/day in the 90-day dermal toxicity studies in rats and rabbits. The NOAEL for this effect was 10 mg/kg bw/day in both species. The route and duration of dosing in these studies is most relevant to an assessment of worker exposure for both the short-term and intermediate-term durations. The toxicity to the liver was shown to be progressive in several studies, with effects noted as early as a week following dosing.

In the 90-day rat dermal study, thymus weight changes were noted at doses of 60 mg/kg bw/day and greater, suggesting that the dermal route may represent a more sensitive route for potential immunotoxicity than the oral route. However, the immunotoxic effects of lindane are considered to be of less concern from a regulatory perspective, because the known cytotoxic action of lindane (increased production of epoxide and superoxide radicals, leading to oxidative stress and lipid peroxidation) would be expected to cause oxidative damage to lympho-reticular cells

secondary to systemic toxicity. The 90-day dermal toxicity study did not include reproductive or neurotoxicity endpoints to evaluate these special considerations via dermal exposure.

Sensitivity of the young was identified in the lindane database in studies conducted via the oral route of administration. The worker population could include pregnant or lactating women; therefore, it is appropriate to ensure adequate protection for the fetus or nursing infant who may receive in utero or lactational exposure. No data to either confirm or refute sensitivity following dermal dosing was available; therefore, concern for potential sensitivity of the young must be acknowledged. The concerns outlined in the *Pest Control Products Act* Hazard Consideration section above would be equally applicable to this exposure scenario. In light of the uncertainty with respect to sensitivity, the concerns regarding endocrine modulation and neurotoxicity and the overall evidence that suggests increased toxicity following repeated exposure, a target MOE of 1000 was selected.

Short-term (1–2 weeks) and intermediate-term (60–90 days of exposure over a 5-month time period) inhalation toxicity endpoint—occupational:
The most appropriate study for the short- and intermediate-term inhalation risk assessments is the 90-day mouse inhalation toxicity study with a NOAEL of 0.08 mg/kg bw/day (0.00025 mg/L). The LOAEL was 0.25 mg/kg bw/day (0.001 mg/L) based on decreased spleen and thymus weights as well as mortality in one male and one female mouse. The route and duration of dosing in these studies is most relevant to an assessment of worker exposure for both the short-term and intermediate-term durations.

The 90-day inhalation toxicity study did not include reproductive or neurotoxicity endpoints to evaluate these special considerations via inhalation exposure. The spleen and thymus weight findings in the 90-day mouse inhalation study may suggest route sensitivity to these potential indicators of immunotoxicity, as noted for the dermal study in the preceding section. However, the immunotoxic effects of lindane are considered to be of less concern from a regulatory perspective because the known cytotoxic action of lindane (increased production of epoxide and superoxide radicals, leading to oxidative stress and lipid peroxidation) would be expected to cause oxidative damage to lympho-reticular cells secondary to systemic toxicity.

The concerns and considerations noted for the establishment of a short-term to intermediate-term dermal toxicity endpoint are also of relevance for the inhalation route of exposure. For this reason, a target MOE of 1000 was considered appropriate for risk assessment.

Dermal Absorption
A dermal absorption value was not required for the non-cancer risk assessment because a dermal toxicity endpoint was used. However, as the cancer potency factor was determined from an oral study, a dermal absorption value was required for the cancer risk assessment.

A number of published in vivo dermal absorption studies performed on rats, monkeys, and humans were collected and reviewed (Moody and Ritter, 1989; Feldmann and Maibach, 1974; World Health Organization, 2003; Zesch et al., 1982).

Based on the variability observed in available human and rat in vivo dermal penetration studies for lindane, it was considered appropriate to use a range of dermal absorption values based on the results from these studies. There were some studies demonstrating dermal penetration outside this range; however, a range of 10-35 % is expected to be representative of the dermal absorption of lindane in humans.

3.2.2   Occupational Exposure and Risk Assessment

Workers can be exposed to lindane through mixing, loading or applying the pesticide during seed treatment and when handling and planting treated seed. The following scenarios were examined in this assessment:

- Workers in commercial seed treatment facilities (activities may include treating, bagging/sewing/stacking, clean-up and repair)
- On-farm planting of commercially treated seeds
- On-farm seed treatment plus planting activities

Occupational handlers of lindane would generally have a short-term (1–2 weeks) to intermediate-term (60–90 days of exposure over a 5-month time period) duration of exposure. Based on use information from the registrant as well as seasonal limitations, it was assumed that workers in commercial facilities would handle lindane for 90 days a year, while farmers would handle lindane 3 days a year when treating seeds on-farm or planting.

The PMRA estimated handler exposure using the maximum level of PPE possible based on the proposed product labels provided by the registrant and the exposure study used to assess a given scenario. Feasibility of this level of PPE was not always considered, as the purpose was to determine what effect this mitigation would have on the resulting exposure estimates and overall risk estimate.

Commercial Seed Treatment: Chemical resistant coveralls over a long-sleeved shirt, long pants, chemical resistant headgear, chemical resistant gloves and a respirator (treaters) or a dust mask (baggers/sewers/stackers).
Planting Treated Seeds: Chemical resistant coveralls over a long-sleeved shirt, long pants, chemical resistant gloves and a closed cab for planting.
On-Farm Seed Treatment: Coveralls over a long-sleeved shirt, long pants, chemical resistant gloves and a closed cab for planting.

Pesticide Handlers Exposure Database (PHED) scenarios were not considered to be representative of exposure to workers treating or handling treated seed. Exposure studies were used instead to estimate exposure. The majority of these studies was not chemical-specific; however, they were the best data available. See Appendix I A for a description of these studies, including limitations and unit exposure values.

As seen in Appendix IV, Table 4, all scenarios had MOEs (dermal and/or inhalation) that were below the target MOE, with the exception of commercial seed treatment (baggers/sewers/stackers) for wheat when the arithmetic mean (average) unit exposure was used.

Although this scenario had dermal and inhalation MOEs that were above the target MOE, commercial seed treatment cannot be supported as other aspects of commercial seed treatment and planting had MOEs that were below the target MOE.

As it is unlikely that workers would encounter high levels of lindane every working day in their lifetime, average unit exposure values were used to estimate cancer risk. As seen in Appendix IV, Table 5, many of the exposure scenarios had cancer risks that were less than 1×10^{-4}. A lifetime cancer risk in the range of 1×10^{-5} to 1×10^{-6} in worker populations is generally considered acceptable.

3.2.3   Residential Exposure and Risk Assessment

Residential risk assessment is concerned with estimating risks to the general population, including children, during or after pesticide application. Because there are no domestic products for lindane, a residential assessment was not conducted.

3.3   Dietary Risk Assessment

Northern communities present a special case distinct from the general Canadian population because lindane species have moved and accumulated in the arctic food chain over time due to past global manufacture and usage. The beta- and, to a lesser extent the alpha isomers reside in the fat of marine mammals, which are an important part of the Arctic diet. Therefore, risk assessment of lindane required two probabilistic analysis, one for the main population using existing food intake databases (Continuing Survey of Food Intakes by Individuals [CSFII]) and one for northern populations using data reported in Kuhnlein et al. (2000) and Richardson (1997).

3.3.1   Determination of Reference Doses

Chronic Dose: Acceptable Daily Intake (ADI)
The most relevant study for use in the chronic dietary risk assessment is the 2-year toxicity study in rats, as the study is of the appropriate duration and route of exposure. The NOAEL was set at 0.47 mg/kg bw/day on the basis of decreased survival as well as liver and spleen effects observed at the LOAEL of 4.8 mg/kg bw/day.

The standard 100-fold uncertainty factor is required to account for interspecies extrapolation (10-fold) and intraspecies variability (10-fold). With respect to the PCPA factor, sensitivity of the young was identified in the lindane database in the developmental toxicity studies in rabbits, the reproductive toxicity study in rats and the developmental neurotoxicity study in rats. In addition, the public literature identifies adverse effects on sperm following lindane dosing as low as 1 mg/kg bw/day for 6 days, and sperm parameters were not assessed in the reproductive toxicity study or the 2-year rat study. On the basis of this information, more fully outlined in the *Pest Control Products Act* Hazard Consideration section above and the greater level of concern for repeated exposure to lindane, the 10-fold PCPA factor was retained. This factor was added to the standard 100 uncertainty factor, resulting in a composite assessment factor of 1000 in the calculation of the ADI.

The resulting ADI is 0.47/1000 = 0.0005 mg/kg bw/day, which is considered protective of unborn and developing children in that it provides margins greater than 2000 to developmental endpoints in the database.

Cancer Dose: Risk Unit (Q_1*)
The Department of Health and Human Services (DHHS), ATSDR, CALEPA and IARC have previously classified lindane as a possible human carcinogen based on an increased incidence of mouse liver tumours. The USEPA has classified lindane as a group 2B/C compound with "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." At doses of 80 ppm and higher, lindane was found to induce liver and/or lung tumours in rodents. The repeatability of the mouse liver tumours across strain, time and in several labs is considered to be supportive evidence of a carcinogenic potential for lindane. Lung tumours were similarly noted in two studies in three strains of mice. These results, coupled with positive hepato-carcinogenicity findings of structurally-related compounds (α- and β-HCH) as well as a major lindane metabolite in rodents and humans (2,4,6-trichlorphenol), provide sufficient evidence to conclude that lindane has carcinogenic potential. Subsequently, a unit risk (denoted by Q_1*, representing the upper 95% confidence limit on the slope of the dose response curve in the low dose region) for Lindane was calculated on the basis of the averaged risk for the lung tumours identified in mice. This unit risk of 6.73×10^{-2} (mg/kg bw/day)$^{-1}$ was applied to the risk assessment for dietary and worker exposure.

The critical toxicology study for acute dietary risk assessment is the developmental neurotoxicity study in rats. The NOAEL in this study was set at 0.8 mg/kg bw on the basis of decreased pup survival, reductions in auditory startle response and increases in motor activity in pups at 4.2 mg/kg bw. The young animal was more sensitive than the maternal animal, as adverse effects in the dams were not observed until a higher dose level, 8 mg/kg bw, with transient reductions in body-weight gains recorded during gestation. Although the decreased pup survival may not be a single dose phenomenon, the neurological insult resulting in changes to the behaviour of a young animal (auditory startle, motor activity) may occur after a single exposure. Thus, this endpoint is considered to be a critical endpoint for establishing an acute reference dose.

The standard 100-fold uncertainty factor is required to account for interspecies extrapolation (10-fold) and intraspecies variability (10-fold). With respect to the PCPA factor, all of the required studies relevant to assessing risks to infants and children were available for this assessment. Sensitivity of the young was identified in the lindane database in the developmental toxicity studies in rabbits, the reproductive toxicity study in rats and the developmental neurotoxicity study in rats. On the basis of the sensitivity of the young and in consideration of the rationale provided in the *Pest Control Products Act* Hazard Consideration section above, the PCPA factor was retained, but reduced to threefold. The reduction of the PCPA factor to threefold was based on a lower level of concern for acute exposure scenarios compared to repeat exposure scenarios. This factor was added to the standard 100-fold, resulting in a composite assessment factor of 300 in the calculation of the ARfD.

Lindane administered to weanling rats as a single dose was noted to decrease spermatid counts, degenerate Sertoli cells and decrease testes weights in males once they reached adulthood. These effects were also noted in several other species, often in the absence of systemic toxicity, and the

age sensitivity for this adverse outcome has not been fully characterised. However, the resulting ARfD is considered sufficiently protective of these effects for all subpopulations, including infants and children.

The resulting ARfD is 0.8/300 = 0.0027 mg/kg bw. The ARfD provides a margin greater than 2000 to the effect levels reported for testicular and sperm toxicity reported in the literature.

3.3.2 Acute Dietary Exposure and Risk Assessment

Main population
The PMRA evaluated risk based on a probabilistic assessment at the 95th percentile to compensate for conservative estimates of dietary burden obtained from a single occurrence of high residue in hay, which could not be further refined due to lack of data. Given this single and conservative value is the major contributor to acute risk, the assessment becomes similar to a tier 2 evaluation, in which a 95th percentile is normally used.

Northern population
Dietary exposure of Northern communities came from market and traditional sources and varied with gender and age. The proportion of market food consumption decreased with age from up to 92% of the diet in children to approximately 50% for seniors, emphasising that traditional diet in the study year 2000 was important only for the elders.

In Appendix V, Table 4, the combined dietary exposure from market and traditional sources was of concern for most population groups at the 99.9[th] percentile, with a strong contribution from market foods (especially beef). The PMRA evaluated the risk at the 95th percentile because the effect of dietary burden present in market food would also affect the northern risk estimate in the same way. The risk was found acceptable.

3.3.3 Chronic Dietary Exposure and Risk Assessment

Chronic exposure estimates exceeded levels of concern for children 1 to 5 years (Table 2) but could be reduced with appropriate estimates of dietary burden. Northern populations have no chronic dietary concern. See Appendix V, Table 2 and Table 4).

3.3.4 Dietary Exposure and Risk Assessment for Cancer

Main population
Cancer risk estimates exceeded acceptable levels ($> 1 \times 10^{-6}$) for the general population and were driven by livestock dietary burden (Appendix V, Table 2).

Northern population
The exposure from combined market and traditional food sources showed that cancer risk exceeded acceptable levels and was also strongly dependent on livestock dietary burden arising from consuming market food. The lifetime cancer risk was about three times less than that of the main population due to dilution from traditional sources (Appendix V, Table 4).

3.4 Exposure From Drinking Water

Expected environmental concentrations (EECs) in surface water were calculated using the PRZM/EXAMS model on the standard Level 1 scenarios: a PEI potato field adjacent to a reservoir and a Manitoba potato field adjacent to a dugout. EECs in groundwater were calculated using the LEACHM model. All scenarios were run using 50-year weather data. The maximum yearly application rate of lindane, applied on canola, is 16 g a.i./kg seed, which corresponds to 144 g a.i./ha (at a seeding rate of 9 kg seed/ha). Spring seeding ranges from late April through May, but planting can also be done in the fall, typically in late October. Therefore, the starting dates used in the models were four dates in the spring and one in late October.

3.4.1 Concentrations in Drinking Water

EECs of lindane in potential drinking water sources are given in Appendix V, Table 3 for the general population. The EECs resulting from this Level 1 assessment were calculated using conservative inputs with respect to maximum application rates, application timing, yearly applications and geographic scenario. Details of model parameters are included in the environment assessment section of this document. EECs for the northern population were estimated from actual measurements in Amituk Lake (Appendix V, Table 5).

3.4.2 Drinking Water Exposure and Risk Assessment

Main Population
The 95th percentile was used to calculate drinking water levels of comparison (DWLOCs). Exposure from groundwater exceeded both acute (in children) and chronic (in all subpopulations) reference doses. Chronic exposure from surface waters exceeded the ADI for children as well. In addition, chronic exposure to both groundwater and surface water exceeded the acceptable lifetime cancer risk levels for the general population. More refined EECs and monitoring data are needed to possibly reduce estimates of drinking water concentrations.

Northern Population
Table 5 shows that lakewater EECs in the Arctic are not of concern.

3.5 Aggregate Risk Assessment

As there is no residential use of lindane, aggregate exposure is from dietary and drinking water exposures only. Chronic exposure exceeded the level of concern for the general population and for children in particular. Acute exposure exceeded the level of concern for children. Cancer risk estimates were unacceptable for the general population. The Northern populations were at risk for cancer due to their consumption of market foods.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on its physical-chemical properties, lindane has low solubility in water (7.3 mg/L), is volatile from soil and water (Henry's Law Constant = 4.9×10^{-7} - 3.7×10^{-6} atm. m^3/mole) and

has the potential to bioaccumulate (log K_{ow} = 3.2–3.7). Lindane is stable to hydrolysis at neutral, acidic and alkaline pH as the hydrolysis half-life values are 752 (pH 5), 732 (pH 7) and 182 days (pH 9). Phototransformation of lindane on soil, in water and in air is minimal. Overall, abiotic processes (hydrolysis and phototransformation) do not significantly contribute to the transformation of lindane in the environment.

In the aquatic environment, lindane is non-persistent to moderately persistent (DT_{50}s = 15–20 days in water; 48–90 days in sediment) and dissipation is primarily attributed to volatilization from water. In the terrestrial environment, lindane is moderately persistent to persistent in soil under field conditions (DT_{50}s = 42–187 days). Biotransformation in aerobic and anaerobic soil is not an important route in the dissipation of lindane. In aerobic soil, the DT_{50} is 133 to >336 days. In anaerobic soil, the DT_{50} is 37 days and is likely attributed to volatilization from flooded soil and not through biotransformation. Lindane is persistent in air (residence time = 87 days). In biota, lindane is non-persistent to moderately persistent (DT_{50} = 1–70 days).

There is inconclusive evidence for the bioisomerization of lindane (γ-HCH) to other HCH isomers (α-HCH, β-HCH and δ-HCH). The isomerization of lindane to α-HCH and β-HCH in soil and grass plants was demonstrated in laboratory studies; however, the reaction rate of this process was not determined and, thus, the extent of this interconversion could not be determined. An 80% conversion of lindane to α-HCH was demonstrated in a simulated lake environment within three months.

Laboratory studies showed that lindane has low potential mobility in soil based on high adsorption (K_{oc} = 871–1671), although it has been detected in groundwater in the United.States (period of 1968–1995). There are no available Canadian data, however, on groundwater concentrations of lindane. Researchers have concluded that lindane is subject to surface runoff resulting from spring-melt mobilization of lindane in soil from previous seedings despite its low potential for mobility. Lindane also partitions into aquatic sediment and binds to organic material in the water column.

Volatilization from soil is the most important route for the dissipation of lindane. In field studies, it was estimated that between 12–30% of the applied lindane was lost through volatilization within 5-6 weeks after planting lindane-treated canola seed. Therefore, it is estimated that 28–191 tonnes of lindane are released annually from canola fields in the Canadian Prairies and subsequently transported in the atmosphere. Similar rates of lindane release from soil are expected for other seed-treated crops (e.g. cereals). Although, the contribution of these lindane emissions from Canadian agricultural uses to regional and global concentrations has not been fully quantified, this large-scale off-site movement (e.g. volatilization from canola fields in western Canada) is an obvious contributor to local and regional environmental levels.

There is substantial evidence for the atmospheric movement of lindane to areas far removed from agricultural use sites within Canada. Lindane is detected in the atmosphere and surface waters in regions across Canada. In the air, lindane is detected in the Prairies, Great Lakes region and the Canadian arctic. Modelling of atmospheric transport predicted the movement of lindane from the Canadian Prairies to the Great Lakes region and the Canadian Arctic. This movement was verified by data which showed elevated air concentrations in the Great Lakes region during

the seeding period for lindane-treated canola seed in the Prairies. In surface waters, lindane is detected in Manitoba, Saskatchewan, Alberta, Ontario, Northern Quebec, Nova Scotia, Prince Edward Island, Newfoundland., the Great Lakes and in the Canadian Subarctic and Arctic. Surface water concentrations were higher in Western Canada than in Eastern Canada and can be attributed to the higher usage of lindane on canola in the Prairies, thus verifying local and regional atmospheric deposition from use (see Appendix VII).

Lindane is also transported via rivers and ocean currents to far-removed regions such as the Arctic. For example, discharge by all circumpolar rivers during the early to mid 1990s was 44 tonnes of lindane/year, most of which came from Russian rivers. The movement of seawater through the Bering Strait was estimated to deliver 12 tonnes of lindane/year.

Lindane is detected in biota such as freshwater and marine fish, benthic marine invertebrates, zooplankton, seabirds and marine and terrestrial mammals. Lindane has been detected at low concentrations (0.003 mg/kg) in seabird eggs from the Pacific coast of Canada and in eggs of peregrine falcons. The accumulation likely results through consumption of contaminated prey and, even where local food items are not highly contaminated with lindane, there is still accumulation in peregrine falcons that is likely attributed to accumulation during wintering in areas of lindane use, such as Central and South America. (see Appendix VII).

Lindane is detected in marine mammals at several locations. Higher concentrations of lindane were found in the blubber of marine mammals from cold and temperate waters compared to those from tropical waters, providing further evidence that colder regions are sinks for lindane (see Appendix VII).

Even though only purified lindane products are used in Canada (since 1971), the fate and toxicity of the α-HCH and β-HCH isomers needs to be considered when examining the use of lindane products. For every tonne of lindane produced, there are six to nine tonnes of waste isomers that must be disposed of or otherwise managed. One registrant reported a process for transforming the waste isomers into trichlorobenzene and hydrochloric acid. However, the PMRA can neither confirm nor ensure that this occurs when lindane is manufactured outside of Canada. Improper storage and disposition of waste from lindane manufacture allows the release of HCH isomers into global water and atmospheric transportation vectors, where they are subject to long-range transportation and possible deposition in the Canadian environment. Available data indicate that, in general, environmental levels of the waste isomers such as α-HCH have decreased since the ban of technical HCH in countries such as China, India and Russia. However, the PMRA does not conclude that chemical waste resulting from the manufacture of lindane is no longer a source of environmental loading.

There is substantial evidence for long-distance atmospheric movement of α-HCH and β-HCH isomers. In arctic air, there are higher concentrations of the waste isomer α-HCH, than concentrations of lindane. For example, mean air concentrations of lindane in the Canadian Arctic (for 1993–1995) were 0.011 ng/m^3 (at Tagish) and 0.010 ng/m^3 (at Alert), while concentrations of α-HCH (for 1993–1995) were 0.074 ng/m^3 (at Tagish) and 0.059 ng/m^3 (at Alert). In surface waters, α-HCH concentrations are higher in the Arctic but similar to slightly higher than lindane concentrations in Western Canada. In wetlands in southern Saskatchewan,

the detection frequency of lindane and α-HCH in water samples were 74% and 9%, respectively. The range of median lindane concentrations was 0.002-0.016 µg/L, with a maximum concentration of 0.40 µg/L. By contrast, α-HCH exhibits the highest detection and concentration in the Arctic. For example, in the Beaufort Sea and the Canadian Archipelago (Arctic), the highest mean concentrations of α-HCH and lindane were 3–7 ng/L and 0.35–0.95 ng/L, respectively. Lindane concentrations were generally higher in the surface waters of the prairie provinces (Manitoba, Saskatchewan and Alberta) compared to those of Eastern Canada and ranged from <0.001 to 0.076 µg/L.

HCH isomers (α-HCH and β-HCH) are also transported via rivers and ocean currents to far-removed regions such as the Arctic. By 1995, ocean currents were supplying about 90% of the α-HCH. For example, discharge by all circumpolar rivers during the early to mid 1990s was 25 tonnes of α-HCH/year, most of which came from Russian rivers. The movement of seawater through the Bering Strait was estimated to deliver 52 tonnes of α-HCH/year. The ocean pathway was always more important for β-HCH, accounting for 80-85% of the input to the Arctic Ocean in 1980 and 90-98% in 1995.

In freshwater and marine biota (invertebrates, fish, seabirds and marine mammals), α-HCH and β-HCH concentrations predominate in the Canadian Arctic. The relative proportion of α-HCH was generally higher than 60% in water, sediment, invertebrates and marine mammals, while β-HCH accounted for more than 60% of the total HCH burden in seabirds. In the fur seal, 59-62% of the HCH in blubber, liver and lung was β-HCH and 28-34% was α-HCH, while in the brain, 91% of the HCH residue was α-HCH. Similarly, in the striped dolphin, β-HCH constituted 84% and 94% of the HCH residues in muscle and kidney, respectively, while α-HCH constituted 73-83% in the brain. α-HCH was the most predominant isomer in the bowhead whale, beluga whale, pilot whale, common dolphin and harbor seal from the North Pacific-Arctic region and from the North Atlantic.

In terrestrial biota (lichens, caribou, wolves, peregrine falcons; and humans—blood, adipose tissue, breast milk), the highest HCH concentrations are that of β-HCH (see Appendix VII), e.g. β-HCH concentrations found in peregrine falcons from the Queen Charlotte Islands (British Columbia). The accumulation of β-HCH likely results through consumption of contaminated prey. Even where local food items are not highly contaminated with HCH residues, there is still accumulation in peregrine falcons which is likely attributed to accumulation during wintering in areas of lindane use, such as Central and South America. α-HCH and β-HCH were the predominant compounds detected in caribou and wolf tissues.

The bioconcentration, bioaccumulation and trophic transfer of lindane, α-HCH and β-HCH in aquatic food webs were examined using laboratory and field data from marine and freshwater species. Bioconcentration profiles evaluated under laboratory conditions indicate that lindane accumulates in a large range of aquatic species with bioconcentration factors (BCFs; wet weight) ranging from 13 to 2000 and with half-lives of approximately 3 days. In freshwater fish, the highest BCF values were 1400 (bluegill sunfish) and 2000 (rainbow trout). In fish from various food webs, the highest bioaccumulation factor (BAF; wet weight) was 4250, while other high BAF values were 2000–3500 (trout); 2000 (whitefish) and 3000 (herring). α-HCH also accumulates in organisms and has BCFs of between 60 and 2750, with slightly more rapid

elimination (half-lives of 48–72 h). β-HCH generally has higher reported BCFs and longer half-lives than lindane and α-HCH. Calculated field BAFs were $1–4 \times 10^3$ for lindane, $1–4 \times 10^3$ for α-HCH and $1–41 \times 10^3$ for β-HCH. Field BAFs were generally higher than lab BCFs by a factor of about 2. Temperature may play a role in this difference as most of the field data is from cold systems (Arctic Ocean, Canadian Shield lakes). Further investigation may be needed to better understand the role of temperature on the bioaccumulation and metabolism of lindane and other HCH isomers.

Trophic magnification factor (TMF) results indicate that lindane does not biomagnify in most aquatic food webs. Lindane does appear to biomagnify, however, in lake trout (TMF = 2.4–6.5) in Western Canadian lakes, suggesting that the trout from this location may not be in equilibrium with the water and food web due to fresh seasonal inputs from summer agricultural uses. In various arctic food webs, the highest biomagnification factors (BMFs) in whales and seals were 2.9–6.7 and 2.1–6.2, respectively. These values indicate that lindane is biomagnifying in these food webs. The TMF for β-HCH was 11.3 in seals, which indicates that β-HCH can biomagnify in various food webs.
In terrestrial food chains (lichens–caribou–wolves), lindane accumulated in caribou and wolves but did not biomagnify. The BMF for β-HCH was 3.4–28 in wolves which indicates that β-HCH can biomagnify in various food chains.

In conclusion, with regards to environmental fate, seed treatment is a major source of widespread environmental loading and accumulation of lindane into air, water and biota. In addition, it is possible that the use of lindane as a seed treatment is contributing to the widespread environmental loading of the waste isomers a-HCH and b-HCH into air, water and biota, through the improper storage and disposal of these unwanted isomers resulting from the manufacturing and purification process of lindane.

4.2   Effects on Non-target Species

The environmental risk assessment determines the potential for adverse ecological effects in each environmental compartment by comparing the ratio of the estimated environmental exposure to the ecotoxicological effect. The estimated environmental concentration (EEC) is the initial or cumulative concentration of pesticide in the various sources of food, water and soil to which the organism is exposed. EECs are calculated by different methods for each media (food, water or soil).

The risk assessment is initially conducted using a screening-level scenario that assumes maximum exposure (EEC) and the most sensitive toxicological endpoint for the organism of interest. Risk to the environment is calculated as a risk quotient (RQ), which is the ratio between the environmental exposure and the toxicological endpoint for the organism (i.e. RQ = EEC/toxicological endpoint). The threshold or level of concern for potentially harmful effects to an organism is an RQ value of 1, where the exposure exactly equals the toxicological endpoint. RQ values greater than or equal to 1 are considered to equal or exceed the level of concern (LOC), which may result in potentially harmful effects to the organism. RQ values less than 1 indicates a negligible risk. In the latter case, no further assessment is carried out. If the RQ is greater than or equal to 1, the level of concern, then a refinement of the risk assessment may be

carried out to assess the level of concern using scenarios which are a better approximation of exposure or toxicological effects and less conservative. Refinements can include exposure from the amount of pesticide predicted in surface runoff. The refinements may also consider the use of monitoring data collected in the field rather than EECs generated by a model.

4.2.1 Effects on Terrestrial Organisms

A risk assessment of lindane to terrestrial organisms was based on an evaluation of toxicity data on lindane to terrestrial invertebrates (chronic contact), two species of birds (acute oral, dietary and chronic) and two species of mammals (acute oral and chronic).
A summary of terrestrial toxicity data for lindane is presented in Appendix VIII). For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following seed treatment with lindane.

In birds, acute and chronic exposure to lindane can result from ingestion of lindane-treated seed. On an acute oral basis, the estimation of the RQ in birds is the ratio of the number of seeds normally ingested by a species to the number of lindane-treated seeds an animal would have to consume to reach the toxicity endpoint of concern. It was determined that individual birds would have to consume 1–16 treated seeds to reach the acute NOEL. To reach the LD_{50}, birds would have to consume 11–22 seeds. The highest risk occurred in small birds consuming lindane-treated canola seed. The RQ values were 268–324 on the basis of the NOEL and 28–32 on the basis of the LD_{50}. In both assessments, the LOC is exceeded. On a chronic basis for reproductive effects (NOEC), the RQ values were 3.8–709. The highest RQs occurred in birds consuming lindane-treated canola seed (RQs = 105–709).

Overall, lindane poses a risk to birds on an acute and chronic basis through ingestion of lindane-treated seed. Lindane is found in the eggs of seabirds and peregrine falcons and, although the necessary means to assess this risk are not available, it should be noted that lindane is a suspected endocrine disruptor and this is a cause for concern.

In small mammals, acute and chronic exposure to lindane can result from ingestion of lindane-treated seed. On an acute oral basis, the estimation of the RQ in mammals is the ratio of the number of seeds normally ingested by a species to the number of lindane-treated seeds an animal would have to consume to reach the toxicity endpoint of concern. It was determined that individual animals would have to consume 0.5–3 treated seeds to reach the acute NOEL. To reach the LD_{50}, animals would have to consume 5–34 seeds. The highest risk occurred in small mammals consuming lindane-treated canola seed as the RQ values were 23–200 on the basis of the NOEL and 2.3–20 on the basis of the LD_{50}. In both assessments, the LOC is exceeded. On a chronic basis for reproductive effects (NOEC), the RQ values were 280–7650. The highest RQs occurred in animals consuming lindane-treated canola seed (RQs = 7650).

