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Docket Control Number EPA-HQ-OPP-2006-0034 - Lindane and Other Hexachlorocyclohexane (HCH) Isomers Risk Assessment; Notice of Availability and Solicitation of Risk Reduction Options (February 8, 2006)

Dear Mr. Howard,

With this letter Pesticide Action Network North America (PANNA), Alaska Community Action on Toxics (ACAT) and the 32 undersigned supporting organizations respectfully submit comments on EPA’s Risk Assessment for the insecticide lindane and other HCH isomers. PANNA is the North America regional center for PAN International, a coalition of hundreds of environmental and other citizen organizations worldwide. Our affiliate groups in North America continue to express much interest and concern about the health and environmental effects of lindane. ACAT is a statewide non-profit organization based in Anchorage dedicated to achieving environmental health and justice. ACAT works to stop the production, proliferation, and release of toxic chemicals that may harm human health or the environment.

Summary of Comments

We are encouraged that EPA has included consideration of all HCH isomers in this revised Risk Assessment for lindane. Given the known and suspected health effects of the other HCH isomers (particularly α- and β-HCH), and given that these isomers are introduced into the environment
only through the production and use of lindane, this represents a significantly more realistic assessment of the human health and environmental impacts of lindane use. We also find it encouraging that EPA is now considering infant exposure to HCH isomers through breastfeeding in its dietary assessment, and is more carefully assessing the impacts of HCH isomers in Indigenous communities in the Arctic regions reliant on traditional foods.

While this Risk Assessment represents a more realistic consideration of exposure, we still find the analysis could be strengthened in several areas, including more thorough consideration of viable nonchemical alternatives to the agricultural uses of lindane, consideration of multiple routes of exposure to HCH isomers, and explicit recognition of lindane as a likely endocrine disruptor for humans as well as other mammals.

In response to EPA's specific information requests (Part V), we have included extensive data on lindane's presence in human breastmilk, additional information on lindane's carcinogenicity, information further supporting our earlier critique of EPA's decision to reduce the ten-fold safety factor to 3X for lindane, extensive data on cultural practices and potential impacts of continued lindane use on subsistence populations, and summaries of studies addressing the question of the potential additive effects of the various HCH isomers on the liver as both a non-cancer and cancer endpoint.

Finally, in response to EPA's call for “risk reduction” options, we firmly believe that given the nature of lindane production, persistence and health and environmental effects, the only effective risk reduction option for this chemical is immediate withdrawal of its registration for continued use.

Specific comments

1. EPA must include full consideration of nonchemical alternatives

In its review of the pesticidal uses of lindane in the United States (Section 1A.1, p.2), EPA includes estimates of the financial impact to grain growers of shifting from lindane to other seed treatment alternatives. Unfortunately, only chemical alternatives are included in this analysis, overlooking information on nonchemical alternatives collected by the Lindane Task Force in the process of developing the North American Regional Action Plan (NARAP) on Lindane and Other HCH Isomers. Specific alternative methods are discussed in Annex F of the NARAP: — Available Non-Chemical Alternatives to Agricultural Seed Treatment Uses of Lindane. The Agency must also incorporate information and solutions presented at the Lindane Task Force Workshop on Alternatives to Lindane Use (North American Commission for Environmental Cooperation workshop held in Mexico City, October 4-6, 2005). A thorough analysis of the transition from lindane must include full consideration of nonchemical alternatives.

2 - Problems with lindane production continue to be underestimated

We are encouraged that EPA includes in this risk assessment a review of the problems associated with the production of lindane. We strongly support EPA's stated concerns
regarding “cracking” of lindane waste isomers, including the viability of this practice and the potential for dioxin formation “during the cracking process or during the incineration of waste isomers or the products of cracking” (p. 13).

We are concerned, however, with EPA’s continued lack of clarity regarding the amount of lindane produced and the nature of the lindane production facilities in Romania and India (p.14). The U.S. is the only UNECE country that continues to use lindane for agricultural purposes, and reportedly imports all lindane from the production facility in Romania. A review of U.S. imports from Romania would thus provide substantive information on production levels in this country.

In previous comments to EPA (See Docket ID #: EPA-HQ-OPPT-2005-0555 - Review of Chemical Proposals for Addition under the Stockholm Convention on Persistent Organic Pollutants; Solicitation of Information for the Development of Risk Profiles), PANNA and ACAT submitted the following information about production in India, which we resubmit here:

Additional information for point #5 - Exposure in Local Areas, and point #1(iii) - Releases, such as discharges, losses and emissions

PANNA and ACAT request that EPA fully consider the information included in the attached report, *Lindane's Dirty Secret: Indian Facilities Dump Toxic Waste*. This report details the exposures and health impacts of lindane production affecting workers and local communities in India, directly addressing point #5 - Exposure in Local Areas. It also documents that lindane manufacturers in India continue to use unsafe disposal practices for the tons of HCH isomer waste created in the production of lindane, addressing point #1(iii) - Releases, such as discharges, losses and emissions.

