Re-evaluation Note REV2009-08

Lindane Risk Assessment

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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

Argentina
Armenia
Bangladesh
Barbados
Belgium
Bulgaria
Burundi
Costa Rica
Croatia
Cyprus
Czech Republic
Denmark
Dominican Republic
Ecuador
Egypt
El Salvador
Finland
Gambia
Georgia
Guatemala
Honduras
Hong Kong
Hungary
Jamaica
Japan
Russia
Singapore
Slovakia
South Africa
St Lucia
Sweden
Taiwan
Thailand
Tonga
Turkey
Uruguay
Vietnam
Yemen

Restricted/Severely Restricted

Algeria
Australia
Austria
Belize
Brazil
Canada
China
Columbia
Cuba
European Community
Fiji
Spain
Sri Lanka
Sudan
Switzerland
Trinidad/Tobago
United Kingdom
United States of America
Venezuela
Yugoslavia

Not registered

Estonia
Guinea-Bissau
Indonesia
Monaco
Mongolia
Niger
Rwanda
Slovenia
Uganda
Vanuatu

Registered

Bolivia
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).

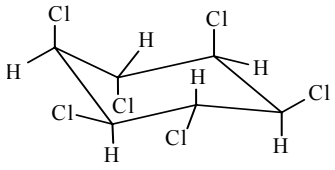
Of the crops for which some former registrants support reinstatement of lindane seed treatment, several are grown primarily for export: canola, mustard, wheat, oats, dry beans, soybeans, dry peas. However, the export market for lindane-treated crops has become increasingly limited as countries have introduced 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

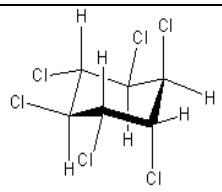
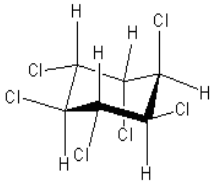
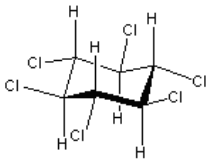
Common Name:	Lindane
CAS Chemical Name:	1α,2α,3β,4α,5α,6β-hexachlorocyclohexane
Other Name:	gamma-hexachlorocyclohexane (γ-HCH); {gamma-benzene hexachloride (γ-BHC) is not technically correct but is still widely used}

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 (Axial/Equatorial):	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 × 10-5 Pa	Low volatility
Henry's Law Constant (atm·m3/mole)	6.0 × 10-6 atm·m3/moleb	Potential to volatilize from moist soil and water	4.2 × 10-7 atm·m3/molec	Low potential for volatilization from moist soil and water
n-octanol/water partition coefficient (log *K*ow)	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 99.9th 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 × 10^3 for lindane, 1–4 × 10^3 for α-HCH and 1–41 × 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 $\geq$1), a refined risk assessment was conducted that considered measured environmental concentrations of lindane. In refining the risk (if the RQ $\geq$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