Reproductive and developmental effects were exhibited in small mammals. In the rat, dietary exposure to 1 mg lindane/kg bw/day exhibited statistically significant smaller testes, lower levels of testosterone, lower number of sperm and spermatid, reduced sexual behaviour and absence of ejaculation in male offspring. An additional study with the rat has shown that single exposure of

2.0 mg lindane/kg bw or repeated exposure of 1 mg lindane/kg bw/day to lindane during critical periods of development caused functional impairment of the immature blood-brain barrier. By considering the body weight of the rat (0.4 kg), the number of seeds potentially ingested by the rat per day, and the amount of lindane per seed, an estimation of the risk to small mammals was determined based on reproductive effects reported at 1 mg/kg bw/day. The RQ was the ratio of the number of seeds ingested by the rat per day to the number of seeds ingested to reach the endpoint (1 mg/kg bw/day). The RQs were 15–404 and indicate that the LOC is exceeded. The highest risk occurs with ingestion of lindane-treated canola (RQ = 404).

Overall, lindane poses an acute and chronic risk to small mammals through ingestion of lindane-treated seed. In particular, lindane poses a risk of reproductive and developmental effects.

Lindane exposure to soil invertebrates is expected to be chronic in nature. The lowest reported chronic endpoint is a NOEC of 0.02 mg lindane/kg soil, equivalent to an application rate of 0.009 kg lindane/ha for canola seed treatment. The conversion to an application rate was based on the most recent label treatment rates, average canola seed size, standard canola planting rates and the assumption that the lindane on treated canola seed would be evenly dispersed in soil to a seeding depth of 3 cm, which has a bulk density of 1.5 g/cm^3. The highest expected concentration of lindane in soil that could result from seed treatment is 0.099 kg lindane/ha. The resulting RQ is 11, indicating that the LOC is exceeded by 11-fold. Thus, lindane poses a risk to soil-dwelling invertebrates.

As the exposure of honeybees and terrestrial plants to lindane via seed treatment is expected to be minimal, the risk of adverse effects is considered to be negligible.

4.2.2   Effects on Aquatic Organisms

Risk to aquatic organisms, acute and chronic, is based on an evaluation of toxicity data on lindane. A summary of aquatic toxicity data for lindane is presented in Appendix VIII. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed through seed treatment with lindane. The endpoints for acute toxicity were derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of 2 for aquatic invertebrates and plants and a factor of 10 for fish and amphibians (based on surrogate data from fish studies).

The aquatic risk assessment was conducted in which toxicity endpoints for the most sensitive species in that taxonomic group were compared to the estimated environmental concentrations predicted by the model PRZM/EXAMS for surface runoff into a shallow water body (see Appendix IX). In cases where the LOC was exceeded (RQ ≥1), a refined risk assessment was conducted that considered measured environmental concentrations of lindane. In refining the risk (if the RQ ≥1), the reported range of lindane concentrations in Canadian surface waters was used as the expected environmental concentration (EEC) in assessing the risk to aquatic organisms. The EEC range of lindane for several Canadian rivers was 0.001-0.076 µg/L. Similarly, the range of mean lindane concentrations in Saskatchewan wetlands was 0.002-0.016 µg/L with the maximum absolute concentration of 0.40 µg/L. Thus, in addition to the modelled PRZM/EXAMS surface water concentrations of lindane, the maximum measured lindane

concentrations of 0.076 µg/L (rivers) and 0.40 µg/L (wetlands) are used to determine the aquatic risk.

In fish, the lowest acute 96-hour LC_{50} was 1.7 µg lindane/L in the brown trout. By applying a factor of 10, the effects endpoint becomes 0.17 µg/L. Based on the maximum 96-hour expected concentration of 0.336 µg/L resulting from surface runoff (Appendix X), the RQ is 1.98, which indicates an exceedence of the LOC. All other tested fish species, however, showed LC_{50} values that are at least an order of magnitude greater (LC_{50} = 23-87 µg/L) than that of brown trout (which represents about 7% of the species tested),indicating that the LOC is not exceeded in nearly all species. Compared to the maximum measured concentrations of 0.076 µg/L (rivers) and 0.4 µg/L (wetlands), the LOC is exceeded in the most sensitive species, the brown trout (RQ = 2.4), for shallow bodies of water. However, the LOC is not exceeded in any other test species. In conclusion, lindane could pose an acute risk in some species of fish.

In freshwater invertebrates, the lowest acute 96-hour LC_{50} for lindane was 4.0 µg/L *(Sigara striata)*. By applying an uncertainty factor of 2, the effects endpoint becomes 2.0 µg/L. Based on the maximum 96-hour expected concentration of 0.336 µg/L resulting from surface runoff (Appendix X), the RQ is 0.17, which indicates the LOC is not exceeded. Compared to the maximum measured concentrations of 0.076 µg/L (rivers) and 0.4 µg/L (wetlands), the LOC is not exceeded in either case as the RQs are 0.04 and 0.2, respectively.

On a chronic basis, the lowest NOEC (28-day) in freshwater invertebrates was 0.80 µg/L in *Gammarus pulex*. Based on the maximum 21-day expected concentration of 0.281 µg/L resulting from surface runoff (Appendix X), the RQ is 0.35, which indicates the LOC is not exceeded. Compared to the maximum measured concentrations of 0.076 µg/L (rivers) and 0.4 µg/L (wetlands), the LOC is not exceeded in either case as the RQs are 0.10 and 0.5, respectively.

In marine invertebrates, the lowest acute LC_{50} was 0.17 µg lindane/L (*Penaeus duorarum*). By applying an uncertainty factor of 2, the effects endpoint becomes 0.09 µg/L. Based on the maximum 96-hour expected concentration of 0.336 µg/L resulting from surface runoff (Appendix X), the RQ is 3.7, which indicates that the LOC is exceeded. In considering the use pattern of lindane, the only regions of Canada where marine habitats would potentially be exposed to lindane is through surface runoff into marine/estuarine systems in the corn-growing areas on the east and west coasts.

On a chronic basis (28-day), there is a risk of endocrine disruption in male green shrimp (*Neocaridina denticulata*), as a lindane concentration of 0.1 µg/L was reported to exert oestrogenic effects (high level of oestradiol and low level of testosterone in the hemolymph) suggesting an impaired sexual behaviour and possible fertility problems (Huang et al., 2004). Compared to the maximum 21-day expected concentration of 0.281 µg/L resulting from surface runoff (Appendix X), the RQ is 2.8, which indicates an exceedence of the LOC. In considering the use pattern of lindane, the only regions of Canada where marine habitats would potentially be exposed to lindane is through surface runoff into marine/estuarine systems in the corn-growing areas on the east and west coasts.

In amphibians, the lowest acute 96-hour LC_{50} for lindane was 2700 µg a.i./L in tadpoles (*Pseudacris triseriata;* Western chorus frog*).* By applying an uncertainty factor of 10, the assessment endpoint becomes 270 µg a.i./L. Based on the maximum 96-hour expected concentration of 0.336 µg/L resulting from surface runoff (Appendix X), the RQ is 0.001, which indicates the LOC is not exceeded.

On a chronic basis, exposure of wood frog tadpoles to 0.1 µg lindane/L resulted in a skewed sex ratio (71% males) in metamorphs. Abnormal concentrations of sex and thyroid hormones indicated that lindane exerted disrupting effects on both gonadal and thyroid systems. However, this occurred only at one concentration and was not dose-dependent. Therefore, no conclusions can be drawn as to which concentrations may cause effects.
In aquatic plants, the lowest EC_{50} (10-day) for lindane was 1300 µg a.i./L (*Chlamydomonas reinhardi;* green alga). By applying an uncertainty factor of 2, the assessment endpoint becomes 650 µg a.i./L. Based on the maximum 96-hour expected concentration of 0.336 µg/L resulting from surface runoff (Appendix X), the RQ is 0.0005, which indicates the LOC is not exceeded. Compared to the maximum measured concentrations of 0.076 µg/L (rivers) and 0.4 µg/L (wetlands), the LOC is not exceeded in either case as the RQs are 0.0001 and 0.0006, respectively. Lindane, therefore, poses a negligible risk to aquatic plants.

5.0   Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's *Toxic Substances Management Policy*, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. During the review process, lindane was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of lindane were also considered, including microcontaminants in the technical product and the waste isomers produced in the manufacture of lindane. The four criteria against which lindane has been assessed are predominantly anthropogenic (source), CEPA-toxic or equivalent, persistence and bioaccumulation.

Source: By definition, the majority of chemical pesticides are considered as arising from anthropogenic sources as they are manufactured and applied to the environment for pest control purposes. As such, lindane is considered to have met the criteria of being predominately anthropogenic.

CEPA-toxicity: Based on a environmental risk assessment, lindane is entering the environment at levels that pose or may pose a risk to terrestrial and aquatic organisms. Therefore, lindane is considered to be "CEPA-toxic Equivalent" under the *Canadian Environmental Protection Act*.

Persistence: Lindane meets the TSMP criteria for persistence based on the half-life in soil (under field conditions) of 187 days, the half-life in air of 4.3–7.9 years and the half-life in seawater (pH 8 and 20°C) of 1.2 years. Lindane has also been detected in remote areas such as the arctic which has resulted from long range atmospheric transport; therefore, it meets the

criteria for persistence in air. α-HCH meets the TSMP criteria for persistence based on the half-life in seawater (pH 8 and 20°C) of 0.8 years. β-HCH meets the TSMP criteria for persistence based on the half-life in soil (under field conditions) of 184 days. The half-life of β-HCH in seawater is not known, but is expected to be even longer than the half-lives of the other isomers due to the general resistance to chemical and microbial mediated transformation.

Bioaccumulation

- The log octanol-water partition coefficient (log K_{ow}) of lindane is 3.2–3.7, which is below the TSMP Track 1 cut-off criterion for log K_{ow} 5.0.

- Bioconcentration factors (BCF; wet weight) of 13–2000 were reported for a range of aquatic species. The highest BCF value of 2000 was reported for a rainbow trout, which is less than the TSMP criterion of BCF 5000. In freshwater fish, BCF values ranged from 180 to 2000.

- In fish from various aquatic and marine food webs, the highest bioaccumulation factor (BAF; wet weight) was 4250; other high BAF values were 2000–3500 (trout); 2000 (whitefish) and 3000 (herring). These values do not exceed the TSMP criterion of BAF 5000. (Note: Other BAFs are reported but using different units, e.g. on a lipid weight or dry weight basis. TSMP criteria are for wet weight).

- In various arctic food webs, the highest trophic magnification factors (TMFs) in whales and seals were 2.9–6.7 and 2.1–6.2, respectively. In western Canadian lake food webs, TMFs were 2.4–6.5 in lake trout. These values indicate that lindane is biomagnifying in these food webs.

- In terrestrial food chains (lichens–caribou–wolves) lindane accumulated in caribou and wolves but did not biomagnify.

- The α-HCH isomer has reported BAFs of 170–4000, and TMFs similar to lindane.

- The β-HCH isomer exhibited a BAF of 41000 in fish (wet weight). This exceeds the TSMP criteria for BAF of 5000. A TMF of 11.3 was observed in seals and a TMF of 3.4-28 was observed in wolves indicating that it is biomagnifying in these food webs.

The TSMP Track 1 criteria of BCF/BAF ≥ 5000 was not exceeded for lindane; however, the TMF data indicate that lindane is biomagnifying in fish in western Canadian lakes and in arctic marine mammals and terrestrial mammals. The TSMP Track 1 criteria of BCF/BAF ≥ 5000 was exceeded for the β-HCH isomer.

Although the TSMP does not have any specific criteria for biomagnification, it is stated that "Track 1 of the policy is particularly concerned with lipophilic substances (i.e., those that have an affinity for fats) that can bioaccumulate and biomagnify to levels causing effects at the top of the food web."

The PMRA has concluded that lindane does not technically meet the TSMP Track 1 substance criteria for bioaccumulation. However, based on the strong evidence for biomagnification, particularly in organisms at the top of food webs, the PMRA has serious concerns about the contamination of food webs.

Conclusion
On the basis of the above available information, lindane does not technically meet the current TSMP Track 1 criteria. Clearly, lindane meets the criteria for persistence, is anthropogenic and is CEPA-toxic under the TSMP. Although the data on bioconcentration, bioaccumulation and biomagnification varies between taxa, overall, lindane is accumulating in biota to levels that are cause for concern. Of particular concern is the potential biomagnification in top predators such as lake trout in western Canadian lakes where fresh input of lindane occurs through deposition from agricultural uses, and in arctic whales where exposure to lindane is a result of atmospheric and oceanic transport. In addition, as both α-HCH and β-HCH meet the TSMP criteria for persistence and β-HCH meets the TSMP criteria for bioaccumulation, the use of lindane must be considered in the context of its contribution to the emission of these waste HCH isomers that result from the manufacturing of lindane. Based on these considerations, the PMRA has concluded that lindane and associated isomers are persistent, toxic and bioaccumulative.

6.0   Summary

6.1   Human Health and Safety

6.1.1   Occupational Risk

The risk assessment to workers treating and planting treated seeds was highly refined using exposure data reflective of modern seed treatment methods (including enclosed commercial facilities) and planting equipment. Maximum PPE, by way of protection factors for dermal and inhalation mitigation, were also applied to the risk assessment where appropriate. Further mitigation measures, such as the use of polymeric coatings on treated seeds and closed cabs for planting treated seeds, were also included in the planting assessment.

Although the risk assessment was considered to be highly refined, some exposure scenarios could be further refined using chemical-specific exposure studies with fewer uncertainties and limitations than those used in this assessment. Biomonitoring exposure studies could also help refine the exposure assessment.

6.1.2   Dietary Risk from Food

In general, risk for the main Canadian population is likely overestimated due to a single and high livestock dietary burden value. As no other study was available, the PMRA considered the 95th percentile of exposure appropriate for regulatory purposes. This resulted in an acceptable acute risk estimate. Chronic risk, however, is a health concern for children 1–5 years.

Northern populations receive their exposure from both market and traditional sources, the latter resulting from long-term accumulation and transport of lindane and other HCH species into the Arctic food chain. Dietary habits are such that the younger population relies mostly on market food while elders depend more on traditional sources. In spite of this important contribution from market food (meat), the acute and chronic dietary risks remains acceptable for the northern populations. Cancer risk, however, is a concern for the whole population due to market food consumption.

6.1.3 Dietary Risk from Drinking Water

For the main population, model calculations show that exposure from groundwater exceeds both acute (in children) and chronic (in all subpopulations) reference doses. Also, chronic exposure from both groundwater and surface waters are of concern for children and are above acceptable lifetime cancer risk levels for the general population. The PMRA concludes that drinking water may pose a short- and long-term risk to children and a cancer risk to the general population. More information is needed to reduce estimates from drinking water concentrations.

There is no drinking water concern for Northern populations.

6.1.4 Residential Risk

Lindane is not registered for use in any residential areas; therefore, a residential risk assessment was not required.

6.1.5 Aggregate Risk

As there are no registered residential uses for lindane, aggregate exposure includes only food and drinking water exposures. The PMRA concludes that drinking water presents an unacceptable risk to the general population (groundwater) and to children (groundwater and surface water). Also, the general population has an unacceptable cancer risk from food and water. This includes the Northern populations through their consumption of market food.

These health concerns are based on conservative estimates of residues in livestock.

6.2 Environmental Risk

The conclusions of the environmental risk are based on the standard environmental exposure scenarios. The risk to non-target organisms is summarized below (Table 6.2.1).

Of the terrestrial organisms, small birds and mammals that feed on lindane-treated seed are most at risk. On an acute basis, individual birds would have to consume as little as 1–16 treated seeds to reach the acute NOEL. To reach the LD_{50}, birds would have to consume as little as 11–22 seeds. The highest risk occurred in small birds consuming lindane-treated canola seed as the RQ values were 268–324 on the basis of the NOEL and 28–32 on the basis of the LD_{50}. In both assessments, the LOC is exceeded. On a chronic basis for reproductive effects (NOEC), the RQ

values were 3.8–709. The highest chronic RQs occurred in birds consuming lindane-treated canola seed (RQ = 205–709).

In small mammals, individual animals would have to consume as little as 0.5–3 treated seeds to reach the acute NOEL. To reach the LD_{50}, animals would have to consume as little as 5–34 seeds. The highest risk occurred in small mammals consuming lindane-treated canola seed as the RQ values were 23–200 on the basis of the NOEL and 2.3–20 on the basis of the LD_{50}. In both assessments, the LOC is exceeded. On a chronic basis for reproductive effects (NOEC), the RQ values were 280–7650. The highest RQs occurred in animals consuming lindane-treated canola seed (RQs = 7650). Reproductive and developmental effects were exhibited in small mammals in which statistically significant effects were: smaller testes, lower levels of testosterone, lower number of sperm and spermatid, reduced sexual behaviour and absence of ejaculation in male offspring. The RQs based on endocrine-disrupting effects are 15-404 and indicate that the LOC is exceeded. The highest risk occurs with ingestion of lindane-treated canola seed (RQ = 404).

Lindane is identified as an endocrine-disruptor in mammals. Also, lindane is found in the eggs of seabirds and peregrine falcons and, although the necessary means to assess this risk are not available, it should be noted that lindane is a suspected endocrine disruptor, which is a cause for serious concern given the potential for biomagnification.

Lindane poses a risk to soil invertebrates as a RQ = 4 was determined for earthworms.

There was no appreciable risk to honeybees and terrestrial plants as the exposure to lindane via seed treatment is expected to be negligible.

Of the aquatic organisms, fish and marine invertebrates are most at risk. On an acute basis, the LOC is exceeded (RQ = 2.4) in the most sensitive fish species (brown trout) based on the maximum measured concentration of lindane (0.4 µg/L) detected in wetlands. A chronic risk in marine invertebrates was identified. On the basis of the maximum 21-day expected concentration of 0.281 µg/L resulting from surface runoff, the RQ is 2.8 for the most sensitive species of marine invertebrate.

The risk is negligible for freshwater invertebrates and aquatic plants as the LOC was not exceeded for these taxa.

Table 6.2.1   Summary of the Risk to Most Sensitive Non-Target Organisms.

Organism	Exposure	Endpoint	Risk Quotient (RQ)	LOC
Small Birds	Acute	LC50	27.6 - 32.4	Exceeded
	Acute	NOEL	276 - 324	Exceeded
Medium-size Birds	Acute	LC50	6.1	Exceeded
	Acute	NOEL	2.5 - 59	Exceeded
	Chronic	NOEC	105 - 709	Exceeded

Organism	Exposure	Endpoint	Risk Quotient (RQ)	LOC
Small Mammals	Acute	LC50	2.3 - 20	Exceeded
	Acute	NOEL	23.4 - 200	Exceeded
	Chronic	NOEC	7650	Exceeded
	Chronic	EC60	404	Exceeded
Soil Invertebrates	Chronic	NOEC	11	Exceeded
Honeybees	Acute	LC50	NA[1]	Not exceeded
Terrestrial Plants	Acute	EC25	NA[1]	Not exceeded
Fish	Acute	LC50	0.45 - 2.4	Exceeded
	Chronic	NOEC	0.03 - 0.14	Not exceeded
Amphibians	Acute	LC50	0.0002 - 0.001	Not exceeded
	Chronic	EC21	2.0 - 4.0	Exceeded
Freshwater Invertebrates	Acute	EC50	0.04 - 0.20	Not exceeded
	Chronic	NOEC	0.10 - 0.50	Not exceeded
Marine Invertebrates	Acute	LC50	3.7	Exceeded
	Chronic	Statistically significant oestrogenic effects	2.8	Exceeded
Aquatic Plants	Acute	EC50	0.0001 - 0.0006	Not exceeded

7.0   Conclusion

This assessment confirms earlier regulatory actions in 2000–2004 to phase out all pesticidal use of lindane in Canada.

List of Abbreviations

AAFC	Agriculture and Agri-Food Canada
ADI	acceptable daily intake
a.i.	active ingredient
Anon.	Anonymous
ARfD	acute reference dose
ARI	aggregate risk index
ARTF	Agricultural Re-entry Task Force
atm	atmosphere(s)
ATSDR	Agency for Toxic Substances and Disease Registry, U.S. Public Health Service
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
CALEPA	California Environmental Protection Agency
CAS	Chemical Abstracts Service
CFIA	Canadian Food Inspection Agency
cm	centimetre(s)
CSFII	Continuing Survey of Food Intakes by Individuals
d	day(s)
DACO	data code
DEEM^{TM}	Dietary Exposure Evaluation Model
DER	Data Evaluation Report
DFR	dislodgeable foliar residue
DT$_{50}$	dissipation time to 50%
DWLOC	drinking water level of comparison
ELSE	Electronic Label Search Engine
EEC	expected environmental concentration [also estimated environmental concentration]
EP	end-use product
EU	European Union
EXAMS	Exposure Analysis Modeling System
F$_0$	parental generation [also abbreviated as P]
F$_1$	first filial generation
F$_2$	second filial generation
FAO	Food and Agriculture Organization of the United Nations
g	gram(s)
GABA	gamma-aminobutyric acid
GAP	Good Agricultural Practice
GD	gestation day
h	hour(s)
ha	hectare
HAP	hours after application
IARC	International Agency for Research on Cancer
IPM	integrated pest management
IRED	Interim Reregistration Eligibility Decision

kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	n-octanol–water partition coefficient
L	litre(s)
LD	lactation day
LEACHM	Leaching Estimation and Chemistry Model
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
m	metre(s)
m^3	metre(s) cubed
min	minute(s)
mg	milligram(s)
mm	millimetre(s)
mm Hg	millimetre mercury
MoA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MTD	maximum tolerated dose
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
nm	nanometre
OC	organic carbon
PACR	Proposed Acceptability for Continuing Registration
PCPA	*Pest Control Product Act*
PDI	potential daily intake
PHI	preharvest interval
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
pKa	-log10 acid dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppb	parts per billion
ppm	parts per million
PRVD	Proposed Re-evaluation Decision
PRZM	Pesticide Root Zone Model
Q_1*	cancer potency factor
RED	Reregistration Eligibility Decision
REI	restricted-entry interval
ROC	residue of concern
RQ	risk quotient

TC	transfer coefficient
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
URMULE	User Requested Minor Use Label Expansion
US ATSDR	United States Agency for Toxic Substances and Disease Registry
USC	Use-site category
USEPA	United States Environmental Protection Agency
USDA	United States Department of Agriculture
USFDA	United States Food and Drug Administration
WHO	World Health Organization

Appendix I Lindane Commercial Class Products for Use to Treat Seeds that Held Registrations in 2001

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee[1]
9505	Commercial	Norac Concepts Inc.	Agrox B-3 Dual Purpose Insecticide Fungicide Seed Treatment Powder	Wettable Powder	LIN 16.6% DIA 11% CAP 33.5%
10339	Commercial	Zeneca Agro	Mergamma N-M Drill Box Dual Purpose Seed Treatment	Dust	LIN 18.75% MAN 37.5%
10662	Commercial	Interprovincial Cooperative Limited	IPCO NM Dual Purpose Drillbox Seed Treatment Powder	Dust	LIN 18.75% MAN 37.5%
10896	Commercial	Norac Concepts Inc.	Agrox D-L Plus Seed Treatment Powder Insecticide	Dust	LIN 25% CAP 15% DIA 15%
11422	Commercial	Chemtura Co./CIE	Vitaflo DP Systemic Fungicide & Insecticide	Suspension	LIN 12.9% THI 8.9% VIT 10.1%
11451	Commercial	Interprovincial Cooperative Limited	CO-OP D-L +C Drill Box Seed Treatment Powder	Dust	LIN 25% CAP 15% DIA 15%
12767	Commercial	Zeneca Agro	Mergamma Flowable Dual Purpose Seed Treatment	Suspension	LIN 132 g/L MAN 262 g/L
13951	Commercial	United Agri Products Canada Inc.	Clean Crop D-iazinon L-indane C-aptan Drill Box Seed Treatment	Dust	LIN 25% CAP 15% DIA 15%
14115	Commercial	Chemtura Canada Co/CIE	Vitavax Dual Solution Systemic Fungicide & Insecticide	Solution	LIN 165 g/L VIT 180 g/L
14887	Commercial	AGSCO Inc.	Agsco DB-Green Seed Disinfectant & Insecticide Dust	Dust	LIN 18.75% MAN 50%
14893	Commercial	Interprovincial Cooperative Limited	IPCO Benolin-R Insecticide-Fungicide Dust (Seed Treatment)	Dust	LIN 50% BML 6% THI 10%
15533	Commercial	Chemtura Co./CIE	Vitavax RS Flowable Systemic Liquid Seed Protectant	Suspension	LIN 680 g/L THI 90 g/L VIT 45 g/L
15537	Commercial	Chemtura Co./CIE	Vitavax Dual Powder Seed Protectant	Dust	LIN 18.8% THI 28.5% VIT 20%
16451	Commercial	Chemtura Co./CIE	Vitavax RS Powder Seed Treatment	Dust	LIN 50% THI 6.7% VIT 3.3%
19035	Commercial	Rhone-Poulenc Canada Inc.	Rovral ST Canola and Mustard Seed Treatment	Solution	LIN 500 g/L IPD 167 g/L
21020	Commercial	Zeneca Agro	Premiere Plus Flowable Seed Treatment	Suspension	LIN 40% THI 4.8% TZL 1.6%
21946	Commercial	Zeneca Agro	Premiere Flowable Seed Treatment	Suspension	LIN 40% THI 4.8% TZL 1.6%
22121	Commercial	Chemtura Co./CIE	Cloak Seed Treatment	Solution	LIN 533 g/L THI 90 g/L VIT 45 g/L

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee[1]
23366	Commercial	AGSCO Inc.	Agsco DB-Green Liquid Seed Fungicide & Insecticide Seed Treatment	Suspension	LIN 108 g/L MAN 323 g/L
24447	Commercial	Zeneca Agro	Premiere No Dye Flowable Seed Treatment	Suspension	LIN 40% THI 4.8% TZL 1.6%
24467	Commercial	Chemtura Co./CIE	Vitavax RS Flowable (undyed) Seed Protectant	Suspension	LIN 667 g/L THI 90 g/L VIT 45 g/L
24482	Commercial	Chemtura Co./CIE	Vitavax RS Dynaseal Flowable Systemic Liquid Seed Protectant	Suspension	LIN 600 g/L THI 80 g/L VIT 40 g/L
24972	Commercial	Rhone-Poulenc Canada Inc.	Rovral CST Canola Seed Treatment	Solution	LIN 500 g/L IPD 167 g/L
25282	Commercial	Rhone-Poulenc Canada Inc.	Foundation Canola and Mustard Seed Treatment	Suspension	LIN 495 g/L IPD 99 g/L THI 66 g/L
25283	Commercial	Rhone-Poulenc Canada Inc.	Foundation CST Canola and Mustard Seed Treatment	Suspension	LIN 495 g/L IPD 99 g/L THI 66 g/L

[1]   BML = benomyl; CAP = captan; DIA = diazinon; IPD = iprodione; LIN = lindane; MAN = maneb; THI = thiram; TZL = thiabendazol; VIT = carbathiin.

Appendix II   Lindane Seed Treatment Uses Registered in 2001

Site(s)	Pests(s)	Formulation Type	Application Methods and Equipment	Maximum Application Rate (g a.i./100 kg seed)[1]	Farm Use	Supported for Reinstatement?[2]
Products included in the lindane use pattern are those registered in 2001 for use to treat seeds: Registration Numbers 9505, 10339, 10662, 10896, 11422, 11451, 12767, 13951, 14887, 14893, 15533, 19035, 21020, 21946, 22121, 23366, 24447, 24972, 25282, 25283. The following products were registered in 2001 for use to treat seeds but are not currently supported by the registrant Chemtura Co./CIE: Registration Numbers 14115, 15537, 16451, 24467, 24482. Information for the unsupported products is included in the table below. For information regarding the maximum application rate reported for unsupported products, see footnote 1.						
The following uses of lindane are not supported by Chemtura Co./CIE: Use of lindane on flax seed; use of lindane on cole crop seeds (broccoli, Brussels sprouts, cabbage, cauliflower and rutabaga); dust or powder formulations of lindane on mustard seed; solution formulation of lindane on grains (barley, oats, rye, wheat); application methods other than closed systems in commercial seed treatment facilities to treat mustard seed. For Registration Numbers 15533 and 22121, Chemtura Co./CIE supports the reinstatement of canola seed treatment to the product label for use in commercial seed treatment facilities using closed systems.						
As lindane is applied as a seed treatment, the maximum number of applications is 1.						
USC 10: Seed treatments for food and feed						
Wheat	Wireworms	Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	39	Y	Y
		Suspension	Liquid metering devices	41.18		
			Commercial seed treatment equipment or auger	39.24		
			Liquid seed treatment device: closed	33.7		
		Solution	Commercial seed treatment equipment or auger	59.4		N
Oat	Wireworms	Dust	Seed drill box, Dry Seed treatment application equipment, Paddle or shovel	69		Y
		Suspension	Liquid metering devices	72.86		
			Liquid seed treatment device: closed	59.62		
		Solution	Commercial seed treatment equipment or auger	49.5		N

Site(s)	Pests(s)	Formulation Type	Application Methods and Equipment	Maximum Application Rate (g a.i./100 kg seed)[1]	Farm Use	Supported for Reinstatement?[2]
Barley	Wireworms	Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	49.5	Y	Y
		Suspension	Commercial seed treatment equipment or auger	49.05		
			Liquid metering devices	52.8		
			Liquid seed treatment device: closed	42.77		
		Solution	Commercial seed treatment equipment or auger	49.5		N
Rye	Wireworms	Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	42		Y
		Suspension	Liquid metering devices	44.35		
			Liquid seed treatment device: closed	28.08		
		Solution	Commercial seed treatment equipment or auger	49.5		N
Flax	Wireworms	Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	52.7	Y	
Broccoli, Brussels Sprouts, cabbage, cauliflower	Flea beetles	Suspension	Mix in jar	1530		N
Rutabaga						N, M
Mustard	Flea beetles	Suspension	Liquid seed treatment equipment	1500		Y
			Commercial seed treatment only: liquid seed treatment equipment	1530	N	
			Mix in jar		Y	
		Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	1500		N

Site(s)	Pests(s)	Formulation Type	Application Methods and Equipment	Maximum Application Rate (g a.i./100 kg seed)[1]	Farm Use	Supported for Reinstatement?[2]
Canola (rapeseed)[3]	Flea beetles	Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	1600	Y	Y
			Commercial seed treatment only: liquid seed treatment equipment	3250	N	
		Solution	Commercial seed treatment only: liquid seed treatment equipment	1500		
			Liquid seed treatment equipment	1500	Y	
		Suspension	Liquid seed treatment equipment	1485		
			Commercial seed treatment only: liquid seed treatment equipment	1530	N	
Corn[4]	Wireworms, seedcorn maggot	Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	55.07	Y	
	Wireworms, seed maggots, root maggots	Wettable powder	Dry powder application equipment	56.44		
			Liquid seed treatment equipment: slurry application	52.29		
			Hand mixed: slurry application	55.78		
Bean[4]	Wireworms, seedcorn maggot	Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	55.07	Y	Y
	Wireworms, seed maggots, root maggots	Wettable powder	Dry powder application equipment	53.12		
			Liquid seed treatment equipment: slurry application	51.46		
			Hand mixed: slurry application	55.78		

Site(s)	Pests(s)	Formulation Type	Application Methods and Equipment	Maximum Application Rate (g a.i./100 kg seed)[1]	Farm Use	Supported for Reinstatement?[2]
Soybean[4]	Wireworms, seedcorn maggot	Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	55.07		
	Wireworms, seed maggots, root maggots	Wettable powder	Dry powder application equipment	53.12		
			Liquid seed treatment equipment: slurry application	51.46		
			Hand mixed: slurry application	55.78		
Peas[4]	Wireworms, seedcorn maggot	Dust	Seed drill box, Dry seed treatment application equipment, Paddle or shovel	55.07		
	Wireworms, seed maggots, root maggots	Wettable powder	Dry powder application equipment	53.12		
			Liquid seed treatment equipment: slurry application	51.46		
			Hand mixed: slurry application	55.78		

[1] For the supported uses of lindane, the maximum application rate reported is summarized only from those products supported by the registrants. Where the use is not supported, the maximum application rate is reported for all products.