The referenced report can be accessed on-line at:

3 - EPA continues to underestimate health effects by not considering multiple exposure pathways

While we are encouraged that EPA is now considering breastmilk as a pathway of exposure to lindane and other HCH isomers, the additive nature of multiple routes of exposure to multiple HCH isomers is not fully considered. These cumulative exposures are of particular concern for agricultural workers, Indigenous groups in the Arctic region, and children. The following points that PANNA made in our October 29, 2001 submission to EPA (OPP-34239 - Lindane Preliminary Risk Assessment) remain unaddressed:

Despite the fact that **EPA severely underestimates occupational exposures by not considering dermal and inhalation exposures in an additive way**, some on-farm activities and most canola seed treatment activities lead to exposure “exceeding the Agency's level of concern.” These exposures are likely to be much higher in a real-world setting, where workers are exposed to lindane via skin and lungs at the same time. While separating these exposure pathways may simplify the analysis, it does not reflect the full
risk experienced by workers involved in the formulation, handling and on-farm application of lindane. EPA should reassess occupational exposures considering additive exposure to workers.

In fact, the Ministry of Agriculture, Fisheries and Food in the United Kingdom ordered that all uses of lindane for seed treatment be stopped in 1999 after determining that “the level of exposure of those treating seeds with lindane is considered to be above acceptable levels.”

**EPA ignores an important route of exposure, pharmaceutical uses of lindane for treatment of lice and scabies.** Pharmaceutical uses for control of lice and scabies represent an important source of exposure to lindane, particularly for children. In the past 17 years, lindane has been applied more than 24 million times to treat scabies. The medicated shampoos are applied directly to the scalp of lice-infected patients - mostly children. Some of the human health effects associated with use of lindane to treat lice and scabies include brain and nervous system damage, convulsions and other illnesses. Lindane exposure has also been linked to aplastic anemia (blood disorder) and brain cancer. The National Pediculosis (headlice) Association recently established a database to track “adverse event” reports related to use of lindane to treat headlice in the U.S. In the first 24 months, more than 500 events were reported.

The Food Quality Protection Act (FQPA) requires that EPA consider “available information concerning the aggregate exposure levels of consumers” from dietary and all other exposures, and does not specify that the agency is only responsible for considering those routes of exposure within its regulatory jurisdiction. It is, therefore, not only irresponsible but also illegal under the FQPA to exclude exposure from pharmaceutical uses of lindane in the agency's risk assessment for lindane.

**EPA discounts evidence of lindane residues in water.** EPA's rationale for discounting the findings of several long-term water monitoring programs is that “there is no correlation of monitoring with actual lindane use” (*Overview of Risk Assessment, p. 7*). A correlation with use, however, is irrelevant, since EPA's responsibility in conducting the risk assessment is to evaluate cumulative exposure from all potential sources, regardless of the original source of the pesticide. Waterways contaminated with lindane pose exposure risks both as potential drinking water and through the biomagnified contamination of fish. One federal study of an urban waterway in Texas found lindane contamination in 11% of the fish and clams found in the waterway. Note that under the Clean Water Act, the federal target for lindane levels in water bodies that are potential drinking water sources is 0.019 parts per billion - well below the 11 parts per billion found in some groundwater samples as reported in the EPA STORET data base (*Overview of Risk Assessment, p. 6*).

**EPA's analysis of dietary risk does not consider residues in food from previous lindane use.** In its most recent Total Diet Study, the Food and Drug Administration found lindane residues in more than 40 food products, from pork chops to cream cheese, from hamburgers to dill pickles and peanuts. Current and previous lindane use in the
U.S., along with ongoing use in other parts of the world, likely account for lindane residues in the U.S. food supply. These documented residues cannot be overlooked in assessing both acute and chronic dietary risk. Focusing solely on the “anticipated residues for all commodities supported for reregistration” (Overview of Risk Assessment, p. 4) is not acceptable given the persistent and bioaccumulative nature of lindane.

4 - Endocrine disruption must be included in consideration of human health effects

While we are encouraged that EPA now includes endocrine disruption in its discussion of the ecological impacts of lindane (these effects were previously set aside for future consideration by the “endocrine disruptor screening program”), we are concerned that these effects are not also addressed in the discussion on the human health impacts of lindane and other HCH isomers. Lindane is ranked as a suspected endocrine disruptor on several target lists of endocrine disrupting chemicals, including the Danish EPA List of Endocrine Disrupting Auxiliaries and the European Union Prioritization List.

We resubmit to EPA the following summary of lindane's hormone disrupting effects, originally included in joint comments (signed by 61 North American public interest groups) on the draft North American Regional Action Plan for lindane submitted to the Commission on Environmental Cooperation's Lindane Task Force:

A summary of observed lindane toxicity in rats found that exposure to the chemical led to impairment of testosterone metabolism and could lead to an alteration of male reproductive systems during prenatal development. Other animal studies show that high doses of lindane can alter oocyte maturation in mice and marine invertebrates. A recent study indicated that prenatal administration of lindane may induce long lasting effects on spermatogenesis in mice. Researchers found experimental lindane exposure resulted in reduced sperm counts, changes in the pattern of testicular germ cell distribution, and abnormalities in chromatin in the sperm cells of mice.