[2] Y = use is supported by the registrant; N = use is not supported by the registrant; and M = use was registered as a User Requested Minor Use Label Expansion (URMULE).

[3] Use of products containing lindane on canola crop were discontinued in 2001.

[4] Only lindane products co-formulated with diazinon are registered for use on this crop.

Appendix III   Toxicology Profile for Lindane

Several studies had limited reporting. Where details in the table are missing the methodological details were not available. Effect levels are not reported for studies that were considered supplemental as a result of study limitations

Table 1   Toxicology Profile for Lindane

Metabolism
Absorption: Oral absorption in rodents has been reported to be greater than 90% for all isomers of HCH. Dermal absorption in humans has been measured between 9% and 100%. There was a high degree of variability (20×) in dermal absorption in human testing.
Distribution: Lindane levels in the guinea pig brain were noted to be up to 10-fold higher than serum levels following a single dermal exposure. Lindane was noted to accumulate in tissues of mice in a time- and dose-dependent manner. The highest tissue content was noted in fat, brain, kidney, muscle, liver, adrenal gland and ovary. Strain differences in metabolism were noted. B6 mice had blood concentrations of lindane that were 41% lower than the similarly dosed D2 mice. Brain concentrations of lindane were 78% higher in D2 mice than in B6 mice, while liver, kidney and spleen concentrations were similar between strains. Dosed Wistar rats did not exhibit high brain concentrations of lindane, demonstrating differences in metabolism between rodent species.
Excretion: Lindane is extensively metabolized following oral dosing and excreted mainly in the urine. The urine of treated rats most notably contained the metabolites 2,3-dichlorophenol, 2,4,6-trichlorophenol, 2,4,5-trichlorophenol and 2,3,5,6-tetrachlorophenol. Humans excrete HCH, principally as metabolites, in urine, breast milk, and semen. 2,4,6-trichlorophenol was one of three major metabolites noted in excreta of production workers. This metabolite is a probable human carcinogen based on evidence of leukemia, lymphomas and liver tumours in rodents and Non-Hodgkin's lymphoma and soft tissue sarcomas in humans.
Metabolism: The metabolism of lindane in humans is considered to be extensive and is not fully characterized. Children metabolize and excrete lindane slower than adults. In mice, the serum was found to contain two main metabolites: 2,4,6-trichlorophenol (carcinogen) and 2,3,4,6-tetrachlorophenol. Even tissue specific metabolite sequestration was evident: gamma-pentachlorocyclohexene was the predominant metabolite in kidneys and brain of rats; pentachlorophenol was most notable in spleen and 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol and gamma-pentachlorocyclohexene were most commonly found in the heart .
Given the discrepancies in metabolism between organ, strain and species, predicting end-organ damage from the ADME data is difficult at best.

Acute Studies			
Study	**Species, Strain**	**LD$_{50}$, LC$_{50}$**	**Result**
Oral WHO (2002)	Mouse, B6C3F1 and NMRI-EMD	LD$_{50}$ = 56-250 mg/kg bw	High toxicity
Oral WHO (2002)	Rat, Wistar	LD$_{50}$ = 140-190 mg/kg bw	High toxicity
Dermal WHO (2002)	Rat, Wistar	LD$_{50}$ = 1000 mg/kg bw	Moderate toxicity
Inhalation WHO (2002)	Rat, Wistar	LC$_{50}$ = 0.002 mg/l	High toxicity
Dermal irritation WHO (2002)	Rabbit, New Zealand White		Not a dermal irritant

Eye irritation WHO (2002)	Rabbit, New Zealand White		Not an eye irritant
Sensitization WHO (2002)	Guinea Pig, Dunkin-Hartley		Not a dermal sensitizer

Subchronic and Chronic Toxicity			
Study	**Species, Strain and Doses**	**NOAEL and LOAEL mg/kg bw/day**	**Target Organ, Significant Effects, Comments**
Mouse			
14-week inhalation Klonne and Kintigh (1988) as reported in WHO (2002) Lindane (99.6%)	Mouse, CD-1 (45/sex/dose) 0.25, 1.04 or 4.94* mg/m^3; gravimetric (0.08, 0.25 or 0.95 mg/kg bw/day) 15/sex/dose sacrificed at week 7, 13 or following a 6-week recovery period * The high dose was 10 mg/m^3 for the first week but was reduced due to mortality	NOAEL = 0.08 mg/kg bw/day LOAEL = 0.25 mg/kg bw/day	**≥0.25mg/kg bw/day:** ↓ spleen and thymus wt (♂/♀), death of one ♂ and one ♀. **0.95 mg/kg bw/day:** ↑ spindle cell hyperplasia (♀), early deaths (days 3–6 at 10 mg/m^3) (12/45 ♀ and 2/45 ♂), 3/45 deaths/sex for the remainder of the study.
90-day dietary (1998) Lindane (99.78%)	Mouse, CD-1 (10/sex/dose) 0, 40, 80, 160 or 320 ppm (0/0, 5.7/8.9, 12.2/16.0, 22.8/32.9 or 46.2/62.6 mg/kg bw/day in ♂/♀)	NOAEL = 12.2/16.0 mg/kg bw/day LOAEL = 22.8/32.9 mg/kg bw/day	**22.8/32.9 mg/kg bw/day:** lung congestion, hepatocyte hypertrophy, clara cell hypertrophy/hyperplasia. **62.6 mg/kg bw/day:** ♀ mortality.
2- to 4-month dietary Karnik et al. (1981) as reported in ATSDR (2004) Technical lindane (purity not stated)	Mouse, Swiss Dose levels not stated (only the dose levels at which effects occurred were reported)		**90 mg/kg bw/day:** hepatocellular carcinomas. **Supplemental**
16- to 36-week dietary Tsukada et al. (1979) as reported in ATSDR (2004) HCH (purity not stated)	Mouse, DD Dose levels not stated (only the dose levels at which effects occurred were reported)		**90 mg/kg bw/day:** hepatocellular hepatomas. **Supplemental**

24-week dietary Nagasaki et al. (1975) as reported in ATSDR (2004) α-HCH (purity not stated)	Mouse, DDY, ICR, CBA/2, C57BL/6 and C3H/He Dose levels not stated (only the dose levels at which effects occurred were reported)		**90 mg/kg bw/day:** hepatocellular carcinomas. **Supplemental**
24-week dietary Ito et al. (1973) as reported in WHO (2002) Lindane (purity not stated)	Mouse, DD (20-40 ♂/dose) 0, 100, 250 or 500 ppm (0, 5, 12.5 or 25 mg/kg bw/day)		**25 mg/kg bw/day:** 8 liver wt (absolute and relative), hepatocellular hypertrophy. Only livers examined microscopically. No other investigative details provided. **Supplemental**
2- to 8-month dietary Thakore et al. (1981) as reported in ATSDR (2004) Technical lindane (purity not stated)	Mouse, Swiss Dose levels not stated (only the dose levels at which effects occurred were reported)		**90 mg/kg bw/day:** hepatocellular carcinomas. **Supplemental**
20-month dietary Munir et al. (1983) as reported in ATSDR (2004) Technical lindane (purity not stated)	Mouse, Swiss Dose levels not stated (only the dose levels at which effects occurred were reported)		**21.3 mg/kg bw/day:** hepatocellular carcinoma **Supplemental**
26-week dietary Goto et al. (1972) Lindane or β-HCH or α-HCH (purity not stated)	Mouse, ICR-JCL (20 ♂/dose) Dose levels not stated (only the dose levels at which effects occurred were reported)		**600 ppm lindane:** liver hepatomas (5/10). **600 ppm α-HCH:** hepatomas in all treated animals. No tumours noted in β-HCH fed animals. No descriptions of non-neoplastic toxicity or methodology. **Supplemental**

32-week dietary Hanada et al. (1973) Lindane or β-HCH or α-HCH (purity not stated)	Mouse, DD (10/sex/dose) 100, 300 or 600 ppm (calculated to be 9, 27 or 54 mg/kg bw/day)		**300 ppm lindane:** atypical hepatocellular proliferation. **300 ppm α-HCH:** hepatomas (incidence not provided). **600 ppm lindane:** hepatocellular tumours (3/4 ♂ and 1/3 ♀ were identified as having liver tumours). **600 ppm β-HCH:** hepatocellular hypertrophy and "nuclear irregularities"; no tumours noted in β-HCH fed animals. Excessive mortality (exceeding MTD, toxicity not specified). **Supplemental**
50-week dietary Tryphonas and Iverson (1983) as reported in ATSDR (2004) α-HCH (purity not stated)	Mouse, HPB Dose levels not stated (only the dose levels at which effects occurred were reported)		**90 mg/kg bw/day:** hyperplastic nodules and hepatocellular adenomas. **Supplemental**
78-week dietary Chase (2000) Lindane (99.78%)	Mouse, Crl:CD-1 (ICR)BR (50/sex/dose) 0, 10, 40 or 160 ppm (0, 1.3/1.82, 5.2/7.1 or 20.5/26.8 mg/kg bw/day in ♂/♀)	NOAEL = 5.2/7.1 mg/kg bw/day LOAEL = 20.5/26.8 mg/kg bw/day	**5.2/7.1 mg/kg bw/day:** ↑ liver hypertrophy, ↑ eosinophilic foci (%); ↓ uterine/cervix wt (relative), ↓ uterine thickness. **26.8 mg/kg bw/day:** ↑ bronchiolar-alveolar adenomas (♀; 3/50, 7/50, 7/50 and 11/50 at 0, 10, 40 and 160 ppm) Survival and bw were unaffected at the high dose. In ♀, no effects other than tumours were seen.
80-week dietary Gulf South Research Institute (1977) Lindane (100%)	Mouse, B6CF3 (10/sex for controls and 50/sex/dose for treated animals) 0, 80 or 160 ppm (0, 11 or 23 mg/kg bw/day)		**11 mg/kg bw/day:** 8 hepatocellular carcinomas, testicular atrophy (%); lymphosarcomas and hypertrophy of the spleen (♀); 8 reactivity, aggression (%) and poor physical condition. **23 mg/kg bw/day:** 8 reactivity (♀). Limited histopathology, no data provided for several parameters. **Supplemental**

80-week diet/gavage/dermal Kashyap et al. (1979) as reported in ATSDR (2004) Technical Lindane (68.7% α-HCH, 6.5% β-HCH and 13.5% γ-HCH)	Mouse, Swiss (30/sex/dose) Diet (100 ppm), gavage (10 mg/kg bw/day) or dermal (0.25 mg/kg bw/day)		**100 ppm diet:** hepatocellular carcinomas (♂/♀). **0.25 mg/kg bw/day dermal:** hepatocellular carcinoma (♂). **10 mg/kg bw/day by gavage:** hepatocellular carcinomas (♂). **Supplemental**
80-week dietary Boehringher (1975) Lindane (99.5%)	Mouse, Chbb-NMRI (100/sex for controls and 50/sex/dose for treated animals) 0, 12.5, 25 or 50 ppm (0, 2.1/2.0, 4.1/3.9 or 8.2/7.8 mg/kg bw/day in ♂/♀)		**4 mg/kg bw/day:** polymorphonuclear sarcomas (2), spindle cell sarcoma (1), 8 mottled and pale lungs. Limited study protocol and reporting. Dosing too low to challenge the animals. **Supplemental**
105-week dietary Walker and Thorpe (1973) Lindane (99.5%) or β-HCH	Mouse, CF1 (45/sex for controls and 30/sex for treated animals) 0 or 400 ppm (calculated to be 52/72 mg/kg bw/day in ♂/♀)		**52 mg/kg bw/day:** 8 hepatocellular carcinomas and adenomas with both Lindane and β-HCH. Excessive mortality (exceeding MTD, toxicity not specified). **Supplemental**
105-week dietary Wolf (1987) Lindane (purity not stated)	Mouse, Agouti, Pseudoagouti and Black hybrid (groups of 36-96 ♀) 0 or 160 ppm (0 or 23 mg/kg bw/day) Recovery was examined in groups of 48-96 Agouti and Black mice fed treated diet for 6 months and then fed control diet for 6 or 18 months	NOAEL not identified LOAEL = 23 mg/kg bw/day	**23 mg/kg bw/day:** 8 liver adenomas and carcinomas (Agouti and Pseudoagouti),8 liver wt (all strains), 8 benzo-pyrene monooxygenase (all strains), 8 lung tumours (Agouti and Pseudoagouti) and irreversible Clara cell hyperplasia in lung (all strains). **Supplemental**

Rat			
15-day dietary Barros et al. (1991) as reported in ATSDR (2004) Lindane and α-HCH (purity not stated)	Rat, Wistar Dose levels not stated (only the dose levels at which effects occurred were reported)		**1.8 mg/kg bw/day:** ↑ lipid peroxidation, cytochrome P450, superoxide dismutase. Effects were noted with Lindane and α-HCH **Supplemental**
15-day dietary Shahid and Shakoori (1998) as reported in ATSDR (2004) Lindane (purity not stated)	Rat, Sprague Dawley Dose levels not stated (only the doses where effects were noted were reported)		**18 mg/kg bw/day:** ↓ hepatocellular cell count, ↑ cell, nucleus and nucleolus size, cytoplasmic vacuolation, fatty degeneration. **Supplemental**
28-day dietary Aymes (1990) as reported in WHO (2002) Lindane (99.5%)	Rat, Wistar (15/sex/dose) 0, 1, 10, 100 or 400 ppm (0, 0.10, 0.98, 9.8 or 39 mg/kg bw/day based on conversion factor of 0.098 reported by study author)	NOAEL = 0.98 mg/kg bw/day LOAEL = 9.8 mg/kg bw/day	**≥9.8 mg/kg bw/day:** ↓ Hg, RBC, Hct, ↑ pt, interstitial chronic nephritis, necrosis and degeneration, ↑ periacinar hepatocellular hypertrophy (♂). **39 mg/kg bw/day:** convulsions, ↑ spleen wt, ↓ Hg, RBC, Hct, ↑ periacinar hepatocellular hypertrophy (♀); ↓ bwg, ↑ liver wt, ↑ P, Ca, chol, BUN, ↓ A:G ratio (♂/♀).
6-week dietary Jones (1988) as reported in WHO (2002) Lindane (99.6%)	Rat, Crl:CD(SD)Br (5/sex/dose) 0, 80, 200, 400 or 800 ppm (0, 8, 20, 40 or 80 mg/kg bw/day based on conversion factor of 0.1 reported by study author)	NOAEL = 8 mg/kg bw/day LOAEL = 20 mg/kg bw/day	**≥8 mg/kg bw/day:** hepatocellular hypertrophy, leukocyte foci (♂). (*considered adaptive*) **≥20 mg/kg bw/day:** mottled kidneys, (♂); mottled livers (%/&). **80 mg/kg bw/day:** ♀ mortality; ↓ bwg, ↓ fc (♂); ↑ liver wt (♂/♀).
7-week dietary Joseph et al. (1992) as reported in ATSDR (2004) Lindane (purity not stated)	Rat, CFT-Wistar Dose levels not stated (only the dose levels at which effects occurred were reported)		**90 mg/kg bw/day:** ↑ liver wt, GTP and β-GLR. **Supplemental**

90-day dietary Suter (1983) as reported in WHO (2002) Lindane (99.85%)	Rat, Wistar (20/sex/dose) 0, 0.2, 0.8, 4, 20 or 100 ppm (0, 0.015, 0.061, 0.3, 1.5 or 7.6 mg/kg bw/day based on conversion factor of 0.076 reported by study author) 5/sex/dose were given a 6 week recovery period	NOAEL = 7.6 mg/kg bw/day LOAEL $ 7.6 mg/kg bw/day	**$0.3 mg/kg bw/day:** 8 BUN (%, not noted during recovery); ↑ hepatocellular hypertrophy (%/&). *(considered adaptive)* **$1.5 mg/kg bw/day:** 8 kidney tubule degeneration and nephritis (%); 8 liver wt (&). *(considered adaptive)* **7.6 mg/kg bw/day:** 8 cytochrome P450 (%/&, not noted during recovery); 8 liver wt (%).
90-day inhalation Hertel et al. (1983) as reported in WHO (2002) Lindane (99.9%)	Rat, Wistar (12/sex/dose) 0, 0.02, 0.1, 0.5 or 5 mg/m^3 (0.005, 0.03, 0.12 or 1.08 mg/kg bw/day) 12/sex/dose (control and high dose) were given a 6 week recovery period	NOAEL = 0.12 mg/kg bw/day LOAEL = 1.08 mg/kg bw/day	**$0.12 mg/kg bw/day:** 8 kidney wt, cloudy swelling of tubule epithelium, tubule dilation (%). *(considered adaptive)* **1.08 mg/kg bw/day:** 8 piloerection and diarrhea, cyto P450 (%/&); 8 reticulocytes and 9 lymphocytes in bone marrow smears, 8 kidney wt, ↑ liver wt (&).
13-week dietary Van Velsen (1986) as reported in ATSDR (2004) β-HCH (purity not stated)	Rat, Wistar 0, 0.18, 4.5 or 22.5 mg/kg bw/day	LOAEL = 0.18 mg/kg bw/day	**$0.18 mg/kg bw/day:** centrilobular hepatocyte hyalinization. **$4.5 mg/kg bw/day:** hepatocyte necrosis & hyperplasia.
90-day dietary Dikshith et al. (1991) as reported in ATSDR (2004) Lindane (purity not stated)	Rat, strain not stated Dose levels not stated (only the dose levels at which effects occurred were reported)		**5 mg/kg bw/day:** 8 GOT and AP. **Supplemental**
13-week dermal 1989 Lindane (99.5 %)	Rat, Crl:(WI)BR (13/sex/dose) 0, 10, 60 or 400 mg/kg bw/day	NOAEL = 10 mg/kg bw/day LOAEL = 60 mg/kg bw/day	**60 mg/kg bw/day:** clinical signs, ↑ thymus wt, ↑ single cell necrosis of the liver (♀); ↑ kidney wt (♂); ↑ liver wt, hepatocellular vacuolation (periportal) and centrilobular hypertrophy (♂/♀). **400 mg/kg bw/day:** ↑ mortality (♀); ↑ adrenal wt (♂/♀).

20-week dietary Schroter et al. (1987)as reported in ATSDR (2004) α-HCH or β-HCH (purity not stated)	Rat, Wistar Dose levels not stated (only the dose levels at which effects occurred were reported)		**2 mg/kg bw/day α-HCH:** preneoplastic hepatic foci. **3 mg/kg bw/day β-HCH:** preneoplastic hepatic foci. **Supplemental**
6-month dietary Gautam et al. (1989) as reported in ATSDR (2004) Lindane (purity not stated)	Rat, Charles Foster Dose levels not stated (only the dose levels at which effects occurred were reported)		**3 mg/kg bw/day:** 9 bwg **Supplemental**
1-year dietary Dikshith et al. (1991) as reported in ATSDR (2004) Lindane (purity not stated)	Rat, strain not stated Dose levels not stated (only the dose levels at which effects occurred were reported)		**2 mg/kg bw/day:** 8 liver wt. **20 mg/kg bw/day:** focal necrosis, hepatocyte hypertrophy, vacuolation, margination, nuclear pyknosis. **Supplemental**
18-month dietary Shahid and Shakoori (1998) as reported in ATSDR (2004) Lindane (purity not stated)	Rat, Sprague Dawley Dose levels not stated (only the dose levels at which effects occurred were reported)		**9 mg/kg bw/day:** 8 cell, nucleus and nucleolus size, cytoplasmic vacuolation, fatty degeneration. **Supplemental**
102-week dietary Aymes (1993) Lindane (purity not stated)	Rat, Wistar (50/sex/dose) 0, 1, 10, 100 or 400 ppm (calculated to be 0, 0.05/0.06, 0.47/0.59, 4.81/6.00, or 19.66/24.34 mg/kg bw/day in ♂/♀)	NOAEL = 0.47/0.59 mg/kg bw/day LOAEL = 4.8/6.0 mg/kg bw/day	**≥4.81/6.00 mg/kg bw/day:** ↑ liver and spleen wt, ↑ periacinar hepatocyte hypertrophy (♂/♀); ↓ survival (♂). **19.66/24.34 mg/kg bw/day:** ↓ survival (♀); ↓ BW (♂); adverse haemolysis, convulsions (♂/♀). Survival: 36, 36, 31, 20, and 16%, (♂) and 49, 38, 44, 35, and 18% (♀). Benign adrenal pheochromocytomas: 14, 16, 16, 6 and 24% Malignant adrenal pheochromocytomas: 0, 0, 6, 8, and 2%. **Evidence of carcinogenicity**

80-week dietary Lindane (100%)	Rat, Osborne-Mendel (10/sex for controls and 50/sex/dose for treated animals) 0, 236 or 472 ppm (calculated by to be 0, 11.8/14.2 or 23.6/28.3 mg/kg bw/day in ♂/♀) Control diet fed to all animals for 30 weeks following the 80-week dosing period-prior to sacrifice.		**≥11.8/14.2 mg/kg bw/day:** ↑ total carcinomas and sarcomas (p<0.01, ♂/♀), ↑ thyroid adenomas (♀) and carcinomas (♂/♀), ↑ pituitary carcinomas (♂/♀); ↑ adrenal gland carcinomas (♂/♀), ↑ malignant tumours of the ovary, ↑ liver adenomas "metamorphosis fatty" (♂/♀) and liver carcinomas (♂) Limited study protocol and reporting. **Supplemental**
Dog			
90-day dietary Noel et al. (1969) as reported in WHO (2002) Lindane (>99%)	Dog, Beagle (4/sex/dose) 0, 25, 50 or 100 ppm (0, 0.25, 0.50 or 1.0 mg/kg bw/day)		No toxicity noted in this study. Only blood parameters measured. No details on possible necropsy protocol were provided. **Supplemental**
2-year dietary Rivett et al. (1978) as reported in WHO (2002) Lindane (>99%)	Dog, Beagle (4/sex/dose) 0, 25, 50 or 100 ppm (0, 0.83, 1.6 or 3.2 mg/kg bw/day)	NOAEL = 0.83 mg/kg bw/day LOAEL = 1.6 mg/kg bw/day	**≥0.83 mg/kg bw/day:** ↑ spleen wt (♂/♀). *(considered adaptive)* **≥1.6 mg/kg bw/day:** adrenal cytoplasmic vacuolation. **3.2 mg/kg bw/day:** ↑ AP, enlarged, dark and friable livers (♂/♀).
Rabbit			
90-day dermal (1990) Lindane (99.5%)	Rabbit, New Zealand White 30/sex/dose with 10/sex/dose terminated at 6 weeks. 0, 10, 60 or 400 mg/kg bw/day (approximate doses calculated based on volume administered) in 5% CMC), 6 hours/day, 5 days/week	NOAEL = 10 mg/kg bw/day LOAEL = 60 mg/kg bw/day	**60 mg/kg bw/day:** centrilobular hypertrophy (♂/♀); ↑ adrenal gland wt (♂).

Reproduction and Developmental Toxicity			
Study	**Species, Strain and Doses**	**NOAEL and LOAEL mg/kg bw/day**	**Target Organ, Significant Effects, Comments**
Prenatal developmental toxicity (1976) Lindane (purity not stated)	Rat, 20/dose. 0, 5, 15 or 30 mg/kg bw/day by subcutaneous injection Gestation days 6–15.		**Maternal** **≥15 mg/kg bw/day:** ↓ bw. **Developmental** No toxicity identified Deficiencies: route of administration was subcutaneous, purity of the test material was not provided, dosing solutions were not analysed, less than 20 litters/group were available, many of the individual maternal and fetal data were not included. **Supplemental**
Prenatal developmental toxicity (1971) Lindane (purity not stated)	Rat, CFY (20/dose) 0, 5, 10 or 20 mg/kg bw/day in 0.5% CMC by gavage from gestation days 6 to 15.	**Maternal** NOAEL = 5 mg/kg bw/day LOAEL = 10 mg/kg bw/day **Developmental** NOAEL = 10 mg/kg bw/day LOAEL = 20 mg/kg bw/day	**Maternal** **≥10 mg/kg bw/day:** ↓ bw and fc. **Developmental** **20 mg/kg bw/day:** skeletal variation. Study was considered acceptable despite the following deficiencies: purity of the test material was not provided, less than 20 litters/group were available, dosing solutions were not analysed and many of the individual animal data were not included. **Supplemental**

Prenatal developmental toxicity (1976) Lindane (purity not stated)	Rabbit, New Zealand White 15/dose 0, 5, 10 or 15 mg/kg bw/day by subcutaneous injection Gestation days 6–18.		**Maternal** **15 mg/kg bw/day**: clinical signs, mortality, ↓ bw. **Developmental** No toxicity identified but high dose pups were not examined. Deficiencies: route of dose administration was subcutaneous, excessive mortality at the high dose, purity of the test material was not provided, dosing solutions were not analysed, much of the individual data was not provided, gross necropsy data were difficult to interpret due to the poor copy quality of the study report **Supplemental**
Prenatal developmental toxicity (1971) Lindane (purity not stated)	Rabbit, New Zealand White (13/dose) 0, 5, 10 or 20 mg/kg bw/day by gavage from GD 6 to 18	**Maternal** NOAEL < 5 mg/kg bw/day LOAEL = 5 mg/kg bw/day **Developmental** NOAEL < 5 mg/kg bw/day LOAEL = 5 mg/kg bw/day	**Maternal** **≥5mg/kg bw/day:** ↑ respiration and drowsiness during dosing period (resolved after the cessation of dosing), ↓ maternal bwg (GD 10-14; 55, 66 and 61% at 5, 10 and 20 mg/kg bw/day); bw similar to controls for remainder of the study (final bws were 97, 98 and 103% of controls at 5, 10 and 20 mg/kg bw/day). **Developmental** **≥5mg/kg bw/day:** ↓ live fetus/dam (9.3, 8.0, 7.8 and 7.1 at 0, 5, 10 and 20 mg/kg bw/day), ↑ fetal loss (8.9, 13.2, 15.3 and 25.5% at 0, 5, 10 and 20 mg/kg bw/day) **20 mg/kg bw/day:** ↓ ossification of sternebrae. **Evidence of sensitivity**

2-generation reproduction and fertility effects (1991) Lindane (purity not stated)	Rat, Charles River CD 30/dose. 0, 1, 20 or 150 ppm in the diet P generation doses: 0, 0.081/0.092, 1.61/1.90 or 12.0/14.18 in ♂/♀ F1 generation doses: 0, 0.088/0.09, 1.60/1.73 or 12.4/13.69 mg/kg bw/day in ♂/♀	**Parental** NOAEL = 0.081/1.90 mg/kg bw/day LOAEL = 1.61/13.69 mg/kg bw/day **Reproductive** NOAEL = 0.081 mg/kg bw/day LOAEL = 1.61 mg/kg bw/day	**Parental** **≥1.61 mg/kg bw/day:** ↑ kidney wt (absolute and relative; P ♂), ↑ interstitial nephritis, tubular cell degeneration, hyaline droplets, tubule necrosis and casts (P and F1 ♂), periacinar hepatocellular hypertrophy (F1 ♂). **13.69 mg/kg bw/day:** ↑ kidney wt (absolute and relative; F1 ♂); ↑ kidney wt (relative; P and F1 ♀), periacinar hepatocellular hypertrophy (P ♂; P and F1♀), ↓ bwg (11%, gestation) in P ♀. **Reproductive** **≥1.61 mg/kg bw/day:** ↓ viability index (99, 98, 93 and 81% for F1 pups at 0, 1, 20 & 150 ppm), delayed tooth eruption (F1 and F2 pups). **13.69 mg/kg bw/day:** ↓ pup bw, delayed hair growth (F2 pups), whole litter losses (3 during PND 1–4). **Sperm parameters and sexual maturation were not examined.** **Evidence of sensitivity**
Neurotoxicity			
Acute neurotoxicity screening battery (1999) Lindane (99.8%)	Rat, Crl:CD BR (10/sex/dose) 0, 6, 20 or 60 mg/kg bw by gavage	NOAEL (♀) = 6 mg/kg bw NOAEL (♂) = 20 mg/kg bw LOAEL (♀) = 20 mg/kg bw LOAEL (♂) = 60 mg/kg bw	**≥20 mg/kg bw :** ↑ grip strength and motor activity (♀). **60 mg/kg bw** tremors, convulsions, ↓ motor activity and ↑ grip strength. (♂).
Subchronic neurotoxicity screening battery (1999) Lindane (99.8%)	Rat, Crl:CD BR (10/sex/dose) 0, 20, 100 or 400 ppm (0, 1.4/1.6, 7.1/7.9 or 28.1/30.2 mg/kg bw/day in ♂/♀).	NOAEL =7.1/7.9 mg/kg bw/day LOAEL = 28.1/30.2 mg/kg bw/day	**28.1/30.2 mg/kg bw/day:** hypersensitivity to touch and hunched posture.

Developmental neurotoxicity (1999) Lindane (99.8%)	Rat, Han:Wistar (24 dams/dose) 0, 10, 50 or 120 ppm in the diet (0, 0.8, 4.2 or 8.0 mg/kg bw/day, based on gestational intake) from GD 6 to PND 10	**Maternal** NOAEL = 4.2 mg/kg bw/day LOAEL = 8.0 mg/kg bw/day **Offspring** NOAEL = 0.8 mg/kg bw/day LOAEL = 4.2 mg/kg bw/day	**Maternal** **8.0 mg/kg bw/day:** ↓ bwg (≈25%, GD 6-20) and ↓ fc. **Offspring** **≥4.2 mg/kg bw/day:** ↓ pup survival days 1-4 [pup (litter) incidence: 3 (2/20), 0, 18 (8/22), 14 (4/15) at 0, 10, 50 and 120 ppm], ↓ bw (12/16% and 17/18% in ♂/♀ at 50 and 120 ppm) and bwg (16/21% and 27/25% in ♂/♀ at 50 and 120 ppm) during lactation (based on gains for LD 1–4 and 1–11), ↑ motor activity, ↓ auditory startle. **8.0 mg/kg bw/day:** ↑ stillborn pups (live birth index of 77% compared to 99% in controls; total litter loss of 9 vs. 0 in controls). **Evidence of sensitivity**
Immunotoxicity			
Oxidative stress and immune suppression in rats Koner, Banerjee and Ray (1998) γ-HCH (97%)	Rat, Wistar 40 or 80 ppm in the diet (≈ 2 or 4 mg/kg bw/day) for 8 weeks		**≥40 ppm:** dose-dependent ↑ in serum thiobarbituric acid reactive substance, dose-dependent ↑ in superoxide dismutase activity in red blood cells, ↓ humoral immune response (assessed by anti-sheep RBC antibody titres). Simultaneous administration of ascorbic acid (100 mg/kg) attenuated effects on lipid peroxidation, superoxide dismutase activity, and humoral immune suppression. Results indicate possible involvement of free radicals in lindane-induced immunotoxicity.

Immunomodulatory effect of Lindane in mice Meera et al. (1992) Lindane (97%)	Mice, 0.012, 0.12 or 1.2 mg/kg bw/day in the diet for 24 weeks		**≥0.012 mg/kg bw/day:** **Week 4**: ↑ thymus medulla cellularity and ↓ thymus cortex cellularity, ↑ delayed type hypersensitivity reactions, ↑ lympho-proliferation to challenge, ↑ IgM plaque formation to antigen stimulation. **Week 12:** normal immune state. **Week 16:** ↓ delayed type hypersensitivity reactions, ↓ lympho-proliferation to challenge, ↓ IgM plaque formation to antigen stimulation. **Week 24:** loss of distinction between thymus cortex and medulla, depression of lymphocyte population, reduced cellularity of the spleen. Ability to respond to bacteria challenge not affected during the study. Literature paper lacks full data for evaluation. **Supplemental**
HCH effect on immune and antioxidant ability of the pig Wang et al. (2006) Technical Lindane	Pig (12/sex/dose) 0, 0.4 or 0.8 mg/kg bw/day in the diet for 90 days		**≥0.4 mg/kg bw/day:** ↑ kidney wt, serum IgG and serum IgM; ↓ superoxide dismutase, glutathione-S-transferase, glutathione reductase, serum catalase and glutathione peroxidase. Results demonstrate a stimulation of the immune system with damage to anti-oxidant systems in young pigs.

Genotoxicity Studies Conducted With Lindane			
Study	**Species/Strain or Cell Type**	**Doses Employed**	**Significant Effects/Comments**
Dominant lethal assay (1977) Lindane (99%)	Rat,	0, 1, 3 or 10 mg/kg bw/day by subcutaneous injection, 5 days/week for 10 weeks	Negative Study was unacceptable due to several deficiencies: no positive control group, the criteria for toxicity were inadequate, animal age was not given, insufficient number of pregnant dams were produced for meaningful evaluation and no rationale was provided for the dose selection, route of administration and dose regime used.

| Gene mutations in mammalian cells (1985)

Lindane (99.8%) | Chinese Hamster V79 cells | 0.5 - 500 µg/ml

Tested with/without metabolic activation, under aerobic and anaerobic conditions | Negative

Study was unacceptable due to several deficiencies: no statistical analysis performed, solvent control values were variable, the anaerobic positive control did not produce a positive response, no verification that anaerobic conditions were achieved. |
|---|---|---|---|
| Comet assay to determine DNA damage in vitro (2002)

Lindane (99%) | Human epithelial tonsil cells | 0.5, 0.75 or 1.0 mM | Positive

Lindane at 0.5, 0.75 or 1.0 mM induced single and double strand DNA breaks in human epithelial tonsil cells. |
| Comet assay to determine DNA damage in vitro (2005)

Lindane (99%) | Human nasal mucosal cells | 0.5, 0.75 or 1.0 mM | Positive

Single and double strand DNA breaks. |
| Micronucleus assay in vitro (2004)

Lindane (purity not stated) | Human breast and prostate cells in culture | 10^{-12} to 10^{-10} M | Positive

Lindane at 10^{-12} - 10^{-10} M induced micronuclei in human breast and prostate cells in culture. Cytotoxicity was not noted until much higher concentrations (10^{-4} M). Lindane caused more micronuclei than either the α- or β-HCH isomers. |
| **Additional Genotoxicity Studies Extracted from WHO (2002)** | | | |
| **In vitro** | | | |
| Bacterial reverse mutation

Röhrborn (1977a) | *S. typhimurium* TA1535, TA1538, TA100, TA98 | 0.93 to 210 µg/plate in DMSO | Negative |
| Bacterial reverse mutation

Röhrborn (1975) | *S. typhimurium* TA1535, TA1538 | 0.31 to 5 mg/ml in DMSO

± S9 | Positive ± S9 |
| Bacterial reverse mutation
Oesch (1980) | *S. typhimurium* TA1535, TA1537, TA100, TA 98; *E. coli* WP2 uvrA | 16 to 5000 µg/plate | Negative |
| Gene mutations in mammalian cells

Glatt (1984) | V79 Chinese hamster, HPRT locus | ± S9, 0.5 to 500 µg/ml | Negative |

Gene mutations in mammalian cells Oesch and Glatt (1985)	V79 Chinese hamster, HPRT locus	+ S9, 5 to 500 µg/ml - S9, 2 to 50 µg/ml	Negative
Chromosomal aberrations Murli (1990)	V79 Chinese hamster, ovary cells	+ S9, 25 to 300 µg/ml	Positive
DNA Repair Cifone and Mckeon (1990)	Fischer 344 rat hepatocytes	0.05 to 15 µg/ml in DMSO	Negative
Aneuploidy Albertini et al. (1998)	*S. cerevisiae* D61.M	0.003 to 0.17 mmol/l	Negative
In vivo			
Chromosomal aberration Röhrborn (1976)	Chinese hamster, bone marrow	0 to 12 mg/kg bw/day for 5 days by gavage	Positive β-HCH also demonstrated a positive result.
Sister chromatid exchange Guenard (1984a)	Mouse, CF-1, bone marrow	♂: 0, 2, 10 or 50 mg/kg bw/day ♀: 1.6, 8 or 40 mg/kg bw day	Negative
Sister chromatid exchange Guenard (1984b)	Mouse, CF-1, bone marrow	0, 1.3, 6.4 or 32 mg/kg bw/day	Positive
Dominant lethal mutation Frohberg and Bauer	Mouse, NMRI 10/dose.	0, 12.5, 25 or 50 mg/kg bw/day administered IP	Negative
Dominant lethal mutation Röhrborn (1977b)	Rat, Chbb:THOM	0, 1.5, 7 or 15 mg/kg bw/day, 8 weeks, via gavage	Negative

Special Studies - NOTE: Effect levels were not set in the special studies due to study limitations.			
Study	**Species, Strain and Doses**	**Target Organ, Significant Effects, Comments**	
Special Studies Conducted With Lindane (γ-HCH) of Known Purity			
Oral			
Reproductive toxicity and tissue concentrations of lindane in adult male rats Dalsenter et al. (1996a) γ-HCH (99.5%)	Rat, Wistar (15/dose) Single dose: 0 or 30 mg/kg bw in peanut oil by gavage Repeat oral dose: 0 or 6 mg/kg bw/day in peanut oil by gavage for 5 days	**Single dose:** **30 mg/kg bw:** 40% ↓ in number of spermatids and 30% ↓ number of sperm 2 weeks after treatment (p≤0.05), ballooning of Sertoli cells accompanied by fragmentation. **Repeat dose:** **6 mg/kg bw/day**: 20% ↓ in number of spermatids 2 weeks after treatment (p≤0.05), ↓ number of sperm (not statistically significant). Lindane detected in testes of animals from both groups 24 hours and 2 weeks post-treatment (467 and 770 ng/g 24 hours after 5 doses of 6 mg/kg bw/day or a single dose of 30 mg/kg bw, respectively) No effect of treatment noted in thymus, brain, heart, spleen or liver. **NOTE: testes, epididymal, seminal vesicle and ventral prostate weights in both treated groups were all comparable to controls, sperm morphology was unaffected, no clinical signs of toxicity were observed**.	
Reproductive toxicity and toxicokinetics of lindane in the male offspring of rats exposed during lactation	Rat, Wistar (9/dose) Single dose: 0 or 6 mg/kg bw in peanut oil by gavage to maternal animals, on LD 9 or 14	**Single dose:** **6 mg/kg bw (dosed either on day 9 or 14):** ↓ relative testes wt (10%), ↓ number of sperm, ↓ number of spermatids, ↓ testosterone during puberty and adulthood.	

Dalsenter et al. (1997) γ-HCH (99.5%)	Repeat dose: 0 or 1 mg/kg bw/day by gavage to maternal animals from LD 9 to 14	↓ # of Leydig cells, necrosis in the layers of spermatocytes of the 1st and 2nd order, loosening of the germinal epithelium with enlarged intercellular spaces and cell debris in the lumen on both day 60 and day 140. **Repeat dose:** **1 mg/kg bw/day:** ↓ relative testes wt (10%), ↓ number of sperm, ↓ number of spermatids, ↓ testosterone during puberty and adulthood Maternal examinations or possible toxicity not reported. Concentration of lindane in testes (≈300 ng/g 24 hours post maternal dosing) found to be comparable to that in the brain and approximately half that of liver.	
Changes in sexual behaviour of male offspring after exposure to lindane during lactation Dalsenter et al. (1996b) γ-HCH (99.5%)	Rat, Wistar (9 dams/dose) 0 or 6 mg/kg bw by gavage corn oil on LD 9. 20 ♂ offspring mated at day 130, reproductive behaviour recorded for 15 min.	**6 mg/kg bw:** ↓ ejaculation (3/20 versus 12/20 in control), ↓ testosterone level (27%). Offspring had liver lindane levels that were one-third the level in maternal animals at 24 hours post dosing. Level in testes of offspring was half of level in offspring liver. Maternal examinations or possible toxicity not reported.	
Serum testosterone and sexual behaviour in rats after prenatal exposure to lindane Dalsenter, Faqi, Chahoud (1997) γ-HCH (99.5%)	Rat, Wistar (20 dams/group) 0 or 30 mg/kg bw by gavage in corn oil, single dose on GD 15 45 ♂ offspring/group examined for reproductive effects	**30 mg/kg bw:** ↓ number of spermatids (23%) at PND 100 (normal at PND 130), possible ↓ in exploratory reproductive activities (i.e. libido), ↓ in copulation (14/15 in control, 1/15 in treated group within 15 min.), ↓ serum testosterone (43%) in male offspring of	

	15 ♂ offspring/group examined for resistant spermatids and caudal sperm count. 15 7-month old ♂ offspring/group used for sexual behaviour assessment	treated females at 7 months of age. No effect of treatment on birth weight or pup viability. Maternal examinations or possible toxicity not reported.	
Embryotoxicity of Lndane in the Golden Hamster Dzierzawski (1977) Lindane (99%)	Hamster, Golden (9/dose) 0, 20 or 40 mg/kg bw by gavage in rape oil on GD 8	**≥20 mg/kg bw:** ↑ Retarded growth, resorbed fetuses, underdeveloped cranial bones	
Embryotoxicity of Lindane in the Albino Rat Dzierzawski (1977) Lindane (99%)	Rat, Albino (10/dose) 0, 50 or 100 mg/kg bw by gavage in rape oil on GD 9 or at 40 mg/kg bw/day on GD 6, 8 and 10	**Single dose:** **≥50 mg/kg bw:** resorbed fetuses**,** underdeveloped cranial bones. **100 mg/kg bw:** retarded fetal growth. **Repeat dose:** **40 mg/kg bw/day:** retarded fetal growth, resorbed fetuses, underdeveloped cranial bones.	
Embryotoxicity of Lindane in the Rabbit Dzierzawski (1977) Lindane (99%)	Rabbit, (9/dose) 0, 40 or 60 mg/kg bw by gavage in rape oil on GD 9	**40 mg/kg bw:** ↑ dead fetuses, ↑ resorbed fetuses, retarded fetal growth. **60 mg/kg bw:** fetuses with open eyes.	
2-generation reproduction toxicity study with endocrine endpoints Matsuura et al. (2001) Lindane (99.5%)	Rat, Crj:CD(SD)IGS (24/sex/dose) 0, 10, 60 or 300 ppm starting 10 weeks prior to initial mating and continuing for 2 successive generations 10 ppm determined to be approximately 0.5 mg/kg bw/day. Literature paper with limited summary data.	**Parental** **≥10 ppm:** hepatocyte hypertrophy, ↑ liver wt, ↑ CYP2B, CYP1A, CYP3A and UDP-GT activities (♂/♀); hyaline droplets in kidneys (♂). **≥60 ppm:** hepatocyte hypertrophy (♀); thyroid follicular cell hypertrophy (F1) (♂). **300 ppm:** ↓ bwg and fc (F0 and F1), ↑ adrenal wt, ↓ pituitary wt (F1), ↑ TSH, ↓ T3/4 (♂/♀); mortality, ↓	

		pituitary wt (F0), thyroid follicular cell hypertrophy (F0) (♀). **Offspring** **≥60 ppm:** ↓ bwg, spleen and thymus wts (♂/♀). **300 ppm:** delayed sexual maturation, ↓ survival (lack of maternal care) (♂/♀).	
TCDD, endrin and lindane induced increases in lipid metabolites in maternal sera and amniotic fluids of pregnant C57BL/6J and DBA/2J mice Hassoun et al. (1996) Lindane (>98%)	Mice, C57BL/6J and DBA/2J 4/dose 30 mg/kg bw, single oral dose on GD 12 (fetotoxic dose)	**C57BL/6J:** **30 mg/kg bw:** 1.5- to 2.0-fold increase in maternal serum lipid metabolites (malondialdehyde, formaldehyde, acetaldehyde, acetone), 1.3- to 1.7-fold increase in amniotic fluid lipid metabolites (malondialdehyde, formaldehyde, acetaldehyde, acetone). **DBA/2J:** **30 mg/kg bw**: 1.2- to 1.5-fold increase in maternal serum lipid metabolites (malondialdehyde, formaldehyde, acetaldehyde, acetone), 1.1- to 1.5-fold increase in amniotic fluid lipid metabolites (malondialdehyde, formaldehyde, acetaldehyde, acetone). Lindane induces oxidative stress and enhanced lipid peroxidation in fetal and placental tissues. Effects observed regardless of Ah-responsiveness of mice. Lipid peroxidation may be related to fetotoxicity.	

Dermal			
Hexachlorocyclo-hexane and its isomers: regional brain levels in the rat after dermal exposure Kumar, Pant, Srivastava (1998) Technical HCH* (12.5% γ-HCH) *Study is included in pure γ-HCH section of table as levels of HCH isomers are assessed individually. Thus, paper is still of value in describing the accumulation of γ-HCH	Rat, Druckery (♂) 50 or 100 mg/kg bw/day in acetone for 60 or 120 days Brain levels of HCH determined at 61 and 121 days.	Technical-HCH generally accumulates in dose- and time-dependent manner in specific regions of brain (corpus striatum, hypothalamus, hippocampus, midbrain, cerebellum, cerebral cortex), which may adversely affect the specific physiological function of these brain regions. γ-HCH accumulation did not appear to be dose-dependent in hypothalmus or cerebral cortex, and did not appear to be dose- or time-dependent in cerebellum. Dose- and time-dependent accumulation appeared to take place in other brain regions.** **Based on assessment of graphical data presented in published paper.	
In vitro			
Effects of Lindane on testosterone metabolism in neuroendocrine organs of male rat Simic and Kniewald (1985) γ-HCH (99.5%)	0.17 to 0.51 μM	**0.17 - 0.51 μM:** inhibition of 5α-reductase (up to 48% inhibition), 3α-hydroxysteroid dehydrogenase (up to 41%) and 17β-hydroxysteroid dehydrogenase (up to 29%) in the anterior pituitary. Inhibited activity of 5α-reductase (up to 39%) in hypothalamus.	

A novel aspect of lindane testicular toxicity: *in vitro* effects on peritubular myoid cells Silvestroni et al. (1999) γ-HCH (99%)	0 to 200 μM	Polarity increase and decrease of dipole dynamics at membrane level (EC_{50} = 20 μM), leading to partial dissipation of the membrane intrinsic dipole potential, ↑ $[Ca^{2+}]_I$ (EC_{50} = 125 μM). Inhibition of $[Ca^{2+}]_I$ increase and contraction induced by natural agonists vasopressin and endothelin-1 (IC_{50}s < 10 μM). This occurs at levels far below those that alter ion homeostasis. Peritubular myoid cells are highly susceptible to lindane, and the testicular toxicity may occur by interfering with hormone-regulated peritubular myoid cell function.	
Antioxidants prevent Lindane-induced inhibition of rat myometrial gap junctions and contractions *in vitro* Krieger and Loch-Caruso (2001) γ-HCH (99%)	100 μM	Time-dependent biphasic inhibition of gap junctional intercellular communication and inhibition of oscillatory contractions of pregnant rat myometrium in vitro, increased lipid peroxidation. Effects reversed by treatment with antioxidants. Observations support hypothesis that lindane acts by establishing an oxidative stress environment.	
Lindane modification of uterine muscle Loch (1997) γ-HCH (99%)		Eliminated gap junctional communication in cell cultures of rat uterine smooth muscle, rapid ↑ in $[Ca^{2+}]_I$ concentration. Note: Abstract refers to effects on parturition, with no specific details given.	

| Transmembrane potential, oxidative activity and ATP-induced calcium release in cultured bovine oviductal cells

Tiemann et al. (1998)

γ-HCH (99.7%)	8 to 128 μM	Lindane had no effect on transmembrane potential, oxidative activity, cytotoxicity and ATP-induced intracellular Ca^{2+} release.	
Inhibitory effects of organochlorine pesticides on intercellular transfer of Lucifer Yellow in cultured bovine oviductal cells

Tiemann and Pohland (1999)

γ-HCH (99.7%) | 8 to 128 μM, incubated for 1 or 5 hours | **1 hour:**
≥ 16 to 128 μM: dose-dependent inhibition of gap junctional intercellular communication (significant at 32 μM).

5 hours:
≥ 8 to 64 μM: dose dependent-inhibition of gap junctional intercellular communication (significant at 32 μM).

Inhibition of gap junctional intercellular communication not associated with a detectable increase in $[Ca^{2+}]_I$.

Results suggest that lindane can influence cells involved in reproduction. | |
| Effects of organochlorine pesticides on DNA synthesis of cultured oviductal and uterine cells and on estrogen receptor of uterine tissue from heifers

Tiemann and Schneider (1996)

γ-HCH (99.7%) | 41 to 200 μM | **41 to 200 μM:** inhibition of DNA synthesis in cultured oviductal endosalpingeal and uterine cells (greater sensitivity in uterine epithelial and stromal cells than in uterine smooth muscle or oviductal endosalpingeal cells).

No effect on estradiol binding to uterine endometrial explants. | |

Special Studies Conducted With Lindane (γ-HCH) of Unknown Purity			
Oral			
Hormone disruptive effects of residual doses of lindane in male rats exposed at prenatal and postnatal periods Pages et al. (2000)	Rat, Sprague Dawley (> 5 ♂/group) 0.5, 1 or 2 ppb (1.7, 3.4, 6.8 μM*) in drinking water exposure started i) in utero, ii) during lactation or iii) at weaning, and lasted for 12 weeks. *Values reported for conversion are incorrect. Numeric values correspond to a conversion from ppb values to nM rather than to μM.	**2 ppb** (exposure commencing in utero or during lactation): ↓ bw at 12 weeks **2 ppb** (unclear from abstract when exposure commenced): ↓ spermatozoid number, ↓ spermatozoid mobility rate, ↓ testosterone (52%). ↓ pup survival rate and ↑ newborn mortality when treated ♂s mated with treated ♀s. Note: Study gives contamination levels for France of 80–50 μg/kg for vegetables and 0.02 μg/L for tap water as justification for dose levels. Demonstrates potential testicular effects at environmental exposure levels.	
Sperm quality in male offspring of female rabbits exposed to Lindane during pregnancy Fausto et al. (2001)	Rabbit, Grimaud (15 ♀) 1 mg/kg bw/day by gavage in corn oil during gestation (starting on GD 8) and every other day during lactation (continuing to PND 35). Male offspring assessed for reproductive parameters.	No effect on pup growth or litter size. No effect on mating time, volume of ejaculates, or total sperm counts. ↑ incidence of sperm with cytoplasmic droplets and coiled tails, indicative of sperm with incomplete maturation.	
Impairment of testosterone metabolism in male mice Di Consiglio et al. (2003)	Mice, CD-1 (pregnant ♀ 25 mg/kg bw/day by gavage from GD 9 to 16	The formation of testosterone hydroxylase metabolites was disrupted in male mice on PNDs 55 and 70, but had recovered by PND 100. There was no effect of treatment on structure of the testes	

		No maternal toxicity noted in this study.	
Histomorphometric analysis of mouse uteri prenatally exposed to Lindane Maranghi et al. (2003)	Mice, CD-1 (pregnant ♀;) 0 or 15 mg/kg bw/day by gavage in corn oil from GD 9 to 16 ♀ offspring were assessed on PND 60	Lindane exposure increased the rate of vaginal opening in the absence of maternal toxicity. The ratio of endometrium to myometrium was reduced in the uteri of female offspring.	
Influence d'une teneur elevée en Lindane (isomere gamma de l'hch) dans un regime equilibre chez la truie reproductrice Duee et al. (1977)	Pig (30 dams) 0, 50 or 500 ppm in the diet during gestation and lactation After birth, each dose group was divided int two groups: one that continued to receive the dose, one that did not (resulting in 6 groups of 5). At day 14, piglets started being fed food (20-40 piglets/dose).	Maternal food consumption and body-weight gain were not affected by the treatment. Litter size was not affected. At weaning, pups that were exposed to 500 ppm had a 30% deficit in body weight compared to control (2 groups). At 2 months, a 26% deficit in body weight was observed in the 500 ppm group. Food consumption was not affected but growth was slowed.	
Transfer of Lindane from mother to newborn rabbit Pompa et al. (1994)	Rabbit, New Zealand White (8/dose) 0 or 5 mg/kg bw/day in corn oil from GD 15 to 21	No maternal toxicity was noted. Offspring were noted to have increased liver wt on PND 5 and 10. Maternal Lindane levels were highest in liver and adipose tissue. Fetal lindane concentration was highest in liver and brain, while newborns had high lindane concentration in brain, lung, liver. Lungs of newborns were also noted to have high [pentachlorobenzene] suggesting that lungs may be an important site of lindane metabolism.	
Reproductive and endocrine function in rams exposed to Lindane from conception Beard et al. (1999)	Lamb 0 or 1 mg/kg bw/day in the diet Maternal animals (13/dose) dosed from 5 weeks prior to mating until weaning at 8	Semen collected from 19 weeks onward, reproductive behaviour assessed at 26 weeks. Serum collected every two weeks, and every 15 min at 27 weeks for 6 hours during both day and night, and for	

γ-HCH (10% commercial formulation, purity unknown, dose levels expressed as mg/kg lindane)	weeks post partum, male offspring (7 ♂ in control group; 12 ♂ in treated group) received dietary treatment from weaning until > 90% of the animals had reached puberty at week 28. Animals necropsied at week 28.	1 hour before and 5 hours after stimulation with GnRH, adrenocorticotropic hormone and thyroid-stimulating hormone. **1 mg/kg bw/day:** ↓ serum LH and ↓ serum oestradiol during reproductive development, ↓ LH pulse frequency at 27 weeks, ↓ testosterone secretion after GnRH treatment, ↓ reproductive behaviour.	
Pituitary, thyroid and testis function in rams exposed to Lindane from conception Beard et al. (1997) γ-HCH (10% commercial formulation, purity unknown, dose levels expressed as mg/kg lindane)	Ram 1 mg/kg bw/day in the diet Mternal animals (13/group) dosed from 4 weeks prior to mating to 26 weeks post partum, (assumed that offspring received dietary treatment from weaning until week 28). Assessed body weight, serum parameters, reproductive behaviour in offspring (7 ♂ in control group; 12 ♂ in treated group).	**1 mg/kg bw/day:** ↓ libido, ↓ serum LH during reproductive development (41%), ↓ LH pulse frequency (54%, 58% for day and night, respectively), ↓ serum oestradiol (40%, 31% for day and night, respectively), ↓ in elevation of testosterone secretion (34%) and endogenous LH production following GnRH Reduced LH and testosterone secretion may result in decreased libido.	

Endocrine and reproductive function in ewes exposed to Lindane Beard, et al. (1999) γ-HCH (10% commercial formulation, purity unknown, dose levels expressed as mg/kg lindane)	Ewe (13 adult ♀/group) 0 or 1 mg/kg bw/day in the diet for 5 weeks premating to weaning.	**1 mg/kg bw/day:** ↓ pregnancy rate, ↑ thyroid follicle size. Assessed mating response, ovulation rate, follicle and corpus luteum size, gestation length, pregnancy rate, lambing rate and lamb birth weight, serum concentrations of lutenizing hormones, follicle stimulating hormone, thyroxin (T4), cortisol, and histopathology of endocrine tissues in ewes.	
Thyroid function and effects on reproduction in ewes exposed to lndane from conception Beard et al. (1999) γ-HCH (10% commercial formulation, purity unknown, dose levels expressed as mg/kg lindane)	Ewe (6 ♀ lambs in control group; 8 ♀ lambs in treated group 1 mg/kg bw/day in the diet, maternal animals treated from 5 weeks prior to mating until weaning, offspring received dietary treatment from weaning at week 8 postpartum until week 67 postpartum. Assessed reproductive performance and serum parameters.	**1 mg/kg bw/day:** ↓ serum T4 (returned to normal by week 10 postpartum), ↓ corpora lutea, ↓ corpora lutea volume, ↑ lutenizing hormone pulse frequency, ↓ length of estrous cycle, ↓ luteal progesterone concentrations. No effects on fertility following mating during natural estrous periods, effects on reproduction only after estrous synchronization.	
Effects of lindane on the metabolic endocrine and reproductive endocrine system in ewes Rawlings et al. (1998) γ-HCH (10% commercial formulation, purity unknown, dose levels expressed as mg/kg lindane)	Ewe (6 adult ♀/group) 0 or 2.5 mg/kg bw, oral (capsule), 2 times per week for 43 days Blood sampled every 12 minutes for 6 hours on day 36.	**2.5 mg/kg bw:** ↓ serum thyroxine, ↑ serum insulin, ↑ serum estradiol, ↓ basal serum LH concentrations. No overt signs of toxicity or body-weight effects.	

Dermal			
Plasma absorption and ultrastructural changes of rat testicular cells induced by lindane Suwalsky et al. (2000) Plomurol® Formulation *1% Lindane)	Rat, strain not stated (4 males/group) 60 mg/kg bw/day dermal, single dose and repeat dose for 4 days	**Single dose:** **60 mg/kg bw/day:** peak plasma concentration at 6 hours. **Repeat dose:** **60 mg/kg bw/day:** concentration of 7.4 µg/g in testicular tissue (4 times plasma concentration), damage or complete disintegration of Leydig cells. 60 mg/kg is recommended dose for treatment of scabies and pediculosis in many countries.	
Intraperitoneal			
Lindane induced changes in morphology and lipids profile of testes in rats Chowdhury et al (1990)	Rat (adult), 4 or 8 mg/kg bw/day by intraperitoneal injection for 45 days	**≥4 mg/kg bw/day:** ↓ bw, ↓ testicular wt, testicular degeneration (partial breakage of peritubular membrane, disintegration or germinal cells, presence of pyknotic nuclei), intratubular edema, ↓ tubular diameter, ↓ spermatogenic cell count, ↓ Leydig cell diameter, ↑ testicular lipid components (cholesterol), fatty degeneration in testicular tissues, ↓ accessory organ weight suggesting androgen deficiency. **8 mg/kg bw/day:** changes in seminiferous tubules (dissolution of germinal cells, presence of cellular debris in lumen), ↑ testicular lipid components (total lipids, triglycerides, cholesterol).	

In vitro			
Influence of organochlorine pesticides on maturation and postfertilization development of bovine oocytes in vitro Alm et al. (1998) DDT, methoxychlor, γ-HCH	7.25, 14.5 or 29.0 µg/mL Effects of lindane on maturation rate, day 2 cleavage rate and day 7 and 8 blastocyte rates, assessed after in vitro fertilization.	**≥7.25 µg/mL γ-HCH:** significant difference in number of morulae and blastocytes on day 7 and 8, chromatin degeneration. Dose-dependent decrease in rate of normal oocyte formation.	
Steroidogenic gene expression: adrenotoxic effects of Lindane Oskarsson et al. (2006)	Human cell line H295R used to assess gene expression in adrenal tissue	Lindane exposure inhibited cortisol secretion, downregulated genes responsible for steroidogenic enzymes, inhibited steroidogenic acute regulatory protein (StAR) required for production of steroidal hormones.	
Influence of organochlorine pesticides on development of mouse embryos in vitro Alm et al. (1996) DDT, methoxychlor, γ-HCH	Eight-cell stage mouse embryos 3.625, 7.25, 14.5 or 29 µg/mL Effect of lindane on preimplantation mouse embryos in culture evaluated by the proportion of eight-cell stage embryos developing to hatched blastocytes.	Relative toxicity: methoxychlor < HCH < DDT **7.25 µg/mL γ-HCH:** 77.6% blastocyte formation, 35.5% hatched blastocytes. **14.5 µg/mL γ-HCH:** 66.7% blastocyte formation, 22.9% hatched blastocytes. **29 µg/mL γ-HCH:** complete degeneration of embryos.	

Partition of the organochlorine insecticide Lindane into the human sperm surface induces membrane depolarization. Silvestroni et al. (1997)	5 to 50 µM	Induces rapid, transient and reproducible membrane depolarization and opening of voltage-dependent Ca^{2+} channels leading to an increase in $[Ca^{2+}]_I$. Ca^{2+} and K^+ found to drive lindane-induced membrane depolarization and repolarization, respectively. Partitions into sperm plasma membrane lowering water molecular dynamics in uppermost region (external leaflet) of membrane. Evidence suggests that lindane alters membrane dipole potential, resulting in activation of membrane located Ca^{2+}-influx pathways.	
Effects of Lindane on steroidogenesis and steroidogenic acute regulatory protein expression Walsh and Stocco (2000)	Mouse MA-10 Leydig tumour cell line	Hypothesized that lindane inhibits steroidogenesis by reducing StAR protein expression, which may contribute to reproductive dysfunction. Dose-dependent inhibition of dibutyryl([Bu](2)) cAMP-stimulated progesterone production in MA-10 cells without affecting general protein synthesis. Inhibition of protein kinase A and/or steroidogenic enzyme expression activity. Dramatic inhibition of (Bu)(2)cAMP-stimulated steroidogenic acute regulatory (StAR) protein levels.	