A study examining the effects of lindane exposure on the reproductive systems of mice concluded that developing oocytes exposed to lindane in vivo had an increase of irreversible damage in two-cell embryos. The authors report that the observed effects occurred at lindane concentrations that greatly exceed the concentrations measured in the human population, but they caution that the cumulative effect of lindane stored in the adipose tissue and exposure to other chemicals with similar mechanisms of toxicity might lead to clinically significant effects on reproduction.

Reproductive effects of HCH isomers during fetal development is of particular concern given the recent findings of the U.S. Centers for Disease Control and Prevention that more than half the participants in a national survey of chemicals in blood and urine carried β-HCH in their blood, with the highest levels found among women of childbearing age. Analysis of maternal and umbilical cord blood shows that HCH isomers are some of the chemicals detected in the highest concentrations among residents of the Arctic. EPA has also noted that lindane is “efficiently transmitted” from mother to child through breastmilk. When women carry HCH isomers in their bodies, infants may be exposed to their damaging reproductive effects both inside and outside the womb.
**Responses to EPA's Call for Additional Information**

A - Infants’ exposure to lindane and the HCH isomers in breastmilk (general population and subsistence populations). The Agency would like to receive information on lindane levels, as well as levels of other HCH isomers, in breastmilk. (p.50)

We are encouraged that EPA is now including in its assessment consideration of infant exposure to HCH isomers through breastmilk. We note that prenatal exposure must also be considered in any assessment of the risk lindane poses to infants and developing children.18

Human breastmilk is the perfect nutrition for infants and crucial for protecting them from infections. Breast-feeding is also very important in the psychological development of infants. However, toxic pesticides like lindane and HCH isomers can contaminate human breastmilk. Breastmilk secretion is the largest route of excretion of lipid-soluble contaminants such as HCH,19,20 impacting the health of breast-fed infants who are exposed to these contaminants in the food that should be the purest, most nourishing source of nutrition for them. Despite serious concerns about lindane and HCH isomers in breastmilk, it remains the best food for infants.

Withdrawal of lindane from agricultural use is the most effective way to protect infants and children, the segment of our population most vulnerable to contaminants, from exposure to harmful HCH isomers. Comparing pound per pound of body weight children consume more food than adults, and for infants whose diet is completely dependent on breastmilk, contamination with lindane and other pesticides presents a large source of pesticide exposure at an age when their bodies can least resist the effects of these toxic chemicals.

Breast-feeding constitutes a major source of bioaccumulated contaminants for nursing infants.21 Chemicals can be excreted into breastmilk by binding to milk protein or adhering to the surface of milk fat globules, or they can be totally contained within the fat globules. Fat-soluble materials such as organochlorines can be stored for long periods of time in maternal body fat. Body fat mobilization and turnover are increased during lactation and fat-soluble substances may also be mobilized. Fat-soluble substances may be released from fat during weight loss, which typically occurs during lactation. Thus past exposures to fat-soluble pesticides pose a risk that the breastfeeding mother cannot avoid at the time of pregnancy and lactation. This represents an important source of pesticide contamination for the fetus and for the infant during breast-feeding.22 The lipophilic HCH isomers are an important contaminant of breastmilk. In its 2002 risk assessment for lindane, EPA concluded that lindane (γ-HCH) is transmitted “efficiently” through breastmilk, and that nursing offspring are exposed to this contamination “during critical periods of post-natal development.”23

Because the β isomer is the most persistent and bioaccumulative isomer of HCH and the α and γ isomers can be converted into the β isomer within organisms, as much as 90% of HCH detected in human tissues and breastmilk is β-HCH.24 Chronic toxicities of HCH isomers, α-HCH, β-HCH, γ-HCH, and δ-HCH, increase in the following order: δ, γ, α, β.25

**Global Monitoring Data Shows HCH in Breastmilk**

Breastmilk monitoring is a noninvasive means of estimating body burdens of persistent organic pollutants like HCH in nursing mother, fetus, infant and child.26 Alarming levels of HCH
isomers have been recorded in several breastfeeding monitoring studies. In addition, the Centers for Disease Control testing of chemicals in the blood and urine of the US population found β-HCH blood levels were highest among women of reproductive age. Table 1 shows data from a World Wildlife Fund (WWF) study, which shows the high values of HCH recorded in different geographic regions between 1971 and 1991. Table 2 illustrates the high levels of HCH isomers detected in different countries in studies from 1991 to 2002.

**Table 1:** Chemical contaminants found in human breastfeeding and some concentrations recorded (data from Jensen and Slorach, 1991)\(^2\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Typical values</th>
<th>High Values recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Milk fat mg/kg (ppm)</td>
<td>Whole milk őg/kg (ppb)</td>
</tr>
<tr>
<td>α HCH</td>
<td>0.2 Europe</td>
<td>160 Punjab, India 1979</td>
</tr>
<tr>
<td>β HCH</td>
<td></td>
<td>900 GDR 1971</td>
</tr>
<tr>
<td>γ HCH</td>
<td></td>
<td>80 Spain 1973</td>
</tr>
<tr>
<td>Total HCH</td>
<td></td>
<td>325 India 1979</td>
</tr>
</tbody>
</table>