Testosterone metabolism and formation of cytosol 5alpha-dihydrotestosterone-receptor complex in the rat prostate *in vitro*: effects of lindane and malathion Simic et al. (1992)		**γ-HCH:** Inhibition of formation of 5alpha-DHT, ↓ in formation of 5alpha-androstane-3,17-dione (androstanedione) in rat prostate tissue. Noncompetitive inhibition of 5alpha-DHT-receptor complex formation in prostatic cytosol. Lindane and malathion exerted a synergistic effect on testosterone metabolism in the prostate as indicated by ↓ 5alpha-DHT formation, ↑ 5alpha-androstane-3alpha, 17 beta-diol formation.	
HCH cytotoxicity by oxidative stress and Na^+, K^+-ATPase inhibition Srivastava (2006)	Cell cultures were exposed to lindane to determine the mode of cytotoxicity	Lindane was noted to produce cytotoxicity mainly be inhibiting antioxidant mechanisms. Glutathione depletion, lipid peroxidation and production of reactive oxygen species secondary to inhibition of superoxide dismutase and catalase were noted. Cellular repolarization was disrupted as indicated by Na^+-K^+-ATPase inhibition; which could precipitate cytotoxic damage.	

Influence of environmental toxicants, lindane and DDT on *in vitro* cultured bovine oviduct epithelial cell function McNutt-Scott et al. (1998)	50 to 500 μM, 30 hours	**≥ 250 μM:** cell death in partially confluent oviduct epithelium monolayers 17.5%, 33% at 250, 500 μM, respectively), (L-stage cells more sensitive than F-stage cells, cells from isthmus region more sensitive than cells from ampula region), modifications of proteins. Dose- and time-dependent toxicity observed.	
Special Studies Conducted With Technical Grade HCH			
Oral			
Benzene hexachloride (BHC) induced testicular impairments in rats Chowdhury and Gautam (1990) Technical grade BHC (mixture of several stereo isomers)	Rat, strain not stated 3 or 6 mg/kg bw/day in the diet for 180 days	**6 mg/kg bw/day:** ↓ testicular weight, degeneration of seminiferous tubules with deformed spermatogenic cells. BHC residue in testis indicates that BHC can cross blood-testis barrier.	
Effects of Lindane on mouse spermatogenesis following in utero exposure Traina et al. (2003) Technical grade HCH	Mouse, CD-1 15 or 25 mg/kg bw/day by gavage from GD 9 to 16. Male offspring were assessed for sperm parameters on PND 60 and 100.	**≥15 mg/kg bw:** ↓ sperm count in testes on PND 60. No maternal toxicity noted.	
Effects of Lindane on oocyte maturation in the mouse Scascitelli and Pacchierotti (2003) Technical grade HCH	Mouse, CD-1 (16-20/dose) 0, 15 or 25 mg/kg bw/day by gavage for 3 days immediately following mating	**25 mg/kg bw/day:** ↑ number of embryos damaged as fragmented blastomeres.	

Age-related change in rat testicular ATPase activities in response to HCH treatment. Roy (1996) Technical grade HCH	Rat, (5 animals/dose/age group; 30 or 90 days old) 0, 10 or 20 mg/kg bw/day by oral intubation in olive oil for 7, 15 and 30 days	**30-day-old rats:** **≥10 mg/kg bw/day:** dose-dependent ↑ activity of Ca^{2+}-Mg^{2+}-ATPase at Day 7 and Day 15, dose-related ↑ Mg^{2+}-ATPase at Day 7, non dose-related ↑ in Mg^{2+}-ATPase at Day 15. **20 mg/kg bw/day:** ↓ Mg^{2+}-ATPase at Day 30. **90-day-old rats:** **≥ 10 mg/kg bw/day:** non dose-dependent ↓ Ca^{2+}-Mg^{2+}-ATPase at 7 days, non dose-dependent ↑ activity of Ca^{2+}-Mg^{2+}-ATPase at Day 15 and Day 30 of treatment, non dose-related ↓ in Mg^{2+}-ATPase at Day 7, non dose-related ↑ in Mg^{2+}-ATPase at Day 15, and Day 30 Testicular ATPase response to HCH is dose-, duration- and age-dependent.	
Age-related changes in rat testicular oxidative stress parameters by hexachlorocyclo-hexane Samanta et al (1999) Technical grade HCH (23.8% γ-HCH)	Rat, Wistar 15 or 90 days old 10 or 20 mg/kg bw/day, oral, in groundnut oil for 7, 15 and 30 days	↓ cytosolic superoxide dismutase activity (SOD; total and CN(-)-resistant, ↓ catalase activity, ↓ ascorbic acid content, ↑ in lipid peroxidation (crude homogenate and subcellular fractions), ↑ in peroxide, ↑ testicular glutathione peroxidase (Gpx; total and non-selenium-dependent) activity, ↓ total epididymal sperm number, ↑ dead and damaged spermatozoa, ↑ in sperm with anomalous heads. Results suggest that alterations in testicular antioxidant defence profile are dependent on duration of treatment and age.	

A limited three-generation reproduction study on hexachlorohexane (HCH) in rats Srivastava and Raizada (2000) Technical grade HCH	Rat, Druckrey (10♂ & 20 ♀/group) 0, 125 or 250 ppm in the diet (≈ 0, 6.25 or 12.5 mg/kg bw/day)	No adverse effects on reproductive function. Mild toxicological effects in P0 generation, no morphological or teratogenic changes in offspring. Presence of HCH residues in vital tissues of F3b pups indicated transmigration of HCH in preceeding generations.	
Dermal			
Effect of dermal application of hexachlorocyclo-hexane (HCH) on male reproductive system of rat. Prasad et al. (1995) Technical grade HCH 98.01% (42.66% α-, 38.40% β-, 12.65% γ-, 4.03% δ-HCH)	Rat, 50 or 100 mg/kg bw/day, dermal, 5 days per week, for 120 days	Alterations of sorbitol dehydrogenase, glucose-6-P-dehydrogenase, gamma-glutamyl transpeptidase and beta-glucuronidase associated with specific cell type. Significant accumulation of HCH and isomers in testes and sperm. ↓ Serum testosterone levels, ↓ epididymal sperm count, ↓ sperm motility, ↑ percentage of abnormal sperm.	
In vitro			
The mechanism for lindane-induced inhibition of steroidogenesis in cultured rat Leydig cells. Ronco et al. (2001) Technical grade lindane (98%)	Rat, Wistar mature males 2-200 μg/mL	Dose dependent inhibition of testosterone production in human chorionic gonadotropin-stimulated Leydig cells associated with a half-reduced LH/hCG receptor number without any modification in the K-d value, ↓ cAMP production. Effects not due to detrimental action on cell viability, but rather result from a direct inhibitory action of lindane on testicular steroidogenesis, partially through a reduction in the classical second messenger production involved in this pathway.	

Special Studies Conducted With HCH of Unspecified Isomeric Composition			
Oral			
Comparative teratological studies on TCDD, endrin and lindane in C57BL/6J and DBA/2J mice Hassoun and Stohs (1996)	Mouse, C57BL/6J and DBA/2J (5-7/group) 30 or 45 mg/kg bw, single oral dose in corn oil, on gestation day 12	**C57BL/6J:** **≥ 30 mg/kg bw:** ↓ fetal weight, ↓ placental weight, dose-ependent ↓ in fetal thymic weight. **DBA/2J:** **≥30 mg/kg bw:** ↓ fetal weight, ↓ placental weight. Maternal mortality (14 to 25%). Fetotoxic effects may involve mechanisms unrelated to the Ah-receptor.	
Oxidative stress and histopathological changes of the heart following Lindane dosing Ananya et al.(2005). Lindane (purity not stated)	Rat, 1.5 or 7 mg/kg bw/day for 21 days. Cardiac tissue examined for biochemical and histological changes. Strain and other details omitted	**≥1.5 mg/kg bw/day:** Lipid peroxidation with decreased GSH levels. Interstitial edema, loss of integrity of the myofibrils, Z-bands and mitochondrial disruption. **7 mg/kg bw/day:** ↑ SOD and catalase.	
In vitro			
Sertoli cells as targets for reproductive hazards Monsees et al. (2000) Lindane (purity not stated)	Rat cultured sertoli cells 25, 50 or 100 μM	**≥50 μM:** ↑ mitochondrial dehydrogenase, inhibin B (regulates FSH) and lactate secretion. No effect on sertoli cell viability.	
Growth stimulation of a rat pituitary cell line MtT/E-2 by environmental estrogens *in vitro* and *in vivo* Maruyama et al. (1999) HCH	Study used an estrogen-responsive (E-2) pituitary cell line	Lindane competed with 3H-E2 binding to the estrogen receptor. Little or no induction of cell growth but strong stimulation of ERE dependent transcription activation.	

Human Data			
Health surveillance and biological monitoring of pesticide formulations in India Kashyap (1986) as reported in ATSDR (2004)	19 workers in a lndane formulating plant	Workers exposed occupationally over a 10 year period were reported to have elevations in liver enzymes (LDH, leucine aminopepidase and GGT).	
Effects of organochlorine xenobiotics on human spermatozoa Silvestroni and Palleschi (1999)	0, 0.1, 1, 5, 15 or 30 μM	Lindane intercalates into sperm membrane and alters the molecular dynamics of the bilayer. Doses of lindane as low as those found in human female genital tract* secretions inhibit the sperm cytological responsiveness to progesterone, the physiological agonist which stimulates the onset of acrosome reactions at the site of fertilization. *Referring to levels in Wagner et al. (1990), in which lndane levels were determined in women with fertility problems.	
Non-Hodgkin's lymphoma and agricultural use of the insecticide lindane Blair et al. (1998) as reported in ATSDR (2004)	987 farmers with occupational exposure to lindane examined	Lindane use significantly increased the odds of developing Non-Hodgkin's lymphoma by 50%. Risks were increased for farmers with initial exposure greater than 20 years previously and with > 5 days of exposure per year than in farmers with less exposure.	

Table 2   Toxicology Endpoints for Health Risk Assessment for Lindane

Exposure Scenario	Dose (mg/kg bw/day)	Endpoint	Study	UF/SF or MOE
Acute dietary	NOAEL = 0.8	Reductions in auditory startle response and increases in motor activity	Developmental neurotoxicity—rat	300
	ARfD = 0.0027 mg/kg bw			
Chronic dietary	NOAEL = 0.47	Decreased survival and liver and spleen toxicity	2-year dietary oncogenicity—rat	1000
	ADI = 0.0005 mg/kg bw/day			
Short- and intermediate-term dermal	Dermal NOAEL = 10	Liver and thymus toxicity	90-day dermal toxicity—rat	1000
Short- and intermediate-term inhalation	Inhalation NOAEL = 0.08	Decreased survival and spleen and thymus toxicity	90-day inhalation toxicity—mouse	1000
Cancer		Liver tumours in rats and lung tumours in mice	2-year dietary oncogenicity—mouse and rat	Q_1* = 6.73 × 10^{-2} (mg/kg bw/day)$^{-1}$

Appendix IV   Summary of Occupational Risk Estimates for Lindane

Summary of Studies Used to Estimate Occupational Risk for Lindane

<u>Commercial Seed Treatment Facilities:</u>

A commercial seed treatment study (Jones and Korpalski study, 2004) was submitted by the registrant. This study was considered to be representative of closed transfer equipment. Dermal and inhalation exposure was measured for workers treating canola seed with a commercially available liquid product, Helix® (active ingredient: thiamethoxam), in commercial closed transfer system facilities. The study was conducted at three different commercial seed treatment plants in Canada and monitored 18 workers representing three job categories (treaters, baggers/sewers/stackers and cleaners). Workers wore Tyvek coveralls over street clothes (generally long sleeved shirts and long pants) and chemical-resistant gloves. Workers also wore additional personal protective equipment (PPE) as specified by the product label when necessary, such as dust masks. Potential dermal exposures were measured using whole-body dosimeters, hand washes and face/neck wipes. Inhalation exposure was monitored using personal air sampling pumps.

There were a number of major limitations with this study:

> - *Whole Body Dosimeters were Corrected for Unacceptably Low Field Recovery:* Field recoveries for whole body dosimeters averaged 2.2% and all were less than 10%. This issue lends major uncertainty to the dosimeter data and, therefore, compromises the validity of the entire study.

> -*Loss of Samples:* Eight replicates had some loss of the handwash sample due to cracked or broken jars; 2 replicates had incomplete face wipe samples due to dropped or discarded samples; 1 replicate had the complete face wipe sample lost; final hand wash was not conducted for 2 replicates; 1 of 3 inner dosimeter field fortification samples from one site was lost during sample preparation. It is unknown what the effect these lost samples would have on the results of the dermal exposure estimates; unit exposure values were not corrected to estimate for sample losses.

> -*The Relevance of Helix to Lindane is Unknown:* Although Helix is used on the same crops as lindane, there is uncertainty regarding the relevance of the Helix formulation as a surrogate for the proposed lindane products. Summary dust-off data from Chemtura suggests that the lindane product used in the study would produce more dust than Helix; however, the full data package has not been received from the registrant at this time.

> -*Potential Contamination of Field Blanks*: Blank handwash samples from the Vermilion and Camrose sites, blank face/neck wipes from the Vermilion site and blank air sampling tubes from the Rivers site had detectable thiamethoxam residues greater than the LOQ (level of quantification) for that matrix. Because only one sample was collected, it is difficult to determine the cause of detectable residues in the blank samples.

-*Number of Field Fortification Events*: Ideally, field fortifications should be conducted on each day of the study. In this study, it was conducted on one day at each site. This is considered to be a minor limitation.

-Other limitations with this study include some discrepancies in the study report regarding monitoring times and limited information provided regarding the equipment and facilities, as well as ventilation and environmental conditions.

Due to the considerable uncertainty in using this study's data, arising primarily from the low field recovery of the inner dosimeters, sample loss, and other major limitations, the PMRA corrected study results for field recovery and selected an upper percentile (90th) for the non-cancer assessment and arithmetic mean for the cancer assessment to take these uncertainties into account.

Table 1   Unit Exposure Metrics Determined from Jones and Korpaski (2004)

| Exposure Metric | Unit Exposures (ug a.i./kg a.i. handled)[a] | | | |
| | Treaters (n=15) | | Baggers/Sewers/Stackers (n=17) | |
	Dermal	Inhalation	Dermal	Inhalation
AM	57.31	0.22	27.42	0.27
90th	138.34	0.45	68.66	0.46
Unit Exposure Values as applied in the assessment (Maximum PPE and respiratory protection)[b]				
AM	55.2	0.022	27.14	0.027
90th	137.71	0.045	68.26	0.046

AM= arithmetic mean, 90[th] = 90th percentile

[a]   Values are representative of closed transfer and workers wearing chemical resistant coveralls over a single layer and chemical resistant gloves. Inhalation unit exposure values were determined using personal air sampling pumps and are not representative of any respiratory protection.

[b]   PPE: Chemical resistant coveralls over a single layer, chemical resistant headgear, chemical resistant gloves and a respirator (for treaters) or a dust mask (for baggers/sewers/stackers). Includes 90% protection factor to the head and neck for headgear, 90% protection factor for a respirator or a 50% protection factor for a dust mask.

On-Farm Seed Treatment and Planting:

An on-farm seed treatment and planting study (Belcher and Korpalski, 2007) was submitted by the registrant. In this study, 16 farmers performing on-farm cereal seed treatment (barley, wheat, oat) at 16 different locations in the Canadian prairies were monitored for potential exposure to workers treating seed and handling treated seed for planting (i.e. loading, calibration, planting, repair). Vitaflo 280 Fungicide containing the active ingredients carbathiin and thiram was used in the study. Although a variety of different treatment techniques were observed, all were considered to be typical of Canadian on-farm techniques. Workers wore long-sleeved shirts and long pants over cotton inner whole body dosimeters. Additional protective gear worn by all workers during the treating and planting activities included cloth coveralls, a dust mask, goggles, chemical resistant gloves and shoes plus socks. Dermal exposure estimates for workers were

based on the sum of hand exposure, head/neck exposure and inner dosimeter. Inhalation was monitored using personal air sampling pumps with an attached OVS sorbent tube.

Although the study was conducted according to current guidelines and the overall study design was acceptable, there were a number of limitations that may result in an underestimation of inhalation exposure and add a level of uncertainty to the study results. Major limitations include the following:

-*Relevance of the Test Chemical to Lindane is Unknown.* Although there are similarities in the use pattern of lindane and carbathiin (formulation, crops, etc), it is unknown how the dust-off potential compares between the two chemicals as there was no dust-off study performed. Summary dust-off data from Chemtura suggests that the lindane product used in the study would produce more dust than Helix; however, the full data package has not been received from the registrant at this time.

-*Low Recoveries for OVS Tubes:* A majority of the inhalation residues were corrected using a low field fortification value (<50%). As most (69%) of the inhalation residues were corrected using the low field recovery value of 45.3%, there is a high degree of uncertainty with the inhalation unit exposure results.

-Other limitations contributing to the uncertainty of the study results include low inhalation flow rate, low field recoveries (sample matrix means range 45.3–78.7 %), field recoveries not performed for each site, only one field blank collected at each field fortification event, and the unknown solubility of the test chemical in the extracting solution.

Due to the uncertainties in the inhalation residue data from correcting a majority of the inhalation residue values using a low field recovery, low flow rate, relevance of the test chemical to lindane and other limitations, the 90th percentile was considered to be the most appropriate exposure metric to estimate non-cancer risk for inhalation exposure. The arithmetic mean was used for the cancer assessment (Table 2).

Table 2   Unit Exposure Metrics Determined from Belcher and Korpaski (2007)

Exposure Metric	Unit Exposures (ug a.i./kg a.i. handled)[a]	
	Dermal	Inhalation
AM	100.3	20.6
90th	N/A	52.3

AM = arithmetic mean, 90th = 90th percentile; N/A = not applicable

[a]   Values are representative of workers wearing coveralls over a long-sleeved shirt, long pants, goggles, shoes plus socks, chemical resistant gloves and using closed cab seeding equipment. Inhalation unit exposure values were determined using personal air sampling pumps and are not representative of any respiratory protection.

The inhalation unit exposure value determined from this study was a single value that represents multiple activities: workers treating seeds, loading treated seed into planting equipment and planting seed using a closed cab. As the respiratory protection required for each activity varies, a respiratory protection factor cannot be applied to the inhalation unit exposure value.

Planting of Treated Seeds:

Dean (1989) monitored four workers at four sites in Manitoba planting canola seed treated with isofenphos. Seed treatment included a polymeric seed coating. Each half-day replicate included monitoring of work activities, which included manually loading treated seed into the hopper and planting. Closed cab tractors were used to pull the planters. Dermal exposure was monitored using inner and outer patch dosimeters and hand rinses. Face/neck exposure was monitored using a patch on the worker's cap, just above the bill. Inhalation exposure was monitored through the use of personal air sampling pumps. Exposure values were representative of a single layer and gloves. Some of the limitations in the study include small sample size, results of field blank samples not provided or reported, only one fortification level for air filter field recovery samples, method validation studies not conducted for the handwash solution and some minor QA/QC limitations.

Although this study was used by the PMRA to assess exposure to farmers planting treated seeds, there is considerable uncertainty as to how the unit exposure values from this study, which was performed on canola, would compare to planting wheat, especially considering that wheat does not often use polymeric coatings, which are known to reduce dust, and wheat has been observed in dust-off studies to produce more dust than canola when tumbled. As such, this study may underestimate exposure to workers planting seeds treated with lindane.

Table 3   Unit Exposure Metrics Determined from Dean (1989)

Exposure Metric	Unit Exposures (ug a.i./kg a.i. handled)[a]	
	Dermal	**Inhalation**
AM	424.17	1.11
Unit Exposure Values as applied in the assessment (Maximum PPE)b		
AM	298.57	same

AM = arithmetic mean

[a]   Values are representative of workers wearing a long-sleeved shirt, long pants, chemical resistant gloves, and using closed cab seeding equipment. Inhalation unit exposure values were determined using personal air sampling pumps and are not representative of any respiratory protection.

[b]   PPE: Chemical resistant coveralls over single layer and chemical resistant gloves. Includes a 90% protection factor for chemical resistant coveralls.

Table 4 Occupational Non-Cancer Risk Estimates For Proposed Lindane Seed Treatment Use

Crop	App Rate (g a.i./kg seed)	Data Source	Amt. Seed Handled (kg/day)	Derm Unit Exp (µg/kg handled)	Derm Expa (µg/kg/day)	Inhal Unit Exp (µg/kg handled)	Inhal Expa (µg/kg/day)	Dermal MOE[b]	Inhal MOE[b]
Commercial Seed Treatment (Treaters): Closed system, PPE = chemical resistant coveralls, chemical resistant headgear, gloves and respirator								**Target = 1000**	
Canola/Mustard	15.3	Jones and Korpalski (2004)	40000	55.20[c] (AM)	483	0.022[d] (AM)	0.19	21	416
Wheat	0.39		65000		20		0.01	500	10041
Barley	0.49		65000		25.1		0.01	398	7992
Canola/Mustard	15.3		40000	137.71[c] (90th)	1204	0.045[d] (90th)	0.39	8	203
Wheat	0.39		65000		50		0.016	201	4909
Barley	0.49		65000		63		0.02	160	3907
Commercial Seed Treatment (Baggers/Sewers/ Stackers): Closed system, PPE = chemical resistant coveralls, chemical resistant headgear, gloves and dust mask								**Target = 1000**	
Canola/Mustard	15.3	Jones and Korpalski (2004)	40000	27.14[c] (AM)	237	0.14[f] (AM)	1.18	42	68
Wheat	0.39		65000		9.8		0.05	1018	1636
Barley	0.49		65000		12.3		0.06	810	1304
Canola/Mustard	15.3		40000	68.26[c] (90th)	597	0.30[f] (90th)	2.01	17	40
Wheat	0.39		65000		25		0.08	405	960
Barley	0.49		65000		31		0.1	322	764
On-Farm Seed Treatment and Planting: Open system, closed cab planting, PPE = coveralls over single layer and gloves								**Target = 1000**	
Wheat	0.39	Belcher and Korpalski (2007)	7000	100.3 (AM)	3.91	20.6 (AM)	0.08	2560	100
Barley	0.49		7000		4.91		0.101	2040	79
Wheat	0.39		7000	100.3 (AM)	3.91	52.3 (90th)	0.205	2560	39
Barley	0.49		7000		4.91		0.257	2040	31

Crop	App Rate (g a.i./kg seed)	Data Source	Amt. Seed Handled (kg/day)	Derm Unit Exp (µg/kg handled)	Derm Expa (µg/kg/day)	Inhal Unit Exp (µg/kg handled)	Inhal Expa (µg/kg/day)	Dermal MOE[b]	Inhal MOE[b]
Planting Treated Seed: Open system, closed cab, PPE = Chemical resistant coveralls over single layer and gloves								**Target = 1000**	
Canola/ Mustard	15.3	Dean (89)	600	298.57[e] (AM)	39	1.1 (AM)	0.14	255	555
Wheat	0.39		7000		11.6		0.04	859	1865
Barley	0.49		7000		14.6		0.05	684	1484

App= application; Exp= Exposure; Derm= dermal; Inhal = Inhalation; Comb= Combined; gloves= chemical resistant gloves, AM= arithmetic mean; 90th = 90th percentile

Shaded cells indicate where the MOE is less than the target.

a   Where exposure (µg/kg/day) = (unit exposure × application rate × amount of seed handled per day)/70 kg bw

b   Dermal MOE is based on a dermal NOAEL of 10 mg/kg/day, target is 1000. Inhalation MOE is based on an inhalation NOAEL of 0.08 mg/kg bw/day, target is 1000.

c   Incorporates a 90% protection factor to the head and neck exposure for chemical resistant headgear.

d   Incorporates a 90% protection factor for respirator.

e   Incorporates a 90% protection factor for chemical resistant coveralls.

f   Incorporates a 50% protection factor for dust mask.

Table 5   Occupational Cancer Risk Estimates For Lindane

Crop	Data Source	10% Dermal Absorption					35% Dermal Absorption				
		ADD[a]	LADD[b]	Cancer Risk[c]			ADD[a]	LADD[b]	Cancer Risk[c]		
				Q1*: 0.0371	Q1*: 0.0673	Q1*: 0.0836			Q1*: 0.0371	Q1*: 0.0673	Q1*: 0.0836
Commercial Seed Treatment (Treaters): Closed system, PPE = chemical resistant coveralls, chemical resistant headgear, gloves, and respirator											
Canola/ Mustard	Jones and Korpalski (2004)d	0.05	6.37 E-03	2.4 E-04	4.3 E-04	5.3 E-04	0.17	2.22 E-02	8.3 E-04	1.5 E-03	1.9 E-03
Wheat		0.00	2.86 E-04	1.1 E-05	1.9 E-05	2.4 E-05	0.01	9.21 E-04	3.4 E-05	6.2 E-05	7.7 E-05
Barley		0.00	3.53 E-04	1.3 E-05	2.4 E-05	3.0 E-05	0.01	1.16 E-03	4.30 E-05	7.8 E-05	9.7 E-05
Commercial Seed Treatment (Baggers/Sewers/Stackers): Closed system, PPE = chemical resistant coveralls, chemical resistant headgear, gloves, and dust mask											
Canola/ Mustard	Jones and Korpalski (2004)d	0.02	3.14 E-03	1.2 E-04	2.1 E-04	2.6 E-04	0.08	1.11 E-02	4.1 E-04	7.5 E-04	9.3 E-04
Wheat		0.00	1.52 E-04	5.7 E-06	1.0 E-05	1.3 E-05	0.00000	4.59 E-04	1.7 E-05	3.1 E-05	3.8 E-05
Barley		0.00	1.85 E-04	6.9 E-06	1.3 E-05	1.6 E-05	0.00	5.76 E-04	2.1 E-05	3.9 E-05	4.8 E-05
On-Farm Seed Treatment and Planting: Open system, closed cab planting, PPE = coveralls over single layer, and gloves											
Wheat	Belcher and Korpalski (2007)d	0.00	5.24 E-06	1.9 E-07	3.5 E-07	4.4 E-07	0.00	9.52 E-06	3.5 E-07	6.4 E-07	8.0 E-07
Barley		0.00	6.58 E-06	2.4 E-07	4.4 E-07	5.5 E-07	0.00000	1.20 E-06	4.4 E-07	8.0 E-07	1.0 E-06

Crop	Data Source	10% Dermal Absorption					35% Dermal Absorption				
		ADD[a]	LADD[b]	Cancer Risk[c]			ADD[a]	LADD[b]	Cancer Risk[c]		
				Q1*: 0.0371	Q1*: 0.0673	Q1*: 0.0836			Q1*: 0.0371	Q1*: 0.0673	Q1*: 0.0836
Planting Treated Seed: Open system, closed cab, PPE = Chemical resistant coveralls over single layer and gloves											
Canola/ Mustard	Dean (89)	0.00	1.78 E-05	6.6 E-07	1.2 E-06	1.5 E-06	0.01	6.07 E-05	2.3 E-06	4.1 E-06	5.1 E-06
Wheat		0.00	5.29 E-06	2.0 E-07	3.6 E-07	4.4 E-07	0.00	1.81 E-05	6.7 E-07	1.2 E-06	1.5 E-06
Barley		0.00	6.65 E-06	2.5 E-07	4.5 E-07	5.6 E-07	0.01	2.27 E-05	8.4 E-07	1.5 E-06	1.9 E-06

Shaded cells indicate where the cancer risk is greater than the $1 \times 10\text{-}4$ (i.e. 1 E-04).

a   ADD = Absorbed Daily Dose (mg/kg bw/day) = daily dermal dose + daily inhalation dose from Table I.B.1. Range of dermal absorption factors applied to the dermal dose (10-35%).

b   LADD = Lifetime Average Daily Dose (mg/kg bw/day) = ADD × treatment frequency × working duration/ (365 days × 75 years). Treatment frequency = 90 days for commercial facilities, 3 days for on-farm treatment and planting. Working duration = 40 years.

c   Cancer risk = LADD × Q1*. The range of Q_1* from the toxicological data base was used (0.0371 - 0.0836 (mg/kg bw/day)$^{-1}$) in addition to the average Q_1* (0.0673 ((mg/kg bw/day)$^{-1}$).

d   ADD was calculated using the arithmetic mean unit exposure values from Table I.B.1.

Appendix V   Dietary (food and water) Exposure and Risk Estimates for Lindane

Table 1   Acute Dietary Exposure Risk of Lindane on Main Canadian Population

Population	95%		99%		99.9%	
	Exp	ADI (%)	Exp	ARfD (%)	Exp	ARfD (%)
General Population	0.92	34	1.82	68	3.70	139
All infants	.59	22	1.66	62	4.37	164
Nursing infants (<1 yr old)	.14	5	0.87	32	3.65	137
Non-nursing infants (<1 yr old)	.72	27	1.90	71	4.55	171
Females 13–19 (not preg or nursing)	.78	29	1.42	53	2.45	92
Females 20+ (not preg or nursing)	.61	23	1.08	40	2.12	79
Males 13–19 yrs	1.05	39	1.96	73	5.57	208
Males 20+ yrs	.84	31	1.50	56	3.01	113
Children 1–2 yrs	2.04	76	3.55	133	5.93	222
Children 3–5 yrs	1.85	69	3.23	121	6.04	226
Children 6–12 yrs	1.33	50	2.27	85	3.98	149
Youth 13–19 yrs	.92	35	1.68	63	3.62	135
Adults 20–49 yrs	.78	29	1.43	54	2.93	110
Adults 50+ yrs	.59	22	1.06	40	2.03	76

Notes: Probabilistic evaluation of exposure at three percentile levels. **Exp**: Exposure $\mu g.kg_{BW}^{-1}.day^{-1}$; **ARfD(%)**: Exposure expressed as percent of Acute Reference Dose (2.7 $\mu g.kg_{BW}^{-1}.day^{-1}$ for whole population). Monte-Carlo iterations = 500, seed = 1.