**Table 2:** International comparison of HCH levels (őg/g lipid weight) in human breastfeeding\(^2\)

<table>
<thead>
<tr>
<th>Country</th>
<th>Survey Year</th>
<th>HCHs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing and Former Socialist Countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalian, China</td>
<td>2002</td>
<td>1400(^a)</td>
</tr>
<tr>
<td>Shenyang, China</td>
<td>2002</td>
<td>550(^a)</td>
</tr>
<tr>
<td>Turkey</td>
<td>1995-96</td>
<td>480(^a)</td>
</tr>
<tr>
<td>Iran</td>
<td>1991</td>
<td>600(^a)</td>
</tr>
<tr>
<td>Brazil</td>
<td>1992</td>
<td>280(^a)</td>
</tr>
<tr>
<td>Mexico</td>
<td>1997-98</td>
<td>60(^a)</td>
</tr>
<tr>
<td>Kenya</td>
<td>1991</td>
<td>96(^a)</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>1994</td>
<td>2300(^f)</td>
</tr>
<tr>
<td>Russia</td>
<td>1996</td>
<td>560(^a)</td>
</tr>
<tr>
<td>Developed Countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>1998</td>
<td>210(^a)</td>
</tr>
<tr>
<td>Sweden</td>
<td>1997</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>1995-97</td>
<td>40(^a)</td>
</tr>
<tr>
<td>Canada</td>
<td>1996</td>
<td>23(^a)</td>
</tr>
<tr>
<td>Spain</td>
<td>1991</td>
<td>280(^a)</td>
</tr>
<tr>
<td>UK</td>
<td>1997-98</td>
<td>100(^a)</td>
</tr>
</tbody>
</table>

\(a=αHCH+βHCH+γHCH; f=αHCH+βHCH; g=βHCH \text{ only;} \ h=β \text{ HCH}+γ\text{HCH}\)
Breastmilk monitoring from around the world illustrates the widespread contamination of breastmilk with HCH isomers. The following summary bullets and tables include some key findings from country-specific scientific studies.

- Testing of 140 human milk samples in sub-Arctic locations of Russia revealed that \( \beta \)-HCH levels in these samples were 10 times higher than corresponding levels in Norway.\(^{30}\)

- A Brazilian breastmilk study\(^ {31}\) of 40 lactating women living in Rio de Janeiro in 1992 revealed concentration of various HCH isomers (in \( \mu \)g/g of milk fat) at: \( \alpha \)-HCH: 0.001; \( \beta \) HCH: 0.27; \( \gamma \) HCH: 0.005

- Human breastmilk collected from Inuit mothers in Arctic Quebec had concentrations of organochlorine (OC) pesticides (including HCH isomers) that were two to 10 times greater than those of samples from southern Quebec.\(^ {32}\) Inuit mothers exhibit the greatest body burden known from exposure to organochlorine residues present in the environment by virtue of their location at the highest trophic level of the arctic food web.\(^ {33}\)

- From 1986 to 1997 more than 3,500 human milk samples were analyzed in northern Germany for OC compounds. Between summer 1995 and summer 1997 the median \( \beta \)-HCH level was 0.036 mg/kg, value expressed on a fat basis.\(^ {34}\)

- In New Zealand, a total of 53 milk samples were collected from October 1998 to May 1999. \( \beta \)-HCH was detected in all the samples and had a concentration of 16.3 ng/g fat. \( \alpha \)-HCH was detected in 96% of samples at a mean concentration of 0.2 ng/g fat.\(^ {35}\)

- A Mexican study\(^ {36}\) of OC pesticides in maternal blood serum, umbilical cord serum and milk found levels of 0.10mg/kg on fat basis in colostrum for sum of all HCH isomers and 0.06 mg/kg in human mature milk. 100% of a sample of 60 breastmilk samples had detectable levels of \( \beta \)-HCH isomer. 0.09 mg/kg on fat basis was the concentration of \( \beta \)-HCH in colostrum and 0.06mg/kg on fat basis in human mature milk.

Table 3: Mean concentrations of HCH in human milk, reported in four of six Canadian surveys\(^ {37}\) (\( \beta \)-HCH, ng/g whole milk)

<table>
<thead>
<tr>
<th></th>
<th>Canada</th>
<th>Ontario</th>
<th>Quebec</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>2.00</td>
<td>3.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1982</td>
<td>8.00</td>
<td>8.00</td>
<td>5.00</td>
</tr>
<tr>
<td>1986</td>
<td>0.92</td>
<td>0.58b</td>
<td>0.83b</td>
</tr>
<tr>
<td>1992</td>
<td>0.71</td>
<td>0.60b</td>
<td>0.54b</td>
</tr>
</tbody>
</table>
Table 4: Levels of HCH residues in 61 human milk samples\textsuperscript{a} from Delhi, India, 1996\textsuperscript{38}.

Note: \(\alpha\), \(\beta\) and \(\gamma\) isomers were detected in 31, 58 and 55 milk samples respectively. The levels of these isomers in human breastmilk were high relative to other studies, reflecting the fact that lindane is produced in India and its use is not restricted.

<table>
<thead>
<tr>
<th>Residue</th>
<th>Whole Milk (ppm)</th>
<th>Milk fat\textsuperscript{b} (mg/kg fat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)-HCH</td>
<td>0.08±0.25 (0-1.86)</td>
<td>1.83±3.89 (0-17.38)</td>
</tr>
<tr>
<td>(\beta)-HCH</td>
<td>0.24±0.49 (0-3.22)</td>
<td>8.83±12.93 (0-62.13)</td>
</tr>
<tr>
<td>(\gamma)-HCH</td>
<td>0.06±0.11 (0-0.80)</td>
<td>2.31±3.08 (0-14.58)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Collected from lactating women within one week after delivery and analyzed for residue levels. Values represent mean \(\pm\) standard deviation and range given in parenthesis.

\textsuperscript{b} Fat content of milk samples ranges from 1.30 to 7.00\% with a mean of 3.70.

Table 5: A Polish study tested breastmilk of 31 lactating women from three Polish industrial towns in September 2001\textsuperscript{39}.

<table>
<thead>
<tr>
<th></th>
<th>Town 1</th>
<th>Town 2</th>
<th>Town 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pg/g fat</td>
<td>Pg/g fat</td>
<td>Pg/g fat</td>
</tr>
<tr>
<td>(\alpha)-HCH</td>
<td>&lt;80</td>
<td>&lt;80</td>
<td>&lt;80</td>
</tr>
<tr>
<td>(\beta)-HCH</td>
<td>14980</td>
<td>18400</td>
<td>16500</td>
</tr>
<tr>
<td>(\gamma)-HCH</td>
<td>960</td>
<td>970</td>
<td>1120</td>
</tr>
</tbody>
</table>

Table 6: WWF-UK's 1999 study\textsuperscript{40} of chemical body burden showed HCH in UK breastmilk samples over time. Table shows comparison of mean and range of levels of HCH isomers in UK breastmilk over time (in mg/kg).

<table>
<thead>
<tr>
<th>Compound</th>
<th>1963-64 (19 samples)</th>
<th>1979-80 (102 samples)</th>
<th>1989-91 (193 samples)</th>
<th>1996-97 (168 samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole Milk</td>
<td>Whole Milk</td>
<td>Milk Fat</td>
<td>Whole Milk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\beta)-HCH</td>
<td>Not measured</td>
<td>0.007</td>
<td>0.22</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ND-0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ND-0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ND-0.030</td>
</tr>
<tr>
<td>(\gamma)-HCH</td>
<td>0.013</td>
<td>0.007</td>
<td>0.25</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ND-0.005</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ND-0.16</td>
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<td></td>
<td>ND-0.002</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(mean=0.001)</td>
</tr>
</tbody>
</table>

Estimates of Breastfeeding Infants' HCH Intake

The pesticide intake of a breast-feeding infant is a combination of intake during pregnancy via the placenta and the concentration of pesticides in the breastmilk, both of which are related to the maternal body burden, as well as the volume and duration of breast-feeding. The actual infant
pesticide burden is related to the amount available in the breastmilk, the amount actually absorbed by the nursing infant, and the ability of the infant to remove these substances from its body. The major routes for elimination of pesticides are through the kidneys and via metabolism, much of which is dependent on effective liver functioning. Both these organs are often poorly developed in the very young infant, which decreases the organs ability to remove toxic substances from the body. Clearance mechanisms can be particularly weak in low birth-weight infants.41

Infant exposure to HCH through breastmilk has been estimated in various studies, three of which are summarized below.

- A Japanese study42 of OC compounds in breastmilk from 1972 to 1998 revealed the following daily β-HCH intake for an infant: An infant consuming human breastmilk for only 3–6 months can take in 30–50% of contaminants in the body of the mother, which have been accumulating from food and other sources for 20–30 years (Yakushiji 1989).

<table>
<thead>
<tr>
<th>Compound</th>
<th>ADI (µg/kg/day)</th>
<th>Concentration of Human Breast Milk Max-Min (µg/g fat)</th>
<th>Daily Intake from Human Breast Milk (µg/kg/day)</th>
<th>Daily Intake/ADI ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCH</td>
<td>12.5</td>
<td>13.47 (’74)- 0.039 (’95)</td>
<td>60.62-0.176</td>
<td>485-1.4</td>
</tr>
</tbody>
</table>

- In an Indian study of HCH contamination of breastmilk the following estimate was made of HCH intake by infants: Assuming an intake of 0.6 L of milk per day by infant of average weight 3.36 kg, the average daily intake of total HCH determined during the study was about 0.065 mg/kg of body weight which was nearly 5 times higher than the acceptable daily intake (0.012 mg/kg body weight/day) of total HCH reported earlier in a study by Krishnamurti (Krishnamurti, 1984)43