Table 2   Chronic and Cancer Exposure Risk for Lindane on the Main Canadian Population

Population	Chronic		Cancer
	Exp	ADI (%)	Q* (10^{-6})
General Population	0.237	47	16
All infants	0.1430	29	
Nursing infants (<1 yr old)	0.0480	10	
Non-nursing infants (<1 yr old)	0.1790	36	
Females 13-19 (not preg or nursing)	0.2060	41	
Females 20+ (not preg or nursing)	0.1480	30	
Males 13-19 yrs	0.3010	60	
Males 20+ yrs	0.2220	44	
Children 1-2 yrs	0.5490	110	
Children 3-5 yrs	0.5180	104	
Children 6-12 yrs	0.3670	74	
Youth 13-19 yrs	0.2550	51	
Adults 20-49 yrs	0.2050	41	
Adults 50+ yrs	0.1480	30	
Females 13-49 yrs	0.1710	34	

Notes: Probabilistic evaluation of exposure to main Canadian population. Acceptable Daily Intake (ADI) for whole population set at 0.5 $\mu g.kg_{BW}^{-1}.day^{-1}$. **Exp:** Exposure ($\mu g . kg_{BW}^{-1}.day^{-1}$); **%ADI**: Exposure expressed as percent fraction of ADI; **Q*:** Cancer risk expressed as ppm fraction of dose response slope (Q*=0.0673). Shaded entries denote concern.

Table 3   Drinking Water Level of Concern (DWLOC) for Lindane on Main Canadian Population

	DWLOC (µg/l)					
	GROUNDWATER		SURFACE			
			Reservoir		Dugout	
	Daily	Yearly	Daily	Yearly	Daily	Yearly
EEC (µg/l)	15.5	15.40	0.67	0.12	0.29	0.04
Cancer		0		0		0
General Population	61.3	9.2	61.3	9.2	61.3	9.2
All infants < 1yr	20.8	3.6	20.8	3.6	20.8	3.6
Children 1-2 years	9.5	0	9.5	0	9.5	0
Children 6-12 years	26.2	2.6	26.2	2.6	26.2	2.6
Females 13-49 yrs	61.8	10.2	61.8	10.2	61.8	10.2

Notes: Tier1 evaluation assuming no livestock residues. Shaded values denote concern. Asterix denotes concern for cancer established at maximal value for Q*. Estimates are based on 95th percentile for acute exposure (daily) and on chronic exposure (yearly). Shaded entries are above Estimated Environment Concentrations (EEC, tier1) and denote concern. Cancer estimates are derived from Q* values for the general population. Reference doses, acute: ARfD=2.67 µg/kg/day; chronic: ADI=0.5 µg/kg/day.

Table 4   Market and Traditional Dietary Exposure of Total HCH on Northern Population

Population		CHRONIC		CANCER	ACUTE					
		50	ADI (%)	Q* (10^{-6})	95	ARfD (%)	99	ARfD (%)	99.9	ARfD (%)
Children	Female	0.07	14	21.6	1.26	47	2.25	84	3.62	136
	male	0.08	16	24.9	1.34	50	2.51	94	4.43	166
Teen	Female	0.03	**7**	10.7	0.74	28	1.24	46	2.48	93
	male	0.06	11	18.1	1	37	1.89	71	3.95	148
Adult	Female	0.03	**7**	10.9	0.68	26	1.44	54	2.23	84
	male	0.05	11	17.1	0.9	34	1.67	62	2.94	110
Senior	Female	0.05	10	15.5	1.17	44	1.86	70	3.41	128
	male	0.05	11	17.2	1.19	45	1.9	71	3.63	136

Notes:Values estimated at percentile 50, 95, 99 and 99.9. Acute Reference Dose (ARfD) for whole population set at 2.7 µg . kg $_{BW}$$^{-1}$. day^{-1}, Acceptable daily intake (ADI), at 0.5 µg . kg $_{BW}$$^{-1}$. day^{-1}, and cancer dose response slope (Q*), at 0.317. **Exp**: Exposure (µg . kg$_{BW}$$^{-1}$.day^{-1}); **ARfD(%)**: Acute reference dose expressed as percent of ARfD; **ADI(%)**: Chronic Exposure expressed as percent fraction of ADI; **Q***: Cancer risk expressed as ppm fraction of Q*. Shaded entries denote concern.

Table 5   Drinking Water Level of Concern (DWLOC) for Lindane on Northern Population

DWLOC (µg/l) Northern Population		Amituk Lake	
		Daily EEC<0.007	Yearly EEC<0.002
Children	female	27	8
	male	21	7
Teen	female	59	14
	male	56	15
Adult	female	62	15
	male	67	17
Senior	female	50	15
	male	48	14

Notes: EECs from highest and median total HCH concentrations at Amituk lake (CACAR, 1997, page 98). Reference doses, acute: ARfD=2.67 µg/kg/day; chronic: ADI=0.5 µg/kg/day. **EEC**: Estimated Environmental concentrations.

Table 6   Lindane Residues Samples (CGC, 2006) for Canadian Grains Registered After 1997

Crop	Size (N)	detects	LOD (ppm)	Period		UCL95 (ppm) median = ½LOD
Barley	171	0	0.005	1994	2004	0.0041
Bean	17	0	0.009	1994	2003	0.0080
Canola	168	0	0.010	1994	2004	0.0075
Corn	54	0	0.006	1994	2003	0.0045
Flax	69	0	0.010	1995	2004	0.0079
Mustard	82	0	0.01	1994	2004	0.0078
Oat	96	0	0.005	1994	2004	0.004
Pea	136	0	0.010	1995	2004	0.0074
Rye	41	0	0.006	1994	2004	0.0048
Soybean	142	0	0.010	1994	2004	0.0076
Wheat	995	0	0.005	1994	2004	0.0038

Notes: Samples taken after harvest at the elevator. Size: sample size; detects: number of samples above LOD; LOD: average limit of detection for the indicated period. P95:95th percentile.

Appendix VI   Food Residue Chemistry Summary

1.1   Metabolism

Results from studies reviewed by Velde-Koerts and Ossendorp (2003) were generally found insufficient. Although a fraction of total radioactive residues (%TRR) was reported, several measurements of total residues concentration were missing, especially in the first days after treatment. Recoveries of radioactive residues also caused problems probably due to unaccounted volatilization of ^{14}C-lindane or matrix interferences.

1.1.1   Plant Metabolism

The PMRA considers plant metabolism studies of seed treatment to be inadequate because the remaining radioactive residues and equivalent concentrations exceed guidelines for metabolites (Dir98-02). Similarly, foliar application studies show significant concentrations of unidentified metabolites (apple) and incomplete determination of residues (cucumber, spinach). The situation has not changed since Daiss (2001). Therefore, the PMRA can only proceed with the assessment by assuming that all metabolites present in plant tissues have toxicity equal to lindane *per se*.

1.1.2   Livestock Metabolism

The PMRA concurs with the USEPA (Morton, 2001), which considered ruminant and poultry metabolism studies adequate if lindane per se is accepted as the only residue of concern. Pending acceptable plant metabolism studies, the USEPA considered total radioactive residue (TRR) as a conservative estimate of exposure from lindane and any of its metabolites.

1.1.3   Residue Definition

Since June 2008, Health Canada regulates pesticide residues in food under the *Pest Control Products Act*. The PMRA maintains a publicly available table "Residue Definitions for chemicals with MRLs Regulated under the PCPA, November 19, 2008" (PMRA 2008), wherein lindane is listed as the gamma isomer of benzene hexachloride (BHC). The table separately recognises all other non-lindane BHC isomers to protect the food supply from past usage of technical actives rich in alpha and beta isomers that may still affect certain imported commodities, such as ginseng root, or from trace residues in present lindane formulations. The PMRA proposes that the Residue Definition (RD) of non-lindane BHC isomers remain in force to allow monitoring of animal fat, in which these isomers are known to bioaccumulate. In the case of lindane (gamma isomer of BHC), the PMRA assigns relative toxicity of all lindane metabolites equal to the parent to compensate for insufficient metabolism studies on their fate and toxicity.

Considering the above, the PMRA proposes no changes to the entries in the Residue Definition table for lindane and other isomers of BHC, as "gamma isomer of benzene hexachloride (BHC)" adequately defines lindane per se as provisional residue of concern, and "all isomers of 1,2,3,4,5,6-hexachlorocyclohexane, except gamma BHC" defines all other isomers as residues of concern for surveillance and enforcement in livestock, poultry and dairy products.

1.2 Analytical Methods

The PMRA has a single residue method on file for the measurement of lindane on canola, wheat, oat and barley using gas chromatography and electron capture detection after purification by gel chromatography. The method has a LOD of 0.01 ppm and recoveries of 70%–80% (PMRA, 1233985). Presently, enforcement is done using multiresidue method PMR-001-V1.4. The PMRA has no studies on file for single residue determination of lindane in animal tissues. Presently, multiresidue method #CSP-008-V1.0 is used for enforcement

1.2.2 Multiresidue Analytical Methods

The USEPA has multiresidue methods #302 and #303 for fruits and vegetables, and method #304 for animal and dairy food (PAM manual, volume 1, Chapter 3). Limits of detection from the PDP program range from 0.1 to 0.8 ppb (1999-2001).

The CFIA uses method #CSP-008-V1.0, a multiresidue method applicable to the analysis of organochlorine pesticide residues in dairy and egg products (CFIA, 1999). Results are based on per gram fat for dairy products and total weight basis for egg products.

In fruits and vegetables, the CFIA (2004a) Method # PMR-001-V1.4 uses gas chromatography with mass specific detection (GC/MSD). An alternate method (#PMR-005-V1.1) for difficult matrixes of fruit and vegetables (CFIA, 2004b) uses the same analytical method with enhanced cleanup. CFIA methods are adequate for enforcement and monitoring.

1.3 Food Residues

Crops grown from treated seeds were monitored by the CFIA residue monitoring program. Fresh imported and domestic bean, broccoli, Brussels sprouts, cabbage, carrot, cauliflower and pea showed no detectable residues during 1998 to 2002 with LODs in the range of 0.0026 to 0.0051 ppm.

1.3.1 Storage Stability

Several storage stability studies were received by the USEPA; however, none are available to the PMRA. The FAO (Velde-Koerts and Ossendorp, 2003) cites the following studies for stability of pesticide residues in stored analytical samples: on wheat, Willard (1999, 2000) fortified samples with 0.05 mg/kg lindane and kept them at -20 $\pm 5^{o}$C. Recoveries of 75 to 102 % occurred up to 553 days. On canola, samples yielded 70 to 108 % after up to 198 days. In all cases, results were not corrected for concurrent method recovery (76-114%), nor for matrix interferences (<0.005 mg/kg).

For animals, cow milk fortified with 1.0 to 5.0 mg/kg lindane at -15°C for 265 days yielded 75 to 103% recovery; however, results were not corrected for method recovery, nor were matrix interferences stated (Merricks, 1987). Other studies were cited by FAO concerning storage stability in store-bought foods. Lindane in eggs, milk, beef and chicken appeared to be adequately recovered, but the studies lacked rigorous procedure or did not report results of control samples.

The PMRA provisionally accepts the above information from the FAO on weight of evidence, even if original studies are not available. This assessment could be refined with storage recovery studies.

1.3.2   Crop Residues

In a previous report (PMRA, 2001) the dietary burden associated with treated seeds was given the default value 0.1 ppm prescribed by the general maximum residue limit (GMRL[3]). This value exceeded dietary risk for children but could not be mitigated further due to lack of reliable data. In contrast, the Canadian Grain Commission's (CGC) monitoring of export grains held in elevators reported no detectable residues between 1994 and 2004, a period representative of lindane treatment both before and after its discontinuation in Canada. Given the importance of seed treatment in this review, the PMRA used a protective estimate of mean residues on grains the 95th percentile (P_{95}) for a log-normal distribution with all its values set below the limit of detection (LOD) except one above the LOD, and assuming a median of ½LOD. Appendix V, Table 6 suggests that treatment before discontinuation had no measurable effect on grain seed residues.

1.3.3   Livestock Residues

Dietary burden estimates were established from American data considering the relative toxicity of lindane metabolites, the recent cancellation of lindane in the United States and the lack of market shares information in Canada. The PMRA considered that even if the RD did not include lindane metabolites, calculations of dietary burden for livestock based on the TRR should take into account the possibility that some metabolites in livestock tissues, such as PCP, have toxicity comparable to or greater than the parent. Therefore, the PMRA adopted the USEPA's conservative approach by assuming that all TRR metabolites are equivalent to lindane (Morton, 2001). The Canadian livestock dietary burden was adjusted by the ratio of TRR/lindane to yield anticipated residues (Table 1). Imported dietary burden (mostly American) was considered essentially zero because its contribution was deemed adequately covered by this conservative approach and not likely to increase in light of the recent cancellation of all lindane in the United States.

Table 1   Anticipated Residues of lindane in livestock from feeding studies

| | Anticipated Residues (ppm) | | | | | |
| | Beef | | Poultry | | Swine | |
	Canada	United States	Canada	United States	Canada	United States
Muscle	0.152	0	0	0	0	0
Liver	0.08	0	0	0	0	0
Kidney/Heart	0.16	0	0	0	0	0
Fat	1.44	0	0.09	0	0.02	0
Milk/egg	0	0	0	0		

[1] Average from PDP monitoring program during 1996-1998 , using LOD for censored data
Residues were taken on the heart for poultry and on kidney for beef and swine.

1.3.4   Confined Accumulation in Rotational Crops

The USEPA's Revised HED risk assessment for lindane (Morton, 2001) stated that confined crop rotation studies were inadequate and indicated that lindane persists in the soil and can be taken up by plants for up to a year. New studies were required unless the registrant agreed to restrict usage to a 30-day plant-back interval for leafy vegetables and 12 months for everything else. American registrants accepted the restrictions. In 2002, the USEPA (2002) confirmed this decision, leaving the registrant with the option of conducting rotational crop studies in support of reducing the above restrictions.

The FAO (Velde-Koerts and Ossendorp, 2003) and the USEPA (Morton, 2001) reviewed the unpublished study of Hursman and Xiao (1991, not on file) conducted in California on lettuce, carrots and barley treated at 0.85 kg a.i./ha. Lindane was the only extractable species in soil and slowly degraded in time to nearly 73% of its initial amount, 267 days after treatment. Only lindane, and none of its soil metabolites, was available for uptake by plants. Accumulation of lindane residue ranged from 0.012 (lettuce) to 0.72 mg/kg (carrot) and wasgreatest at a planting interval of 121 days. Exposure of leaf surfaces to rain and sun explained the lesser accumulation in lettuce.

The PMRA has a study on crop rotation of potato and carrot, following planting of radish and cabbage on a field treated with 1.88 kg a.i./ha lindane (PMRA, 1222246). No residues (<0.005 ppm) accumulated in potatoes planted after one year even if soil still contained 0.12–0.13 ppm lindane. Carrots planted after one year retained 0.22– 0.4 ppm. No residues were found when planted in the second year, even if the soil still contained 0.006 ppm.

A lesser treatment of 1.5 kg a.i./ha in a field cultivated with sugar beet, summer wheat and corn showed similar results: when planted after one year, potatoes showed no residues, carrot had 0.1 ppm and soil contained 0.13 ppm. Another trial with unspecified vegetables treated at 1.5 kg/ha under glass showed low residues for potato (0.006 ppm), carrot (0.04 ppm) and soil (0.09 ppm). The authors concluded that residues accumulate in carrot but not in potato. In contrast, lindane

degraded more rapidly in the tropics. Agnihotri et al. (1977) found degradation of up to 99% after 180 days for a variety of organochlorines applied to an uncultivated sandy loam in India.

Considering the above, the PMRA concludes that lindane significantly accumulates in non-leafy crops in temperate climates as a function of its retention in soil, which can last for up to one year. The PMRA therefore accepts the USEPA's decision to restrict rotation crops to 30 days for leafy vegetables and 12 months for other commodities. This assessment can be refined with relevant field and confined rotational crop studies.

Appendix VII   Summary of Environmental Concentrations of Lindane, α-HCH and β-HCH

There are many reports of hexachlorocyclohexane (HCH) residues detected throughout North America in air (Jantunen and Bidleman, 1996; Poissant and Koprivnjak, 1996), precipitation (Blais et al., 1998 and Brun et al., 1991; Welch et al., 1991) and surface water (Alberta Environment, 1999; McConnell et al., 1998; Jensen et al., 1997; Ridal et al., 1997; Ridal et al., 1996; and Currie and Williamson, 1995). HCH residues were also detected in the Arctic (Li et al., 1998; Jantunen et al., 1996; and Muir et al., 1992) and Antarctic (Iwata et al., 1994; Iwata et al., 1993; and Tanabe et al., 1982).

The most common HCH isomers found in the environment are α-HCH, β-HCH, and lindane. Willett et al. (1998) report that α-HCH is the predominant isomer in air and ocean water and β-HCH, the predominant isomer in soils, animal tissues and fluids. Muir et al. (1995) found that β-HCH was the predominant isomer (45–65% of total HCH) in the sediments of four northwest Ontario lakes,and Chernyak et al.(1995) reported that β-HCH made up 13–15% of the total HCH in seawater samples. By contrast, concentrations of lindane and α-HCH are higher in Arctic lakes, indicative of the higher volatility of these isomers compared to β-HCH (Willett et al.,1998). In snowpack samples from the Northwest Territories, lindane and α-HCH made up more than 75% of the total organochlorines (Gregor et al., 1989). It was calculated that the annual loading of α-HCH, β-HCH and lindane to the Arctic was 4600, 78 and 820 kg, respectively (Li et al., 1998).

In Air

Elevated local air concentrations of lindane coincided with seeding periods. In Saskatchewan, lindane concentrations in air above a canola field were <0.1–6.1 ng/m^3 at 2–6 weeks following seeding with treated seed. In a grassy field 2 km away from the canola seeding, lindane concentrations in air were <0.01–2.9 ng/m^3 (Waite et al. 2001). At Villeroy, Québec in 1992, the mean lindane concentration of 0.037 ng/m^3 in air coincided with treated corn seeding (Poissant and Koprivnjak, 1996). A follow-up study in 1993–1995 again found that the highest lindane concentrations in air occurred during the spring corn-planting season. The ranges of concentrations found were 0.005–0.55 ng/m^3 at Villeroy and St. Anicet in southern Québec and 0.006–0.12 ng m/m^3 at Mingen, a remote site on the lower St. Lawrence River (Garmouna and Poissant, 2004). In a 1999 study initiated by Alberta Environment, lindane was found in air at concentrations of 3 ng/m^3 after seeding with treated canola, after which concentrations declined over the summer to non-detectable levels (<0.02 ng/m^3).

There is evidence for the atmospheric movement of lindane to the upper Laurentian Great Lakes, which lie downwind of the "corn-belt" region and the Prairie "canola belt". Results of an atmospheric transport model simulation showed that lindane transport to the Great Lakes during spring-summer came mainly from use on canola in the prairies, with minor contributions from the Lower Great Lakes and St Lawrence lowland "corn belt". Concentrations measured at five lakes were within 50–134% of modelled concentrations during the summer, 16–51% during the fall and 3–20% during the winter. This indicates that regional transport of lindane was the main source to the Great Lakes in summer. A similar data analysis for measurements made at Point Petre (north side of Lake Ontario) suggested that peak air concentrations detected on May 22–

23, coincided with time of lindane application. Lindane concentrations were detected in the air above a Saskatchewan field planted with lindane-treated canola seed. Maximum air concentrations were reached two weeks after planting for both study years. An estimated 12–30% of the lindane present in the seed coating volatilized. If this estimate is extrapolated to the entire canola-growing region of the Canadian prairies for 1998, this could amount to a release of 66-189 tonnes of lindane to the atmosphere during the 6 weeks following canola planting. Similarly, lindane concentrations were measured in air near Regina at the time with little or no canola cultivation, indicating that lindane was being transported into the region from cultivation elsewhere. Also, elevated lindane concentrations measured in the atmosphere at sites in Québec coincided with corn seeding (Waite et al., 2007).

The mean air concentrations of lindane in the Canadian Arctic for 1993-95 were: 0.014 ng/m^3 (at Kinngait), 0.011 ng/m^3 (at Tagish) (Hung et al., 2005) and 0.010 ng/m^3 (at Alert) (Hung et al., 2002). Older data are also available for Resolute Bay, Ice Island and Alert, where air concentrations were in the range of 0.008–0.070 ng/m^3, with the highest concentrations detected at Ice Island (0.031–0.070 ng/m^3) (Bidleman et al., 1995; Falconer et al., 1995; Patton et al.1991; Patton et al., 1989; Hargrave et al., 1988). The upper end of these concentrations is comparable to the lindane air concentrations detected with corn seeding in Québec.

Concentrations of α-HCH in Arctic air were greater than that of lindane. Values for 1993–1995 at the three Arctic stations mentioned above were: 0.074 ng/m^3 (at Tagish) (Hung et al., 2005) and 0.059 ng/m^3 (at Alert). Older measurements showed mean air concentrations in the Canadian Arctic (Resolute Bay, Ice Island and Alert) ranging from 0.057–0.577 ng/m^3; with the highest concentrations detected at Ice Island (0.27-0.577 ng/m^3) (Bidleman et al., 1995; Falconer et al., 1995; Patton et al.1991; Patton et al., 1989; Hargrave et al., 1988).

Lindane and α-HCH were detected in Canadian surface waters including the Arctic. Lindane concentrations were generally higher in the surface waters of the prairie provinces (Manitoba, Saskatchewan and Alberta) compared to those of eastern Canada and ranged from <0.001 to 0.076 µg/L. In general, the α-HCH isomer was detected at a higher frequency and concentration compared to lindane (see Tables 1 and 2).

Table 1   Concentrations of Lindane and α-HCH in Several Canadian Rivers

Surface water/Location	Sampling Period(s)	Lindane (µg/L)	α-HCH (µg/L)	Reference
Assiniboine River (Headingley, Manitoba)	1975-1978 1989-1993	0.001-0.003	<0.001-0.004	Currie and Williamson 1995
Qu'Appelle River (St. Lazare, Manitoba)	1975	—	0.002-0.006	Currie and Williamson 1995
Dauphin River (near Anama Bay, Manitoba)	1975-1978 1989-1993	<0.001-0.003	<0.001-0.02	Currie and Williamson 1995
Overflowing River (Overflowing River, Manitoba)	1978-1984	—	<0.001-0.01	Currie and Williamson 1995
Red Deer River (near mouth of Lake Winnipegosis, Manitoba)	1978	<0.001-0.0015	—	Currie and Williamson 1995
Swan River (Manitoba)	1978	0.001-0.003	—	Currie and Williamson 1995
Pembina River (Windygates, Manitoba)	1975-1993	—	<0.001-0.011	Currie and Williamson 1995
Red River (Emerson, Manitoba)	1975-1993	—	<0.001-0.094	Currie and Williamson 1995
Red River (Emerson, Manitoba)	1972-1993	<0.001-0.02	—	Currie and Williamson 1995
Roseau River (Gardenton, Manitoba)	1975-1993	<0.001-0.06	—	Currie and Williamson 1995
Saskatchewan River (above the Carrot River, Manitoba)	1975-1993	—	<0.001-0.03	Currie and Williamson 1995
Saskatchewan River (above the Carrot River, Manitoba)	1972-1993	<0.001-0.076	—	Currie and Williamson 1995
Gainsborough Creek (Manitoba)	1973-1975	<0.001-0.0029	—	Env. Canada; (cited in Currie and Williamson 1995)
Antler Creek (Coulter, Manitoba)	1973-1978	<0.001-0.003	—	Ibid
Pipestone Creek (Cromer, Manitoba)	1975-1993	<0.001-0.021	<0.001-0.01	Ibid
Souris River (near Coulter, Manitoba)	1973-1992	<0.002-0.01	—	Ibid
Souris River (near Coulter, Manitoba)	1975-1992	—	<0.001-0.03	Ibid
Souris River (Wawanesa, Manitoba)	1975-1989	—	<0.001-0.006	Ibid
Souris River (Wawanesa, Manitoba)	1972-1978	<0.001-0.006	—	Ibid
Winnipeg River (Point du Bois, Manitoba)	1978–1993	—	<0.001–0.01	Ibid

Surface water/Location	Sampling Period(s)	Lindane (µg/L)	α-HCH (µg/L)	Reference
Hayes River (Manitoba)	1979–1994	—	<0.001–0.009	Ibid
/ Alberta	1971–1993	0.05 (max.)	<0.001–0.023	Anderson, 1994 (cited in Currie and Williamson 1995)
Hudson Bay Lowland – 5 rivers (Ontario)	—	0.0004–0.0015	0.005–0.0084	McCrea and Fischer 1986 (cited in Currie and Williamson 1995)
Rainy River (Southern Ontario)	—	<0.0001–0.01	<0.0001–0.004	Merriman 1988 (cited in Currie and Williamson 1995)
Qu'Appelle River (Saskatchewan)	1972–1993	0.005 (max.)	<0.001–0.01	Dunn 1994, 1995 (cited in Currie and Williamson 1995
Churchill River (Saskatchewan)	1972–1993	—	<0.001–0.01	Dunn 1995 (cited in Currie and Williamson 1995)
Carrot River (Saskatchewan)	1972–1993	——	<0.001–0.03	Ibid
Assiniboine River (Saskatchewan)	1972–1993		<0.001–0.02	Ibid
/ N. Quebec	1980–1987	0.0007	0.006	Environment Canada, 1992
/ Nova Scotia	1980–1987	0.0001	0.002	Environment Canada, 1992
/ PEI	1980–1987	0.0001	0.0001	Environment Canada, 1992
/ Newfoundland	1980–1987	0.0002	0.004	Environment Canada, 1992

Table 2   Concentrations of Lindane in the Canadian Subarctic and Arctic Surface Waters

Location	Year	Concentration (ng/L)	Reference
Canadian Basin	1994	0.92	Jantunen and Bidleman, 1996
Canadian Basin	1987	0.81	Jantunen and Bidleman, 1996
Canadian Basin	1986	0.61	Jantunen and Bidleman, 1996
Resolute Bay N.W.T.	1992	0.44	Bidleman et al., 1995
Resolute Bay N.W.T.	1992	0.23–0.54	Falconer et al., 1995
Amituk Lake, N.W.T	1992	0.28	Bidleman et al., 1995
Bering Sea	1993	0.46	Jantunen and Bidleman, 1995
Chukchi Sea	1994	0.56	Jantunen and Bidleman, 1996

Concentrations of lindane found in Manitoba rivers between 1972 and 1993 were in the range of <0.001–0.076 µg/L; concentrations of α-HCH were in the range of <0.001–0.03 µg/L. Currie and Williamson (1995) reported that lindane concentrations exceeded the Canadian Water Quality Guidelines for protection of aquatic life in approximately 1% of the samples. The guideline for the protection of aquatic life is 0.01 µg a.i./L for HCH (CCME,1999). α-HCH concentrations exceeded this guideline in 5.8% of detections (Anderson, 1994).

Dunn (1994, 1995), reported lindane concentrations of <0.001–0.03 µg/L in four Saskatchewan rivers. The maximum concentration of lindane detected in Alberta rivers from 1971–1993 was 0.05 µg/L; the α-HCH concentrations were <0.001–0.023 µg/L (Anderson, 1994). α-HCH occurred to a greater extent than lindane in Alberta rivers; the detection frequencies of lindane and α-HCH were 19.2% and 69.2%, respectively, in samples collected from 1972–1993 (Alberta Environment, 1999). α-HCH in Alberta samples exceeded the aquatic life protection guideline in 3.2% of detections (Currie and Williamson, 1995).

In five rivers in the Hudson Bay Lowlands in Ontario, lindane concentrations were 0.0004–0.0015 µg/L, while α-HCH concentrations were 0.005–0.0084 µg/L (McCrea and Fischer, 1986). Concentrations of HCH in rivers were generally lower in eastern Canada. In southern Ontario (Rainy River), lindane concentrations were <0.001–0.01 µg/L (Merriman, 1988). For Québec, Nova Scotia, PEI and Newfoundland, mean lindane concentrations found for the 1980–1987 period were 0.0007, 0.0001, 0.0001 and 0.0002 µg/L, respectively. α-HCH concentrations were generally higher, with reported values of 0.006, 0.002, 0.0001 and 0.004 µg/L, respectively (Environment Canada, 1992). More recent data from Environment Canada indicate that α-HCH concentrations in Atlantic region surface waters then increased to reach the levels of the prairies. Mean α-HCH concentrations for Quebec, Nova Scotia, PE, NB and NF were determined to be 0.0181, 0.0051, 0.0051, 0.006, and 0.0025 µg/L, respectively. Further investigation is needed in order to explain these results.

Lindane and α-HCH were also detected in wetlands. In one study of wetlands in southern Saskatchewan, the detection frequency of lindane and α-HCH in water samples were 74% and 9%, respectively. Concentrations of lindane in wetlands increased with increasing precipitation. The detection frequency of lindane increased from 49% in wetlands receiving <20 mm precipitation during the previous 15 days to 89% in those receiving >90 mm precipitation. The range of median lindane concentrations was 0.002–0.016 µg/L; with a maximum concentration of 0.40 µg/L. Between 10–60% of the lindane concentrations reported exceeded the Canadian guideline for protection of aquatic life for HCH (0.01 µg/L, CCME, 1999). The authors also estimated that 9–24% of the wetlands in southern Saskatchewan are subject to lindane concentrations that exceeded this guideline. This estimation was based on a Ducks Unlimited wetlands database, Environment Canada precipitation data from 217 stations, a 44% adjustment for the proportion of land area seeded to crop and the proportion of wetlands sampled in each precipitation category with lindane concentrations that exceed the guideline (Donald *et al.*, 1999).

In the northern regions of Canada, lindane concentrations were at least an order of magnitude less than concentrations detected in eastern and western Canada (Li et al., 2003). Concentration ranges (ng/L) for arctic and subarctic seawater (including the Beaufort, Bering and Chukchi seas) were: 1.0–7.1 (α-HCH), 0.071–0.39 (β-HCH) and 0.18–0.95 (lindane). The ranges of concentrations in small Canadian lakes sampled between 1993 and 1997 were (ng/L) the following: Ontario lakes 0.04–0.43 (α-HCH), ND–0.91 (lindane), Yukon lakes 0.92–1.7 (α-HCH), 0.13–0.41 (lindane), arctic lakes 0.64–1.0 (α-HCH), 0.13–0.23 (lindane), Great Lakes 0.34–201 (α-HCH), 0.26–0.95 (lindane). Wetlands and streams in Ontario contained 0.11–0.86 ng/L α-HCH and ND–0.45 ng/L lindane (all from Law et al., 2001). Another study of temperate Canadian lakes found surface water concentrations ranging from 0.06 to 0.25 ng/L α-HCH and 0.055 to 0.17 ng/L lindane (Muir et al., 2004). Surface water concentrations of α-HCH in the arctic, however, are higher than those of eastern and western Canada. In surface waters of the Canadian subarctic and arctic, lindane concentrations were reported to be 0.24–0.81 ng/L (Bidleman et al., 2007; Jantunen and Bidleman, 1998; Jantunen and Bidleman, 1996; Jantunen and Bidleman, 1995; Bidleman et al., 1995; Falconer et al., 1995; Hargrave et al., 1997; Helm et al., 2002). At Resolute Bay (Nunavut), 1992–1993 concentrations of α-HCH were 3.6–4.7 ng/L (in seawater). (Bidleman et al., 1995a; Falconer et al., 1995; Hargrave et al., 1997). Arctic streams flowing into Amituk Lake contained 0.6–1.5 ng/L α-HCH, 0.029–0.039 ng/L β-HCH and 0.21–0.38 ng/L lindane (Helm et al., 2002).