- A 1996 Indian study44 measured HCH isomers in breastmilk, maternal serum and cord serum. Breastmilk samples (hind milk), sampled after first feeding, showed 80% more residues of HCH than maternal serum. Consumption of such a feed involved a direct entry of almost 88% additional residues in the new-born to its pre-existing levels. Further primigravidae donors (those who were first time mothers) showed 2.3 times more HCH residue in the breastmilk when compared to multigravidae mothers (those with more than one live child), suggesting bioconcentration of the pesticide in the breasts of primigravidae mothers from their birth until the first lactation. The level of pesticide in the maternal serum in both donor types did not show any significant impact on the transfer of pesticides to the newborn, since the levels in maternal and cord serum were almost similar and many fold lower than the breastmilk. Hence breastmilk was the main source of pesticide contamination to the newborn. However, the placenta was no barrier to the movement of chlorinated hydrocarbon pesticides to the fetus since the levels of pesticides in the maternal serum were almost identical to those of cord serum.
These data clearly indicate a significant bioconcentration of HCH residues in breastmilk and that the newborn is a recipient of this bioconcentrated form of pesticides. This also demonstrates that more HCH is transferred from the mother through breast-feeding than placental transfer.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$\Sigma$-DDT Mean ± S.E.</th>
<th>$\Sigma$-HCH Mean ± S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BREAST MILK</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primigravidae</td>
<td>1.302 ± 0.367</td>
<td>0.486 ± 0.320</td>
</tr>
<tr>
<td>N=12</td>
<td>(12)</td>
<td>(12)</td>
</tr>
<tr>
<td>Multigravidae</td>
<td>1.120 ± 0.306</td>
<td>0.206 ± 0.061</td>
</tr>
<tr>
<td>N=12</td>
<td>(12)</td>
<td>(12)</td>
</tr>
<tr>
<td><strong>MATERNAL SERUM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primigravidae</td>
<td>0.112 ± 0.019</td>
<td>0.042 ± 0.005</td>
</tr>
<tr>
<td>N=12</td>
<td>(12)</td>
<td>(12)</td>
</tr>
<tr>
<td>Multigravidae</td>
<td>0.431 ± 0.116</td>
<td>0.054 ± 0.008</td>
</tr>
<tr>
<td>N=12</td>
<td>(12)</td>
<td>(12)</td>
</tr>
<tr>
<td><strong>CORD SERUM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primigravidae</td>
<td>0.103 ± 0.022</td>
<td>0.021 ± 0.006</td>
</tr>
<tr>
<td>N=12</td>
<td>(12)</td>
<td>(10)</td>
</tr>
<tr>
<td>Multigravidae</td>
<td>0.178 ± 0.069</td>
<td>0.047 ± 0.015</td>
</tr>
<tr>
<td>N=12</td>
<td>(10)</td>
<td>(12)</td>
</tr>
</tbody>
</table>

N = Number of samples
*Figures in parentheses indicate number of positive samples

**HCH Levels in Breastmilk Reflect Policy Choices**

Data from countries where HCH has been restricted or banned reveals falling HCH isomer levels in breastmilk as compared to countries where $\gamma$-HCH (lindane) is freely used. Solomon and Weiss found that HCH levels in breastmilk are extremely variable and often reflect differences in regional use and exposure patterns. Countries that have restricted HCH and monitored breastmilk for HCH residues over time have witnessed a steady decrease. Downward trends have been reported in the North Rhine Westphalia region of Germany and in Stockholm, Sweden, between 1974 and 1984. Since Japan banned HCH in the 1970s, levels of the pesticide in breastmilk have decreased.

Unusually high levels of HCH in breastmilk have been associated with areas of high use. In China and Japan, HCH was commonly used as an insecticide in rice fields, and levels as high as 6,500 ng/g of HCH in lipid have been measured in these countries. A 1982 study in Norway, a decade after HCH was banned in that country, found higher levels of $\beta$-HCH in women who had immigrated from developing countries. Immigrant women had an average level of 433 ng/g $\beta$-HCH in their lipid, whereas native Norwegian women had an average of 80 ng/g. The difference was attributed to the likelihood of higher exposures in developing countries.

In general, HCH levels in most European countries are low and have averaged around 0.2ppm in fat, although higher levels have been found in Czechoslovakia, France, and Italy. Parts of Asia,
particularly in India and China, have much higher levels of \( \beta \)-HCH, with averages around 6ppm (ranging from 0.89-19ppm) in milk fat in China in the 1980s (Jensen and Slorach, 1991).\(^{46}\)

**B. Cancer classification**

*In comments, the public has expressed disagreement with the Agency’s cancer classification for lindane as presented in the lindane RED. The Agency would like to obtain additional information that may be available on the carcinogenicity of lindane. (pg 50)*

As reported in the North American Regional Action Plan (NARAP) of CEC's Lindane Task Force, the International Agency for Research on Cancer (IARC) has determined that there is sufficient evidence demonstrating that lindane and technical HCH are carcinogenic in mice and, based on these observations, IARC has classified lindane and the other HCH isomers as possibly carcinogenic to humans.\(^{47}\) EPA has classified lindane as “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential” based on an increased incidence of benign lung tumors in female mice. The Agency for Toxic Substances and Disease Registry (ATSDR) and the World Health Organization consider lindane a liver carcinogen, as is noted in the NARAP.

A 1999 report from the Austrian government cited “lack of adequate data” on lindane's carcinogenicity as the basis for a recommendation to suspend use of the pesticide across the European Union. In response to this report, most lindane uses were banned throughout Europe by 2000.\(^{48}\) This precautionary action in the face of a data gap stands in stark contrast to U.S. inaction in the face of EPA’s assessment that the data are “suggestive” of lindane's cancer causing effects in humans. Recent studies provide further evidence of lindane's carcinogenicity. Some of the key findings are summarized below:

- Testicular cancer is the most common malignancy of young men in industrialized countries and has risen dramatically in Europe and North America. Chronic exposure to environmental chemicals has been suspected, because widely used pesticides are able to promote carcinogenic effects in rodents and are known to concentrate in the testis. “The prevailing model is that these chemicals mimic or interfere with the action of sexual steroid hormones and by inference they are referred to as endocrine disrupters.” This 2003 study\(^ {49}\) explores the mechanisms by which these chemicals might lead to testicular neoplasia by testing the effects of lindane in the cells of mice. The researchers exposed cellular materials to lindane, stained them, and took pictures with a 63x magnification lens using a confocal laser-scanning Leica microscope fitted with a 488 or 543 nm krypton/argon laser allowing simultaneous analysis of the stained cells. They stated that “Altogether, these findings provide the first evidence that Lindane-altered Cx43 endocytosis requires ERK activation [extracellular signal-regulated kinases].” The researchers point out that their findings demonstrate that lindane inappropriately activates a specified mitogenic pathway (MAPK) while also inactivating a specified tumor suppressor (Connexin 43). They further conclude that lindane may participate in the promotion of neoplastic cell growth in testes and in other similar tissues.
• In a 2004 study,\textsuperscript{50} researchers state that “environmental contaminants possessing hormonal activity have long been suspected of playing a role in cancer causation.” They make reference to studies that support this statement: “Whilst lindane poisoning may result in tremors, ataxia, convulsions, stimulated respiration, prostration and, in especially severe cases, degenerative hepatic and renal tubule changes, there has been speculation that such agents may also play a role in the aetiology of cancer. The primary route of exposure in the general population is through dietary intake, particularly via meat and dairy products. Lifetime feeding studies in mice revealed that technical grade HCH and some of its isomers, including lindane, increased the incidence of hepatocellular tumours. In such animal models lindane-induced damage may result from the generation of superoxide anion radicals and/or DNA single-strand breaks (SSBs) or via epigenetic mechanisms.”

“Incidence rates for cancers of both breast and prostate, which are hormone-responsive tissues, are higher in more developed countries than in less-developed regions. Factors that influence hormonal exposures may modulate risk associated with these cancers. Lindane interferes with reproductive activity in animals, an effect that may be mediated through a direct inhibition of adrenal and gonadal steroidogenesis. This chemical also interferes with gap junction intercellular communication and induces cytochrome P450 metabolic enzymes, factors that may each play a significant role in tumour-producing activity. As a lipophilic agent, lindane becomes concentrated in the ovary and testis, which could be relevant to the increasing incidence of testicular cancer.”

The researchers looked at the mechanism by which environmental contaminants possessing hormonal activity could cause cancer. They used lindane on breast and prostate human cells to analyze chromosomal damage, cell viability, and cell cycle kinetics. They concluded that in their own study “the effects produced in cells treated with low doses of lindane... may be important in the context of considering the effects of environmentally relevant concentrations. These results suggest that environmental concentrations of lindane can induce a number of subtle alterations in normal breast and prostate cells in the absence of cytotoxicity.”

• In 2004, researchers conducted a comprehensive literature review to assess the role of environmental agents in breast cancer.\textsuperscript{51} They identified a study that assessed the relationship between serum levels of five DDT metabolites, 13 other organochlorine pesticides, and 27 PCBs and the development of breast cancer and reported that “women with serum levels in the upper quartile of HCH concentrations were at twice the risk for breast cancer as those with lower-quartile concentration of the chemical.” Miltra et al. were referring to a 1999 article by Joanne F. Dorgan and co-authors entitled Serum Organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA)—published in Cancer Causes and Control. Vol.10, No. 1. pp. 1-11. These researchers used the Columbia, Missouri Breast Cancer Serum Bank to conduct a case-control study of
105 women diagnosed with breast cancer. For each case, two controls matched on age and date of blood collection were selected. Although they showed that women in the upper three quartiles of hexachlorobenzene were at twice the risk of breast cancer compared to those in the lowest quartile, they concluded that the results of the study “do not support a role for organochlorine pesticides... in breast cancer etiology.” There was no evidence for a dose-response relationship, and the association was limited to women whose blood was collected close to the time of diagnosis.

- According to the California Environmental Protection Agency's 1998 summary of lindane health effect studies, adverse effects observed in oncogenicity studies on rats and mice dosed with lindane include neoplastic nodules in rat livers, pituitary and thyroid adenomas and carcinomas. Liver toxicity patterns were observed in dosed mice including hepatocarcinogenicity. For γ-HCH elevated frequencies of tumors in livers of mice were significant at the p<0.01 level. Liver tumors were observed in male mice fed α-HCH and γ-HCH in three other studies as well.