Freshwater and Marine Biota
The accumulation of HCH isomers varies among invertebrates, fish, seabirds and marine mammals in the Canadian Arctic (Moisey et al., 2001; Braune et al., 2005; Ryan et al., 2005). The relative proportion of α-HCH was generally higher than 60% in water, sediment, invertebrates and marine mammals, while β-HCH accounted for more than 60% of the total HCH burden in seabirds. In arctic cod (*Boreogadus saida*), the relative percentage of α-HCH was low (<50%) when compared to that of fish from Yukon lakes. It has been suggested that arctic cod, considered as a trophic key link between invertebrates and marine mammals or seabirds, had either a greater bioaccumulation of β-HCH and lindane or a greater metabolism of α-HCH or both (Moisey et al., 2001). Preferential HCH isomer accumulation in the tissues of marine mammals is indicated by other data sets. In the fur seal, 59–62% of the HCH in blubber, liver and lung was β-HCH and 28–34% was α-HCH, while in the brain, 91% of the HCH residue was

α-HCH (Mossner et al., 1992). In the striped dolphin, β-HCH constituted 84% and 94% of the HCH residues in muscle and kidney, respectively, while α-HCH constituted 73–83% in the brain (Kawai et al., 1988). Although there is preferential accumulation of certain HCH isomers in animal tissues, these have not been linked directly to toxicological effects in wildlife, and no toxicological effects were associated with similar HCH accumulation patterns in laboratory rat tissues (Portig et al., 1989).

A range of HCH isomer concentrations detected in Arctic biota were reported for fish, marine invertebrates, zooplankton and seabirds (Tables 3, 4 and 5).

Table 3   Mean (±SD) Concentration (ng/g ww) of HCH Isomers in Fish from Yukon (Kusawa, Laberge, Quiet) and Alaska Lakes (1992–2003)

Species	Location	Period	α-HCH	β-HCH	Lindane	Σ-HCH	Reference
Lake trout muscle	Kusawa	1992–2003	1.08 (0.33)	0.01 (<0.01)	0.12 (0.03)	1.21 (0.36)	Ryan et al., 2005
			1.36 (0.17)	0.07 (0.01)	0.25 (0.05)	1.68 (0.23)	
			0.75 (0.11)	0.04 (0.01)	0.12 (0.02)	0.91 (0.14)	
			0.52 (0.07)	0.03 (0.01)	0.07 (0.01)	0.62 (0.08)	
	Laberge		3.70 (0.55)	0.16 (0.05)	0.82 (0.20)	4.69 (0.78)	
			4.71 (1.17)	0.34 (0.11)	1.45 (0.52)	6.50 (1.79)	
			0.89 (0.21)	1.27 (0.89)	0.14 (0.03)	2.30 (1.08)	
			0.44 (0.04)	0.22 (0.04)	0.14 (0.01)	0.80 (0.07)	
			1.24 (0.40)	0.09 (0.03)	0.26 (0.07)	1.58 (0.50)	
			0.4 (0.08)	0.05 (0.04)	0.09 (0.02)	0.54 (0.10)	
	Quiet		0.67 (0.36)	0.05 (0.01)	0.10 (0.02)	0.82 (0.37)	
			0.20 (0.03)	<0.01 (<0.01)	0.04 (0.01)	0.25 (0.04)	
			0.08 (0.02)	<0.01 (<0.01)	0.03 (<0.01)	0.11 (0.02)	
			0.06 (0.02)	<0.01 (<0.01)	0.02 (<0.01)	0.08 (0.02)	
Burbot (*Lota lota*) liver	Kusawa		1.27 (0.11)	<0.01 (<0.01)	0.62 (0.19)	1.89 (0.17)	
			1.26 (0.09)	0.49 (0.06)	3.39 (0.48)	5.14 (0.59)	
	Laberge		27.57 (4.53)	0.74 (0.19)	5.79 (0.97)	39.71 (6.42)	
			29.96 (5.33)	1.10 (0.27)	5.47 (1.03)	36.53 (6.58)	
			36.29 (5.13)	1.15 (0.23)	6.54 (1.21)	43.98 (6.48)	
			15.97 (2.27)	0.72 (0.14)	2.54 (0.33)	19.23 (2.73)	
			6.75 (0.62)	0.12 (0.08)	1.29 (0.19)	8.17 (0.76)	
	Quiet		9.41 (0.77)	0.36 (0.04)	1.57 (0.21)	11.34 (1.00)	
			12.02 (1.73)	0.51 (0.06)	2.09 (0.32)	14.61 (2.09)	
			4.28 (0.59)	0.69 (0.10)	4.54 (0.93)	9.50 (1.62)	
Pink salmon (*Oncorhynchus gorbuscha*) fillet	Alaska	1997–1999	ND	ND	ND	1.36 (0.58)	Hoekstra et al., 2005
Arctic char (*Salvelinus alpinus*) fillet	Alaska	1997–1999	ND	ND	ND	1.81 (0.88)	
Broad whitefish (*Coregonus nasus*) fillet	Alaska	1997–1999	ND	ND	ND	0.22 (0.09)	
Arctic grayling (*Thymallus arcticus*) Fillet	Alaska	1997–1999	ND	ND	ND	0.26 (0.29)	

Species	Location	Period	α-HCH	β-HCH	Lindane	Σ-HCH	Reference
Burbot (*Lota lota*) Liver	Alaska	1997–1999	ND	ND	ND	4.41 (1.58)	

ND, not determined

Table 4   HCH Concentrations (ng/g) in Biota from Pacific and Yukon Region Lakes (1994–1995)

Species	α-HCH	β-HCH	Lindane	Reference
Mountain whitefish Liver	0.38–1.02	2.60–6.35	—	Environment Canada database
Mountain whitefish Muscle	0.11–00.91	0.21–17.87	0.07–2.23	
Peamouth chub Liver	0.29–1.68	0.86–11.67	0.30–9.07	
Peamouth chub Muscle	0.02–0.15	0.10–2.91	0.05–1.49	
Starry flounder Liver	0.25–0.28	0.25–0.38	0.70–0.70	
Starry flounder Muscle	0.02–0.02	0.08–0.44	0.23–0.23	

Table 5   Mean (±SE) Concentrations of HCH Isomers (ng/g lipid) in Marine Invertebrates and Seabirds Collected from the Northwater Polynya, Baffin Bay, in 1998

Species	lipid	α-HCH	β-HCH	γ-HCH	Σ-HCH	Reference
Benthic invertebrates	2.5 (0.3)	315.9	ND	31.7 (7.2)	347.6	Moisey et al., 2001
A. nugax	8.5 (1.2)	(109.6)	ND	7.1 92.1)	(115.4)	
Basket star	1.6 (0.2)	33.5 (8.4)	0.4 (0.4)	0.3 (0.1)	40.7 (10.4)	
Starfish	2.2 (0.0)	1.0 (0.5)	0.3 (03)	0.1 (0.1)	1.7 (1.0)	
Clam		0.7 (0.4)			1.1 (0.7)	
Zooplankton	5.0 (0.5)		0.9 (0.4)	1.9 (0.4)		
M. occulata	2.1 (0.3)	7.4 (1.7)	0.9 (0.5)	2.5 (0.6)	10.3 (2.4)	
Sagitta spp.	5.4 (0.3)	7.7 (2.1)	ND	4.2 (0.3)	11.1 (2.8)	
E. glacialis	6.3 (0.7)	20.4 (1.0)	0.5 (0.2)	5.5 (7.7)	24.6 (1.2)	
C. hyperboreus	2.1 (0.1)	24.9 (6.7)	ND	17.7 (0.6)	30.5 (7.7)	
M. longa	2.2 (0.4)	18.6 (2.7)	ND	36.4 (12.0)	36.2 (3.3)	
T. libellula		45.9 (7.5)			82.3 (13.9)	
Seabirds	66.0 (1.5)		138.5 (9.6)	16.8 (2.9)		
Dovekie	60.0 (2.2)	66.7 (13.6)	57.7 (8.9)	6.7 (0.5)	222.0 (19.9)	
Thick-billed murre	60.0 (6.0)	20.1 (1.7)	199.0 (36.8)	10.0 (1.8)	84.5 (9.6)	

Species	lipid	α-HCH	β-HCH	γ-HCH	Σ-HCH	Reference
Black guillemot Black-legged Kittiwake Glaucous gulls Ivory gull Northern fulmar	72.4 (3.9) 71.6 (4.5) 81.1 (5.0) 71.9 (4.0)	76.0 (10.0) 6.9 (0.9) 14.9 (4.0) 11.4 (3.4) 19.8 (1.5)	36.0 (5.0) 424.2 (49.1) 127.5 (31.3) 41.2 (4.5)	4.4 (0.6) 3.6 (0.5) 4.1 (0.8) 4.1 (0.6)	285.0 (46.7) 47.3 (6.3) 442.7 (51.9) 143.0 (32.7) 65.1 (5.8)	

In marine invertebrates, the HCH content was dominated by the α-HCH isomer. Water solubility is a key factor in explaining α-HCH concentrations in Arctic marine zooplankton (Fisk et al., 2003). A study by Hoekstra et al. (2002a) determined HCH concentrations in marine zooplankton *(Calanus hyperboreus)* copepods from northern Baffin Bay (Nunavut) to be >30 ng/g dw.

Lindane has also been detected at low concentrations (0.003 mg/kg) in seabird eggs from the Pacific coast of Canada (Elliott et al., 1989) and in eggs of peregrine falcons (Environment Canada, 1992). β-HCH concentrations found in peregrine falcons from the Queen Charlotte Islands (British Columbia) were attributed to the consumption of contaminated prey (ancient murrelet). β-HCH concentrations in ancient murrelet tissues ranged from non-detectable levels to 0.179 mg/kg (1986 data) in eggs, 0.584 mg/kg in the fat (1972 data) and 0.997 mg/kg in the whole body (1969 data). β-HCH accumulated to a greater extent in birds than did the other isomers. The accumulation likely results through consumption of contaminated prey. Even where food items are not highly contaminated with HCH residues, there is still accumulation in peregrine falcons (Elliott et al., 1989). The authors postulated that peregrines accumulate HCH during wintering in areas of lindane and technical HCH use, such as Central and South America. Support for this argument came from evidence that other (non-migratory) raptors in the area show relatively little HCH accumulation and, thus, the majority of the HCH in these peregrine falcons likely stems from consumption of contaminated prey outside Canada (Elliott et al., 1989).

Recent reports indicate that concentrations of HCH in eggs of common and thick-billed murres (*Uria aalge* and *Uria lomvia*) from five Alaskan nesting colonies were dominated by β-HCH (>90%) (Vander Pol et al. 2004). The HCH concentrations in eggs from the study (1993, 1998, 1999 and 2000 data) were in the range of 2.3–25.0 ng/g ww.

Lindane, α-HCH and β-HCH were detected in marine mammals at several locations. Higher concentrations of HCH were found in the blubber of marine mammals from cold and temperate waters compared to those from tropical waters (Prudente *et al.*, 1997), providing further evidence that colder regions are sinks for HCH isomers. In general, lindane concentrations were the lowest of the three isomers in marine mammal blubber. α-HCH was the most predominant isomer in the bowhead whale, beluga whale, pilot whale, common dolphin and harbor seal from the North Pacific-Arctic region and from the North Atlantic (Mossner and Ballschmiter, 1997). β-HCH was the most prevalent isomer in fur seals (Mossner and Ballschmiter, 1997; Mossner et al., 1992; and Tanabe et al., 1994) and in other mammals, such as Dall's porpoise and white-sided dolphin in the North Pacific and near Japan (Vetter et al., 1996). Even within species of seal, whale, dolphin and porpoise, there are substantial differences in the α-HCH and β-HCH

compositions found in different populations. These patterns may reflect different sources of contamination, modes of uptake and/or metabolism; however, the exact explanations for these observations are largely unknown.

In the Canadian Arctic (Arctic Bay and Barrow Strait, Nunavut; 1993), total HCH concentrations in ringed seal blubber ranged from 201–382 µg/kg lipid (Muir et al., 1994, 1996). In polar bear fat (Baffin Bay, Nunavut; 1989–90), the total HCH concentrations were 212–321 µg/kg lipid (Norstrom et al., 1997). Recent data by Verreault *et al.* (2005) indicate no changes in HCH concentration in polar bears from Baffin Bay from 1996 to 2002. Higher HCH concentrations are reported in Alaska bears (398–1269 µg/kg lipid). In Canada, the authors identified a regional pattern, with higher HCH concentrations in polar bears in the western Canadian Arctic (Beaufort Sea and Amundsen) compared to those in eastern Arctic (Hudson Bay, Labrador Coast, and Baffin Island). It is believed that this could be indicative of ongoing contributions of HCH from China, Southeastern Asia, and North America. In Northern Québec (Inukjuak and Akulivik), walrus blubber contained total HCH concentrations of 116–267 µg/kg lipid (Muir et al., 1995). Although these particular analyses were not isomer specific, residue data from another study (Nakata *et al.*,1998) indicate that the majority of HCH residues in marine mammals consists of the α-HCH and β-HCH isomers. As a result of their relatively high degree of contamination, polar bears from Alaska are at higher health risk from contaminant exposure than conspecifics from the Arctic and Subarctic populations.

Table 6   Mean (±SD) Concentration (ng/g ww) of HCH Isomers in Marine Mammals from Alaska Lakes from 1997–2000

Species	Location	Period	α-HCH	β-HCH	γ-HCH	Σ-HCH	Reference
Bobhead whale (*Balaena mysticetus*) liver	Barrow/Alaska	1997–2000	6.2 (0.4)	2.3 (0.2)	0.8 (0.1)	9.5 (0.5)	Hoekstra et al., 2002b
Bobhead whale (*Balaena mysticetus*) blubber	Barrow/Alaska	1997–2000	114 (11)	57 (2.9)	29 (2.6)	203 (13)	
Beluga whale (*Delphinapterus leucas*) blubber	Alaska	1997–1999	ND	ND	ND	212 (161)	Hoekstra et al., 2005
Ringed seal (*Phaca hispida*) blubber	Alaska	1997–1999	ND	ND	ND	203 (127)	
Bearded seal (*Erignathus barbatus)* blubber	Alaska	1997–1999	ND	ND	ND	89.3 (36.4)	

ND, not determined.

Appendix VIII   Summary of Environmental Toxicology

Birds

Table 1   Acute Oral Toxicity of Lindane to Avian Species

Avian Species	LD50 (mg a.i./kg)
Bobwhite quail (*Colinus virginiaus*)	120; 122 (NOEL <46.4)
Mallard duck (*Anas platyrhynchos*)	>2000
House sparrow (*Passer domesticus*)	56
Redwing blackbird (*Agelaiusphoeniceus*)	75
Starling (*Sturnus vulgaris*)	100
Common grackle (*Quiscalus quiscula*)	>100
American crow (*Corvus brachyrhynchos*)	>100
Ringed turtle dove (*Streptopella risoria*)	350
Pigeon (*Columba livia*)	>600
Ring-necked pheasant (*Phasianus colchicus*)	60–100

(In: Environment Canada review, 1992)**.**

Table 2   Acute Dietary Toxicity of Lindane to Avian Species

Avian Species	LC50 (mg a.i./kg diet)
Bobwhite quail (*Colinus virginiaus*)	882; 919 (NOEC = 163) 1250–1430 (NOEC <155)
Mallard duck (*Anas platyrhynchos*)	695 (NOEC<163) >5000
Japanese quail (*Coturnix coturnix japonica*)	205; 490
Redwing blackbird (*Agelaiusphoeniceus*)	(NOEC<155)
Ring-necked pheasant (*Phasianus colchicus*)	561

(In: European Commission ECCO meetings draft evaluation of lindane, 1999).

Lindane had substantial effects on avian reproduction. In the bobwhite quail, there were significant reductions in the number of eggs laid, eggs set, viable embryos, live 3-week embryos, normal hatchlings and 14-day old survivors, percentage of normal hatchlings/eggs laid, normal hatchlings/eggs set, normal hatchlings/live 3-week embryos, 14-day survivors/eggs set, 14-day survivors/normal hatchlings, egg shell thickness and hatchling weights. The NOAEC and LOAEC were reported to be 80 and 320 mg a.i./kg diet, respectively. In the mallard duck, there were also significant reductions in the number of viable embryos, live 3-week embryos and normal hatchlings at concentrations of 45 and 135 mg a.i./kg diet, respectively. The NOAEC and LOAEC were found to be 15 and 45 mg a.i./kg diet, respectively (USEPA, 2000).

Mammals

Table 3   Acute Oral Toxicity of Lindane to Mammals

Species	NOEC (mg a.i./kg)	LOEC (mg a.i./kg)	LD50 (mg a.i./kg)	Reference[1]
Rat (M+F)	<64 <170	64 170	1633 89	Frohberg, 1972 Pasquet, 1981
Mouse (M+F)	<40 40 <40	40 80 40	64 145 116	Wolfe, 1980 Wolfe, 1980 Paul, 1981

1 References from European Commission ECCO meetings draft evaluation of lindane, 1999

Table 4   Subchronic and Long-term Toxicity of Lindane in Mammals

Species	Study type	Study duration	NOEC (mg/kg diet)	LOEC (mg/kg diet)	Reference[1]
Rat (M+F)	Subchronic	3 months	4	20	Suter *et al.*, 1983
Rat (M+F)	Chronic carcinogenicity	104 weeks	10	100	Amyes, 1990
Rat (M+F)	Reproduction	2 generations	1	20	King, 1991
Rabbit	Effects on pregnancy	29 days	20	20	Palmer and Neuff, 1971

1 References from European Commission ECCO meetings draft evaluation of lindane, 1999

Other sublethal effects observed in mammals exposed to lindane indicate that lindane has both estrogenic and antiestrogenic effects in mammals (Cooper et al., 1989). A reproductive toxicity study was conducted in rats by Dalsenter et al. (1997). Two groups of 9 lactating dams received a single oral dose of 6 mg lindane/kg bw on day 9 or day 14 of lactation. Another group of 9 lactating dams was treated with a daily dose of 1 mg lindane/kg bw from day 9 to day 14 of lactation. Control groups received peanut oil. The reproductive effects on male offspring rats were reported on days 65 and 140 postnatally. Decreased testosterone levels were observed in all lindane-treated groups. The relative testicular weight and the number of sperm and spermatids

were lower in all lindane-treated adult rats. Decreased number of Leydig cells was noted in all lindane-treated groups. Sexual behaviour was reduced and absence of ejaculation was the main effect observed in male offspring. It was concluded that exposure to lindane during lactation induces reproductive effects in male-offspring rats that are detectable at adulthood.

Beard et al. (1999) investigated reproductive and endocrine function in second generation ram lambs born to control and lindane-treated ewes (treated from week 5 before breeding until weaning of offspring). The second generation rams were maintained on treated (n = 12) or untreated (n = 7) feed from weaning until they reached puberty and were sacrificed at 28 weeks of age. Blood samples were taken from the rams before and after administration of gonadotropin-releasing hormone (GnRH), thyroid-stimulating hormone (TSH) and adrenocorticotrophic hormone (ACTH). Rams given lindane-treated feed had decreased luteinizing hormone (LH) and estradiol concentration, reduced sexual behaviour, and showed attenuated testosterone and LH responses after stimulation with GnRH. Sperm density in the head and tail of epididymides was not significantly reduced. The responses to TSH and ACTH were not affected by lindane treatment, as no significant changes were noted in serum concentrations of thyroxine, cortisol and progesterone.

In a multigeneration study, mink (*Mustela vison*) at 8 weeks of age were fed either an untreated diet or a diet treated with 1 mg lindane/kg bw/day (Beard and Rawlings, 1998). The second generation mink (male, n = 8; females, n = 10) and the third generation mink (male, n = 8; females, n = 8) were treated continuously from conception to maturity. Although no signs of toxicity were noted, exposure of mink to lindane resulted in a decrease in reproductive success (60%) and reduced testis size in third generation males from the lindane-treated group. Serum concentrations of cortisol, testosterone, estradiol and thyroxine were not affected by lindane treatment (Beard and Rawlings, 1998). Another study showed increased embryo loss after implantation and decreased serum concentration of cortisol in mink treated with 1 mg lindane/kg bw/day from before mating until weaning (Beard et al., 1997). It is worth noting that lindane-induced embryo loss was shown to be reversible by oestradiol in mice (Sircar and Lahiri, 1989), confirming that lindane exhibits an antiestrogenic effect in this case.

Adult male albino rats and mice were exposed daily to 8.8 or 5.9 mg/kg lindane, respectively, through oral intubation for 3 days. The status of the blood-brain barrier (BBB) was evaluated by determining brain sodium fluorescein dye uptake and brain uptake index (BUI) in relation to serum dye level. The brain dye uptake and BUI in pesticide-exposed rats did not differ significantly in comparison to that of controls. However, the BBB in the mice was more sensitive to lindane-induced breach and dye uptake and BUI were increased significantly (79%, 26%) in this species. This variation in response may have a role in determining the outcome of pesticide neurotoxicity in even closely-related species (Sinha and Shukla 2003). This study showed that the developing BBB is highly vulnerable to single or repeated exposure of lindane, even at concentrations equivalent to 1/50th to 1/10th the LD50. They also suggest that young, developing animals may be far more at risk than adults.

Terrestrial Invertebrates

Table 5   Acute and Chronic Toxicity of Lindane in Earthworms

Species	Exposure	Endpoint	Effects	Reference
Folsomia candida *Eisenia fetida* *Enchytraeus albidus*	Acute 14 days	LC_{50}: 2.21 mg/kg dw LC_{50}:165 mg/kg dw LC_{50}:107 mg/kg dw	Mortality	Lock et al., 2002
Folsomia candida	Chronic 28 days	NOEC: 0.056 mg/kg dw (# juveniles)		
Eisenia fetida	Chronic 21 days	NOEC: 10 mg/kg dw (# juveniles) NOEC: 10 mg/kg dw (# cocoons) NOEC: 18 mg/kg dw (cocoon fertility)		
	Chronic 42 days	NOEC: 10 mg/kg dw (# juveniles)		
Enchytraeus albidus	Acute 96 hours	NOEC:0.02 mg/kg dw		
Eisenia foetida	14-day	LC_{50} = 136 mg/kg soil	Mortality	(Haque and Ebing, 1983)
Lumbricus terrestris	14-day	LC_{50} = 114 mg/kg soil		

The acute oral LD_{50} to honeybees was 0.45–0.76 µg a.i./bee and the acute contact LD_{50} was 0.20–0.46 µg a.i./bee (Review of Lindane; Pesticides Safety Directorate, 1996). These low values indicate that lindane is highly toxic to bees and are equivalent to application rates of 0.5–0.85 and 0.22–0.51 kg a.i./ha on an acute oral and acute contact basis, respectively.

Fish

Table 6   Acute Toxicity of Lindane Technical Active to Fish

Species	96-hr LC$_{50}$ (µg a.i./L)
Coho salmon *(Oncorhynchus kisutch*)	23–50
Chinook salmon (*Oncorhynchus tshawytscha)*	40
Rainbow trout (*Oncorhynchus mykiss*)	27–38
Brown trout (*Salmo trutta*)	1.7
Lake trout (*Salvelinus namaycush*)	32
Stickleback (*Gasterosteus aculeatus*)	44–50
Carp (*Cyprinus carpio*)	90
Fathead minnow (*Pimephales promelas*)	87
Black bullhead (*Ictalurus melas*)	64
Channel catfish (*Ictalurus punctatus*)	44
Green sunfish (*Lepomis cyanellus*)	83
Bluegill sunfish (*Lepomis macrochirus*)	68
Largemouth bass (*Micropterus salmoides*)	32
Yellow perch (*Perca flavescens*)	68

(In: Review of Lindane; Pesticides Safety Directorate, 1996).

Table 7   Acute Toxicity of Lindane Formulations to Fish

Species	Formulation	96-hr LC$_{50}$ (µg a.i./L)	NOEC (µg a.i./L)
Rainbow trout (*Oncorhynchus mykiss*)	40% flowable lindane		8.2
Rainbow trout (*Oncorhynchus mykiss*)	25% wettable powder	22	6
Rainbow trout (*Oncorhynchus mykiss*)	20% emulsifiable concentrate	24	5.4
Bluegill sunfish (*Lepomis macrochirus*)	40% flowable lindane	63	30
Bluegill sunfish (*Lepomis macrochirus*)	25% wettable powder	50	14
Bluegill sunfish (*Lepomis macrochirus*)	20% emulsifiable concentrate	57	16

(In: European Commission ECCO meetings draft evaluation of lindane, 1999).

Table 8   Chronic Toxicity of Lindane Technical Active to Fish

Species	Test type	NOEC (µg a.i./L)	LOEC (µg a.i./L)
Rainbow trout (*Oncorhynchus mykiss*)	early life stage; 85-d flow-through	13 (larval survival) 28 (larval length) 2.9 (larval weight)	28 (larval survival) >28 (larval length) 6 (larval weight)
Bluegill sunfish (*Lepomis macrochirus*)	flow-through	>9.0	NA
Fathead minnow (*Pimephales promelas*)	flow-through	9.1	NA
Brook trout (*Salvelinus fontinalis*)	flow-through	8.8	NA

(In: Review of Lindane; Pesticides Safety Directorate, 1996; and European Commission ECCO meetings draft evaluation of lindane, 1999).

Table 9 **Comparative Acute Toxicities of α-HCH, β-HCH, Lindane, and δ-HCH in Freshwater Fish**

Species	Exposure	Endpoint	Effects	Reference
Lindane Guppy fish (*Poecilia reticulata*) Zebra fish (*Brachydanio rerio*) Neon fish (*Paracheirodon axelrodi*)	Acute 96 hrs Acute 96 hrs Acute 96 hrs	LC_{50}: 0.36 ppm LC_{50}: 0.16 ppm LC_{50}: 0.14 ppm	Mortality	Oliverira-Filho and Paumgartten, 1997
α-HCH Guppy fish (*Poecilia reticulata*) Zebra fish (*Brachydanio rerio*) Neon fish (*Paracheirodon axelrodi*)	Acute 96 hrs Acute 96 hrs Acute 96 hrs	LC_{50}: 1.49 ppm LC_{50}: 1.11 ppm LC_{50}: 1.52 ppm	Mortality	Oliverira-Filho and Paumgartten, 1997
β-HCH Guppy fish (*Poecilia reticulata*) Zebra fish (*Brachydanio rerio*) Neon fish (*Paracheirodon axelrodi*)	Acute 96 hrs Acute 96 hrs Acute 96 hrs	LC_{50}: 1.66 ppm LC_{50}: 1.52 ppm LC_{50}: 1.10 ppm	Mortality	Oliverira-Filho and Paumgartten, 1997
δ-HCH Guppy fish (*Poecilia reticulata*) Zebra fish (*Brachydanio rerio*) Neon fish (*Paracheirodon axelrodi*)	Acute 96 hrs Acute 96 hrs Acute 96 hrs	LC_{50}: 2.83 ppm LC_{50}: 1.58 ppm LC_{50}: 0.84 ppm	Mortality	Oliverira-Filho and Paumgartten, 1997

Amphibians

Table 10   Acute Toxicity of Lindane to Amphibians

Species	Exposure	Endpoint	Effects	Reference
Lindane *Bufo arenarum*	Acute 96 hours 0.02–2.00 ppm	NOEC: 0.02 ppm	Mortality, hyperactivity, bent tail, organ malformation.	Anguiano et al., 2001
Xenopus laevis	chronic 0.5, 1, and 2 ppm	LOEC: 0.5 ppm	Decreased hatching rate, delayed metamorphosis, mortality	Marchal-Segault and Ramade, 1981

Lindane is known to induce developmental and reproductive impairment in amphibians (see previous table on selected acute and chronic effects of lindane and α-HCH to terrestrial invertebrates and fish). In a reproductive toxicity study by Serben (2003), the exposure of wood frog tadpoles (*Rana sylvatica*) to lindane at 0.1 µg/L affected sex ratios of metamorphs ($p < 0.005$), resulting in 71% males, but ratios in the two higher lindane treatments (1.0, and 10 µg/L) did not differ from the control groups. Concentrations of circulating hormones in the lowest lindane treatment were also significantly higher than those in solvent controls; corticosterone by 44%, and the T4 (tetraiodothyronine):T3 (triiodothyronine) ratio by 30%. These low-dose effects, combined with evidence for hormesis in body condition, suggest that endocrine disruption occurs in Wood frogs exposed to environmental concentrations of lindane in water. Another study using higher concentrations also suggested endocrine disruption. When young *Xenopus laevis* were exposed to lindane at 500 µg/L from the early egg stage through metamorphosis (12 weeks), hatching rate was decreased, growth was retarded and skin pigmentation was greatly darkened relative to controls, suggesting endocrine dysfunction (Marchal-Segault and Ramade 1981). Histological analysis of thyroid glands from the same study confirmed that hormone secretion had been deficient (Marchal-Segault 1982). Due to the imbalance in sex ratio of metamorphs, fertility problems in lindane-exposed wildlife population can be expected.

Aquatic Invertebrates

Table 11   Acute Toxicity of Lindane to Aquatic Invertebrates

Species	Formulation	48-hr LC$_{50}$ (µg a.i./L)	LOEC (µg a.i./L)	NOEC (µg a.i./L)
Daphnia magna	40% flowable	2600	110	<110
	25% wettable powder	1600	520	220
	20% emulsifiable concentrate	1600	440	240
Gammarus pulex	technical lindane	17.3–19.5		
Crassostrea virginica (eastern oyster)	technical lindane	2800		
Chironomus riparius	technical lindane	55		

(In: Review of Lindane; Pesticides Safety Directorate, 1996; and European Commission ECCO meetings draft evaluation of lindane, 1999)

Table 12   Chronic Toxicity of Lindane Technical Active to Aquatic Invertebrates

Species	Test type	NOEC (µg a.i./L)	LOEC (µg a.i./L)
Daphnia magna	21 d flow-through	110 (adult survival) 54 (reproduction)	>110 (adult survival) 110 (reproduction)
Daphnia magna	21 d flow-through	11 (survival and reproduction)	
Chironomus tendans	flow-through	2.2 (survival and emergence)	
Gammarus fasciatus	flow-through	4.3 (survival and reproduction)	

(In: Review of Lindane; Pesticides Safety Directorate, 1996; and European Commission ECCO meetings draft evaluation of lindane, 1999)

Table 13   Toxicity of Lindane Technical Active and α-HCH to Freshwater and Marine Invertebrates

HCH	Group	Species	Exposure	Exposure Type	Test, Effects, Endpoints	Reference
Lindane	Marine crustacean	*Neocaridina denticulata*	0.1 and 1µg/L	28 days	Increase in estrogen, reduction in testosterone, morphological alterations of the masculine appendage.	Huang et al., 2004
Lindane	Freshwater crustacean	*Daphnia magna*	56, 100, 180, 320, 560, 750 µg/L	48 and 96 hours	After 48h: the enzymatic activity of, glycogen phosphorylase increased at 100 µg/L, but decreased at 180 µg/L; lactate dehydrogenase decreased at all concentrations, except at 180 µg/L; 750 µg/L; pyruvate kinase increased at 750 µg/L; isocitrate dehydrogenase increased at 560 and 750 µg/L. After 96 hours: the enzymatic activity of glycogen phosphorylase was reduced at 56 and 180 µg/L but was increased at 320 µg/L; pyruvate kinase increased at all concentrations, glucose-6-phosphate dehydrogenase was elevated at 560 µg/L and isocitrate dehydrogenase was elevated at 320 µg/L.	De Coen et al., 2001
Lindane	Freshwater ciliate	*Tetrahymena pyriformis*		48 hours, static	Single species lab. test–growth inhibition NOEC: 610 µg/L; EC50: 1900 µg/L	Girling et al., 2000
Lindane	Freshwater rotifer	*Brachionus calyciflorus*		24 hours, static	Single species lab. test – mortality: LC50: 23E3 µg/L	Girling et al., 2000
Lindane	Freshwater rotifer	*Brachionus calyciflorus*		5 min., 1 hour and 5 hours, static	Single species lab. test – swimming activity: 5 min. EC50: 14E3 µg/L; 1 h EC50: 17E3 µg/L; 5 h EC50: 19E3 µg/L	Girling et al., 2000
Lindane	Freshwater rotifer	*Brachionus calyciflorus*		5 hours, static	Single species lab. test – feeding activity: 5 hours NOEC: 2000 µg/L; 5 h LOEC: 5000 µg/L; 5 h EC50: 9000 µg/L	Girling et al., 2000
Lindane	Freshwater rotifer	*Brachionus calyciflorus*		72 hours, static	Single species lab. test – population growth: 72 h NOEC: 10E3 µg/L; 72 h LOEC: 20E3 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Gammarus pulex*		2 hours, static	Single species lab. test – juvenile immobilization: 48 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*		48 hours, static	Single species lab. test – second instar mortality: 55 µg/L	Girling et al., 2000

HCH	Group	Species	Exposure	Exposure Type	Test, Effects, Endpoints	Reference
Lindane	Freshwater ciliate	*Tetrahymena pyriformis*		96 hours	Single species lab. test – growth inhibition 96 h NOEC: 660 µg/L; 96 h EC10: 1700 µg/L	Girling et al., 2000
Lindane	Freshwater rotifer	*Brachionus calyciflorus*		96 hours	Single species lab. test – partial-life-cycle 96 h NOEC: 10E3 µg/L; 96 h LOEC: 15E3 µg/L	Girling et al., 2000
Lindane	Freshwater rotifer	*Brachionus calyciflorus*		10 days	Single species lab. test – fulll-life-cycle 10 d NOEC: 10E3 µg/L; 96 h LOEC: 15E3 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Gammarus pulex*		96 hours and 10 days	Single species lab. test – juvinile mortality 96h LC50: 79 µg/L; 10 d LC50: 7 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Gammarus pulex*		96 hours	Single species lab. test – juvenile immobilization: 11 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Gammarus pulex*			Single species lab. test – precopula separation: NOEC: 7.5 µg/L; LOEC: 4 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*		96 hours and 10 days	Single species lab. test – second instar mortality 96 h EC50: 34 µg/L; 10 d LC50: 13 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*			Single species lab. test – percentage egg hatch NOEC: >82 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*		10 days	Single species lab. test – second instar growth: 10 d NOEC: 0.09 µg/L; 10 d LOEC: 0.2 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*			Single species lab. test – increased egg hatching time: NOEC: 1.4 µg/L; LOEC: 7.3 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*			Single species lab. test – slower larval development: NOEC: 1.1 µg/L; LOEC: 9.9 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*			Single species lab. test – sreduced emergence: NOEC: 1.1 µg/L; LOEC: 9.9 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*			Single species lab. test – delayed emergence: NOEC: 0.1 µg/L; LOEC: 1.1 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Gammarus pulex*		28 days	Stream mesocosm – feeding rate: > 20 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Gammarus pulex*		28 days	Stream mesocosm – population density: NOEC: 0.8 µg/L; LOEC: 3.1 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Gammarus pulex*			Stream mesocosm - drift: NOEC: 0.8 µg/L; LOEC: 3.1 µg/L	Girling et al., 2000

HCH	Group	Species	Exposure	Exposure Type	Test, Effects, Endpoints	Reference
Lindane	Freshwater insect	*Ephemerella ignitia*			Stream mesocosm – drift: LOEC: 3.1 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Ephemerella ignitia*		28 days	Stream mesocosm – population density: LOEC: 3.1 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Baetis rhodani*			Stream mesocosm – drift: NOEC: 0.222 µg/L; LOEC: 0.59 µg/L	Girling et al., 2000
Lindane	Freshwater flatworm	*Polycelis spp.*		28 days	Stream mesocosm – population density: NOEC: 800 µg/L; LOEC: 2400 µg/L	Girling et al., 2000
Lindane	Freshwater flatworm	*Polycelis spp.*			Stream mesocosm – drift: NOEC: 800 µg/L; LOEC: 2400 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Daphnia longispina*		39 days	Pond mesocosm – long-term population dynamics: NOEC: > 50 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Gammarus pulex*			Pond mesocosm – precopula separation: NOEC: 4µg/L; LOEC: 12 µg/L	Girling et al., 2000
Lindane	Freshwater crustacean	*Eucyclops serrulatus nauplia*		39 days	Pond mesocosm – long-term population dynamics: NOEC: 2 µg/L; LOEC: 6 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*		10 days	Pond mesocosm - second instar mortality: LC50: 2 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*		10 days	Pond mesocosm – second instar growth: NOEC: < 1 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chironomus riparius*			Pond mesocosm – Delayed/reduced emergence: NOEC: <0.8 µg/L; LOEC: 0.8 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chaoborus flavicans*		96 hours and 10 days	Pond mesocosm – 4th and 5th instar mortality: 96 h LC50: 4 µg/L; 10 d NOEC: < 1 µg/L; 10 d LOEC: 1 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Chaoborus flavicans*		39 days	Pond mesocosm – long term population dynamics: NOEC: < 2 µg/L; LOEC: 2 µg/L	Girling et al., 2000
Lindane	Freshwater insect	*Sigara striata*		96 hours and 10 days	Pond mesocosm – mortality: 96 h LC50: 4 µg/L; 10 d NOEC: < 2 µg/L; 10 d LOEC: 1 µg/L	Girling et al., 2000
Lindane	Freshwater rotifer	*Keratella quadrata*		39 days	Pond mesocosm – long term population dynamics: NOEC: 6 µg/L; LOEC: 12 µg/L	Girling et al., 2000
Lindane	Freshwater rotifer	*Asplanchna spp.*		39 days	Pond mesocosm – long term population dynamics: NOEC: 2 µg/L; LOEC: 6 µg/L	Girling et al., 2000

HCH	Group	Species	Exposure	Exposure Type	Test, Effects, Endpoints	Reference
Lindane	Marine echinoderm	*Paracentrotus livitus*		48 hours, static	Single species lab. test – embryogenesis success from fertilized egg egg to normal larvae: LOEC: 750 µg/L; EC50: > 91E3 µg/L	Bellas et al., 2005
Lindane	Marine tunicate	*Ciona intestinalis*		24 hours, static	Single species lab. test – embryogenesis success from fertilized egg egg to normal larvae: NOEC: 1600 µg/L; LOEC: 3200 µg/L; EC50: 4412 µg/L	Bellas et al., 2005
Lindane	Marine crustacean	*Maja squinado*		24 and 48 hours	Single species lab. test – larval mortality: 24 h NOEC: 0.8 µg/L; 24 h LOEC: 4.0 µg/L; 24 h EC50: 2.23 µg/L; 48 h NOEC: 0.8 µg/L; 48 h LOEC: 4.0 µg/L; 48 h EC50: 2.18 µg/L	Bellas et al., 2005
Lindane	Marine crustacean	*Palaemon serratus*		24 and 48 hours	Single species lab. test – larval mortality: 24 h NOEC: 0.1 µg/L; 24 h LOEC: 0.5 µg/L; 24 h EC50: 5.20 µg/L; 48 h NOEC: 0.1 µg/L; 48 h LOEC: 0.5 µg/L; 48 h EC50: 5.59 µg/L	Bellas et al., 2005
Lindane	Marine crustacean	*P. vannamei (larva)*		7 days	nuclei acid content: LOEC: 0.19 µg/L	Blockwell *et al.,* 1996a
Lindane	Freshwater crustacean	*Gammarus pulex (juvenile)*		14 days	growth: LOEC: 6.1 µg/L	Blockwell et al., 1996a
Lindane	Freshwater crustacean	*Gammarus pulex (adult)*		24 hours	changes in hepatopancreatic ceca: LOEC: 29.8 µg/L	Blockwell et al., 1996b
Lindane	Freshwater crustacean	*Bryocamptus zschokkei*	3.2-3200 µg/L	10 days	ssl 10 d LC50: 241 µg/L; development to adult was significantly longer at 100 µg/L; fewer eggs and viable offsprings produced at 32 µg/L; increase in offspring produced at concentrations of 3.2 and 10 µg/L	Brown et al., 2003
Lindane	Marine crustacean	*Mysidopsis bahia*		96 hours	ssl 96 h LC50: 6.3 µg/L	Schimmel et al., 1977
Lindane	Marine crustacean	*Penaeus duorarum*		96 hours	ssl 96 h LC50: 0.17 µg/L	Schimmel et al., 1977
Lindane	Marine crustacean	*Palaemonetes pugio*		96 hours	ssl 96 h LC50: 4.4 µg/L	Schimmel et al., 1977

HCH	Group	Species	Exposure	Exposure Type	Test, Effects, Endpoints	Reference
Lindane	Freshwater crustacean	*Hyalella azteca*	5-150 µg/L (adult), 10-75 µg/L (neonate)	24, 48, 96 and 240 hours exposure	ssl Adult LC50: 48h: 47.6 µg/L, 72h: 45.4 µg/L; 96h: 42.8 µg/L; 120h: 38.5 µg/L; 240h: 26.9 µg/L. Neonate (0-7 days): 24h: 29.5 µg/L, 48h: 14.8 µg/L, 72h: 13.2 µg/L; 96h: 12.9 µg/L; 120h: 11.1 µg/L; 240h: 9.8 µg/L.	Blockwell et al., 1998a
α-HCH	Saline crustacean	*Artemia salina*		4 days exposure followed by 31 days in untreated synthetic saltwater	LC50: 500 µg/L	Canton et al., 1978
α-HCH	Freshwater crustacean	*Daphnia magna*		48 hours,	48-h LC50: 800 µg/L	Canton et al., 1975
α-HCH	Freshwater mollusc	*Lymnea stagnalis*		48 hours growth inhibition/mortality or immobilization	48-h EC50: 1200 µg/L	Canton and Slooff, 1977

Aquatic Plants

Table 14 Toxicity of Lindane Technical Active to Freshwater Algae

Species	Exposure type	Test, Effects, Endpoints	Reference
Anabaena sp.		EC50: 2.5 mg a.i./L growth inhibition	In: Review of Lindane; Pesticides Safety Directorate, 1996
Chlamydomonas reinhardi	24 and 72 hours, static	Single species lab. test – growth inhibition 24 h NOEC: 3000 µg/L; 72 h NOEC: 1600 µg/L; 72 h EC50: 4000 µg/L	Girling et al., 2000
Chlamydomonas reinhardi	24 hours, static	Single species lab. test – 24 h EC10 (Effective photosynthesis rate: static exposure): 1500 µg/L	Girling et al., 2000
Scenedesmus subspicatus	24 and 72 hours, static	Single species lab. test – growth inhibition 24 h NOEC: 1300 µg/L; 72 h NOEC: 1400 µg/L; 72 h EC50: 3200 µg/L	Girling et al., 2000
Scenedesmus subspicatus	24 hours, static	Single species lab. test – 24 h EC10 (Effective photosynthesis rate: static exposure): 3000 µg/L	Girling et al., 2000

Species	Exposure type	Test, Effects, Endpoints	Reference
Euglena gracilis	72 hours, static	Single species lab. test – growth inhibition in light 72 h NOEC: 30E3 µg/L; 72 h EC50: >1000E3 µg/L	Girling et al., 2000
Euglena gracilis	72 hours, static	Single species lab. test – growth inhibition in light 72 h NOEC: > 200E3 µg/L; 72 h EC50: > 200E3 µg/L	Girling et al., 2000
Chlamydomonas reinhardi	96 hours, 7 days and 10 days, flow-through	Single species lab. test – growth inhibition 96 h NOEC 1300 µg/L; 96 h EC50: 1600 µg/L; 7 d NOEC: 1300 µg/L; 7 d EC50: 1400 µg/L; 10 d NOEC: 1300 µg/L; 10 d EC50: 1300 µg/L	Girling et al., 2000
Euglena gracilis	5 days	Single species lab. test – growth inhibition in light 5 d NOEC: > 1000E3 µg/L; 5 d EC50: > 1000E3 µg/L	Girling et al., 2000
Euglena gracilis	5 days	Single species lab. test – growth inhibition in dark 5 d NOEC: 35E3 µg/L; 5 d EC50: > 200E3 µg/L	Girling et al., 2000
Algal community		Alterations in the phytoplankton composition with decreases in the cryptophyte and diatom populations and an increase in cyanophytes (blue-green algae)	In: European Commission ECCO meetings draft evaluation of lindane, 1999

Endocrine Disrupting Effects in Vertebrates

Table 15   Endocrine Disrupting Effects of Lindane on Vertebrate Reproductive System

Species	Exposure to lindane	Effect	References
Catfish (*Heteroneustes fossilis*) and carp (*Carassius auratus*)	0.1, 1,0, or 10 mg/L four weeks during the active pre-spawning phase	Decreases in plasma sex steroids (T, 11-KT, E2), GtH, GSI and total phospholipid	Singh and Canario, 2004; Singh et al., 1994
Rainbow trout hepatocytes	10-5 M for 24 hours	Increased ER, and Vg mRNA levels	Flouriot et al., 1995
Male green neon shrimp (*Neocaridina deticulata*)	0.1, or 1.0 µg/L for four weeks	Decrease in hemolymph T; increase in hemolymph estradiol. No effect on Vg levels.	Huang et al., 2004
Male rat	50 or 100 mg/kg bw 120 days dermal exposure.	Decreases in serum T levels, epididymal sperm count, and sperm mobility	Prasad et al., 1995.

Species	Exposure to lindane	Effect	References
Rat during lactation	6 mg/kg bw single oral dose on day 9 or 14 of lactation; 1 mg/kg bw daily oral dose from day 9 to 14 of lactation	Decrease in relative testicular weight, T levels, number of sperm & spermatid & Leydig cells in all treated groups. Reduced sexual behaviour	Dalsenter et al., 1997.
Female rat	3 or 6 mg/100 g bw 7 days oral intubation	Inhibition of oestradiol-receptor complex formation	Tezak et al., 1992.
Mouse	15 or 25 mg/Kg bw by gavage from GD 9 to 16	Elongated or round spermatids in the epididymal sperm from mouse exposed *in utero* to 25 mg lindane /kg bw; diploid, or tetraploid testis cells	Traina et al., 2003
Sheep (F2 generation Rams)	1 mg/kg/day bw fed to parents and F2 generation	Decrease in plasma E2 and LH; decreased T and LH responses to GnRH; reduced sexual behaviour; No effect on response to TSH and ACTH	Beard et al., 1999
Mink (*Mustela vision*)	1 mg/kg/day bw fed to parents (before mating until weaning) and F2 and F3 generations (from conception to maturity)	Decreased reproductive success (60%) and reduced testis size in F3 generation. No effect on serum concentrations of cortisol, T, E2, and thyroxine in F3 generation	Beard and Rawlings, 1998.
Duck (*Anas platyrhychos domesticus*)	20 mg/kg bw oral daily dose	Egg shell thinning	Chakravarty and Lahiri, 1986

T: testosterone; 11-KT:11-ketotestosterone, GtH: gonadotropin, GnRH: gonadotropin-releasing hormone; GSI: gonadosomatic index, E2: 17 β-estradiol, Vg: vitellogenin, GD: gestation day; ER: estrogen receptor; Vg, vitellogenin, LH: luteinizing hormone; ACTH: adrenocorticotropic hormone; TSH: thyroid-stimulating hormone.

Appendix IX   Summary of Environmental Risk Assessment

Birds

Table 1   Risk to Birds Consuming Lindane-Treated Seeds Based on the Acute LD$_{50}$

Species	Number of seeds ingested to reach LD$_{50}$			Number of seeds ingested/day[a]			Risk Quotient (RQ)		
	Wheat	Corn	Canola	Wheat	Corn	Canola	Wheat	Corn	Canola
Bobwhite quail	1137	159	343	261	34	2090	0.2	0.2	6.1
Mallard duck	113684	15882	34286	1094	144	8750	0.01	0.01	0.3
House sparrow	77	11	23	80[b]	10[b]	637[b]	1.0	1.0	27.6
Red-winged blackbird	158	22	48	193[c]	25[c]	1541[c]	1.2	1.2	32

a   Calculated from food consumption data in Urban and Cook, 1986.
b   Based on food consumption data for the field sparrow in Urban and Cook, 1986.
c   Based on highest yearly percentage found in the gizzard of red-winged blackbirds from Portage La Prairie, Manitoba (Bird and Smith, 1964).

Table 2   Risk to Birds Consuming Lindane-Treated Seeds Based on the Acute NOEL

Species	Number of seeds ingested to reach NOEL			Number of seeds ingested/day[a]			Risk Quotient (RQ)		
	Wheat	Corn	Canola	Wheat	Corn	Canola	Wheat	Corn	Canola
Bobwhite quail	114	16	34	261	34	2090	2.3	2.2	59
Mallard duck	11368	1588	3429	1094	144	8750	0.1	0.1	2.5
House sparrow	7.6	1	2.3	80[b]	10[b]	637[b]	10.5	11	268
Red-winged blackbird	15.8	2.2	4.8	193[c]	25[c]	1541[c]	12.2	11.5	324

a   Calculated from food consumption data in Urban and Cook, 1986.
b   Based on food consumption data for the field sparrow in Urban and Cook, 1986.
c   Based on highest yearly percentage found in the gizzard of red-winged blackbirds from Portage La Prairie, Manitoba (Bird and Smith, 1964).

Table 3   Risk to Birds Ingesting Lindane-Treated Seed on the Chronic NOEC

Species	NOEC (mg/kg diet)	NOEC (mg/kg bw/day)	Estimated dose (mg/kg bw/day)[a]			Risk Quotient (RQ)		
			Wheat	Corn	Canola	Wheat	Corn	Canola
Bobwhite quail	80	7.2	29.5	27.5	752	4.1	3.8	105
Mallard duck	15	0.63	17.5	16.3	447	28	26	709

[a] Calculated from food consumption data in Urban and Cook, 1986.

Mammals

Table 4   Risk to Mammals Ingesting Treated Seed Based on the Acute LD$_{50}$

Species	Number of seeds to reach LD$_{50}$			Number of seeds ingested/day[1]			Risk Quotient (RQ)		
	Wheat	Corn	Canola	Wheat	Corn	Canola	Wheat	Corn	Canola
Rat	3432	479	1035	315	41	2421	0.09	0.09	2.3
Mouse	34	5.1	10.2	25	3.3	200	0.74	0.66	20

[1] Calculated from food consumption data in Urban and Cook, 1986.

Table 5   Risk to Mammals Ingesting Treated Seed Based on the Acute NOEL

Species	Number of seeds to reach NOEL			Number of seeds ingested/day[1]			Risk Quotient (RQ)		
	Wheat	Corn	Canola	Wheat	Corn	Canola	Wheat	Corn	Canola
Rat	343.2	47.9	103.5	315.3	41.1	2421.3	0.9	0.9	23.4
Mouse	3.4	0.5	1	25	3.3	200	7.4	6.6	200

[1] Calculated from food consumption data in Urban and Cook, 1986.

Table 6   Risk to Mammals Ingesting Lindane-Treated Seed Based on Chronic Toxicity

Species	NOEC (mg/kg diet)	NOEC (mg/kg bw/day)	Estimated dose (mg/kg bw/day)[a]			Risk Quotient (RQ)		
			Wheat	Corn	Canola	Wheat	Corn	Canola
Rat	1	0.05	15	14	383	300	280	7650

[a] Calculated from food consumption data in Urban and Cook, 1986.

Table 7   Risk of Reproductive Effects in Small Mammals Associated with Feeding on Lindane-Treated Seed (Using Endpoint = 1 mg Lindane/kg bw/day)

Species	Number of seeds ingested to reach endpoint (1 mg/kg/d)[1]			Number of seeds ingested/day[2]			Risk Quotient (RQ)[2]		
	Wheat	**Corn**	**Canola**	**Wheat**	**Corn**	**Canola**	**Wheat**	**Corn**	**Canola**
Rat	21	3	6	315	41	2421	15	14	404

[1] Based on body weight of the rat, amount of lindane per seed and potential number of seeds ingested per day (see Appendix X).
[2] Values based on calculations in Appendix X.

Table 8   Summary of Risk Assessment of Lindane to Aquatic Organisms

Organism	Exposure	Endpoint	Assessment endpoint*	Species	RQ	LOC
Freshwater Invertebrate	96-h acute	EC50 = 4.0 µg/L	2.0 µg/L	*Sigara striata*	0.04–0.20**	Not exceeded
	28-d chronic	NOEC = 0.80 µg/L		*Gammarus pulex*	0.10–0.50**	Not exceeded
Marine Invertebrates	96-h acute	LC50 = 0.17 µg µg/L	0.09 µg/L	*Penaeus duorarum*	3.7***	Exceeded
	28-day chronic	statistically significant oestrogenic effects	0.1 µg/L	*Neocaridina denticulata*	2.8****	Exceeded
Fish	96-h acute	LC50 = 1.7 µg/L	0.17 µg/L	Brown trout	0.45–2.4**	Exceeded
	Chronic	NOEC = 2.9 µg/L	2.9 µg/L	Rainbow trout	0.03–0.14**	Not exceeded
Plants	Acute	EC50 = 1300µg/L	650 µg/l	*Chlamydomonas reinhardi*	0.0001-0.0006	Not exceeded
Amphibian	Acute	LC50 = 2.7 mg/L	0.27 mg/L	*Pseudacris triseriata*	0.001**	Not exceeded
	Chronic	EC21 = µg/L	0.1 µg/L	wood frog	0.76–4.0**	Exceeded

*Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC50 or LC50 from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
**Based on the maximum measured concentrations of 0.076 µg/L (rivers) and 0.4 µg/L (wetlands)
***Based on the maximum 96-hour expected concentration of 0.336 µg/L resulting from surface runoff simulated by the PRZM/EXAMS Model.
****Based on the maximum 21-day expected concentration of 0.281 µg/L resulting from surface runoff simulated by the PRZM/EXAMS Model.

Appendix X   Summary of Surface Water Concentrations Resulting from Surface Runoff

To assess the surface water concentrations resulting from surface runoff from agricultural fields seeded to lindane-treated seed, the PMRA utilized the PRZM/EXAMS Model4 at a screening level (Level 1). The scenario used is surface runoff from a 10-ha lindane-treated canola field entering a 80-cm deep 1-ha wetland. The simulations were conducted for the regions of Alberta, Manitoba, Saskatchewan, Ontario and Québec. The model estimated the 90th percentile of the highest yearly values for the peak, 96-hour, 21-day, 60-day, 90-day and the mean yearly concentrations. The estimation of the concentrations takes into account the persistence of lindane in water; thus, the values are a summation of the deposition in that year plus the carryover remaining from previous years. Table 1 outlines the EECs in aquatic habitats resulting from surface runoff.

Table 1   Simulated Maximum Concentrations in a Wetland Resulting from Surface Runoff of Lindane.

Region	Concentrations (µg/L)*					
	Peak	96-hour	21-day	60-day	90-day	yearly mean
Alberta (North)	0.208	0.186	0.153	0.14	0.136	0.127
Alberta (South)	0.297	0.254	0.186	0.153	0.15	0.136
Manitoba	0.238	0.224	0.182	0.161	0.156	0.14
Ontario	0.37	0.336	0.281	0.245	0.237	0.203
Quebec	0.276	0.252	0.218	0.193	0.188	0.178
Saskatchewan	0.237	0.206	0.149	0.136	0.135	0.121

*Values generated by PRZM/EXAMS are 90th percentile of the highest yearly concentrations

Appendix XI   Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

The following tables (1, 2 and 3) list violations of MRLs from 1995 to 2003 for all domestic and import commodities surveyed by the CFIA. All violations occurred on or before cancellation of lindane usage in Canada. In particular, domestic Ginseng root is noteworthy as violations arose after cancellation in 2001 and for a use not registered in Canada. A similar violation on domestic radish appears to be an isolated case. Residues in mature crops produced from treated seed are expected to be small. This assumption is supported by low number of violations (tables 1 and.2), both before and after the 2001cancellation.

The situation for livestock residues raises attention. Although the original violation on beef before 2001 can be understood to come from lindane used as insect repellant in the past, several detections during 2003 to 2005 in the fat of domestic buffalo, mutton, sow and veal are consistent with local usage still permitted in Canada (until 2004) to exhaust the channels of trade. It is expected that livestock residues will vanish in the next few years.

Table 1   Violations of Lindane MRLs for Imported Commodities

Imported	size	Detects	MRL (ppm)	Violations			
				number	conc (ppm)	Period	Origin
Ginseng Root	24	6	0.1	6	0.11–1.12	1998–1999	CHINA(5) US(1)
Ginseng Root	9	2	0.1	2	0.254–0.669	2001–2002	CHINA(2)

Size: total number of samples taken during 1998–2003; **Detects**: number of samples with readings above LOD. **MRL**: Maximum Residue Limit as per sub B.15.002 of the FDR; **number**: number of violations during period; **conc**: concentration range; **period**: violation period; **Origin**: country of origin with total number of detects for that country.

Table 2   Violations of Lindane MRLs for Domestic Commodities

(Conventions as in Table 1. An asterix (*****) indicates non-registered usage.)

Domestic	total	Detects	MRL (ppm)	Violations		
				Number	Range (ppm)	Period
Beef	2328	9	2	1	44.3–44.3	1999–2000
Chicken	2302	6	0.7	1	4.194–4.194	1995–1996
Ginseng Root*	55	5	0.1	3	0.125–0.389	2000–2003
Radish*	101	1	0.1	1	0.18–0.18	2000–2001

Table 3   Violations of BHC MRL for Imported Commodities

(Conventions as in table 1.)

Imported	size	Detects	MRL (ppm)	Violations			
				number	conc (ppm)	Period	Origin
Ginseng Root	24	12	0.1	10	0.104–8.4	1998–1999	China(11) Korea(1)
Ginseng Root	5	2	0.1	2	0.303–0.659	2001–2002	China(2)

For its part, the USEPA proposed revocation of all tolerances for lindane in August, 2006 except for livestock fat to allow "passage through the channels of trade". Then, a final rule (Federal Register: September 19, 2007, volume 72, number 181) established a deadline of October 2, 2009 on all livestock fat. This action completes the revocation of all lindane tolerances in the United States.

The PMRA proposes to replace all current MRL values with 0.01 ppm, the level of quantitation. In order to harmonize with the United States' actions, the change in Canadian livestock MRL's would be deferred until October 2, 2009. This action would harmonize with similar dispositions by CODEX, which at the moment (2006) allows 0.01 ppm on the fat of animals and 0.1 ppm otherwise.

Table 4   Current Existing and Import MRLs
(Canadian registered use as of 2001 appears in bold and is for seed treatment only; a hyphen (- **)** indicates no MRL.)

Commodity	FEB 06 Canadian MRL[1] (ppm)	MAR 06 CODEX MRL[2] (ppm)
Apple	3	-
Apricot	3	-
Asparagus	3	-
Avocado	3	-
Bean	**0.1**	-
Broccoli	**3**	-
Brussels sprouts	**3**	-
Cabbage	**3**	-
Cauliflower	**3**	-
Celery	3	-
Cherry	3	-
Collards	3	-
Cucumber	3	-
Eggplant	3	-
Grape	3	-
Fruits and vegetables		
Guava	3	-

Commodity	FEB 06 Canadian MRL[1] (ppm)	MAR 06 CODEX MRL[2] (ppm)
Kale	3	-
Kohlrabi	3	-
Lettuce	3	-
Mango	3	-
Melon	3	-
Mushroom	3	-
Mustard greens	**3**	**-**
Nectarine	3	-
Okra	3	-
Onion, dry bulb	3	-
Peach	3	-
Pea	**0.1**	-
Pear	3	-
Pecan	0.1	-
Pepper	3	-
Pineapple	3	-
Plum	3	-
Plum, prune, fresh	3	-
Pumpkin	3	-
Quince	3	-
Rutabaga	**0.1**	-
Soybean	**0.1**	
Spinach	3	-
Squash	3	-
Squash, summer	3	-
Strawberry	3	-
Swiss chard	3	-
Tomato	3	-
Milk and Dairy	0.2	0.01
Egg	0.2	0.01
Cereals, grains		
Barley	**0.1**	**0.01**
Canola	**0.1**	**-**
Corn	**0.1**	**0.01**
Flax	**0.1**	**-**
Oat	**0.1**	**0.01**
Rye	**0.1**	**0.01**
Sorghum	0.1	0.01
Wheat	**0.1**	**0.01**
Meat		
Cattle	2	0.1
Hog	2	0.1
Horse	2	0.1
Sheep	2	0.1

Commodity	FEB 06 Canadian MRL[1] (ppm)	MAR 06 CODEX MRL[2] (ppm)
Poultry	0.7	0.05
Offal, edible fat		
Cattle	2	0.01
Goat	2	
Hog	2	0.01
Horse	2	0.01
Sheep	2	0.01
Poultry	0.7	0.01

[1]   MRLs for which values have not been specified take the default value of 0.1 ppm. This is under review. The US proposed cancellation of use and revocation of all tolerances for lindane in August 2006 following request by registrants.

[2]   CODEX MRL at 0.01 ppm are equivalent to the level of quantitation (determination)

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(Note: Proprietary studies from former registrants were also reviewed for the lindane risk assessment.)

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