C. 10x FQPA Safety Factor

“In several comments, the public has disagreed with EPA’s rationale for reducing the FQPA ten-fold safety factor to 3x for lindane. The Agency would like to receive additional information on the rationale presented by commenters for retaining the 10x FQPA safety factor on lindane." (p. 50)

PANNA submitted the following comment in our October 29, 2001 comment on EPA's Preliminary Risk Assessment for Lindane (OPP-34239):

**Reduction of the FQPA safety factor from 10X to 3X for acute dietary food risk is irresponsible given the numerous pathways of exposure not included in EPA's analysis.** EPA has neglected to consider lindane exposure from a range of sources - contaminated breastmilk, food residues from previous lindane use, public health uses of lindane and known contaminants in waterways. Two of these exposure pathways, contaminated breastmilk and public health uses, impact children's exposure levels directly. Given the agency's limited consideration of possible exposures, it defies logic to reduce the FQPA safety factor. Indeed, it would be more logical to increase the safety factor to account for the known exposures not considered in the analysis. This would not, however, be an adequate substitute for the full and careful analysis of exposure risks that EPA should conduct to responsibly complete the lindane risk assessment.

While we are encouraged that EPA is now including consideration of infant exposure to lindane and its isomers in breastmilk, the other exposure pathways remain unaddressed (see Specific Comment #3 above). EPA's consideration in the current Assessment of the additional and potentially cumulative risks posed by other HCH isomers provides additional evidence that reduction of the FQPA safety factor is not justified.
In addition to these comments, we support by reference here the comments on this topic submitted to the docket by our colleagues at the Natural Resources Defense Council.

D - Cultural Practices and Potential Impacts to Subsistence Populations

“...the Agency would like to receive additional information on actual dietary intake and other practices taking place in Alaskan subsistence cultures that may impact the assumptions used in this assessment of lindane and the other HCH isomers.” (p.50)

EPA’s dietary risk assessment “indicates potential risks from dietary exposures to the α and β HCH isomers to communities in Alaska and others in the circumpolar Arctic region who depend on subsistence foods such as caribou, seal, and whale.” The information presented in this section of our comments supports this conclusion.

While we commend the Agency for significant improvements to the Dietary Risk Assessment in considering all HCH isomers and providing a more accurate representation of the dietary profile, the assessment must take into consideration the complexity and diversity of foods that comprise the traditional diets among Indigenous peoples in different regions of Alaska and the circumpolar north. The Dietary Profile used for the Dietary Exposure and Risk characterization oversimplifies the Alaska Native diet and excludes important dietary components that may contribute significant sources of additional exposures to HCH residues.

Almost no information exists in the literature on the contaminant content of subsistence foods as consumed (such as seal oil, dried or smoked fish). Preparation methods may change contaminant content of foods, either by removing, concentrating, or changing the form of contaminants. The Risk Assessment must also address the adverse cultural effects caused by contamination of traditional foods and possible health outcomes involving exposures to multiple persistent organic pollutants (not just HCHs), heavy metals, and radio-nuclides.

The Alaska Traditional Diet Project (March 2004) found “substantial regional and seasonal variation in food intake patterns among Alaska Natives” and “substantial reliance on many subsistence foods such as fish, terrestrial mammals, marine mammals, and wild plants.” Alaska Native people rely on traditional foods because of cultural importance, availability, preferences in taste and nutrition to store-bought foods. “For Alaska Natives, harvesting and eating subsistence foods is essential to personal, social, and cultural identity.”

The Alaska Traditional Diet Project also found that “the most common concerns expressed about subsistence foods were observations of fish and animals with parasites, diseases, or lesions; reduced numbers of fish and [other] animals; and the possible presence of contaminants in fish and [other] animals…there were many comments about unhealthy fish and animals, contamination, or generally reduced quality of subsistence foods. It appears that fears about safety have not yet caused these participants to avoid subsistence foods, but the anxiety they expressed is nevertheless real.”

“For thousands of years Alaska Natives have remained intimately tied to their environment. The Inupiat, Athabascan, and Yupik of the north; and the Aleut, Sutiax, Eyak, Tlingit, Haida, and Tsimshian of the Gulf of Alaska region all developed cultures
based on the natural resources of their area. Land and sea animals, plants and birds were all harvested to provide food, medicine, and traditional cultural uses. Each group used a wide range of local resources and was self-sufficient in their territory.”

“Information on contaminants and the quality of Alaska’s wild foods must be provided in a meaningful manner to Alaska Natives and rural residents. Alaskans are already concerned or aware that many resources may be contaminated. Much of the current information on contaminants is generally large-scale. The information is not specific to the health of a stock or geographic area. Residents become distrustful of wild foods and may avoid foods that are safe to eat, or eat foods or use resources that have been unknowingly contaminated.

In several instances foods have been tested positive for contaminants but rural residents are left in a quandary. They may be advised that the nutritional value of the foods outweighs the risk from contaminants. Or they may be told that scientists are unsure if the level of contamination is a risk with limited human consumption. In western Alaska, Natives may harvest over 500 pounds per person of wild foods, hence, consumption can be significant for foods such as herring in the Bethel area, beluga in the Bristol Bay area, or shellfish in the Gulf of Alaska.

When rural residents stop eating local foods the negative impacts can be considerable. Traditional foods are replaced by store bought foods. Aside from draining limited cash resources, the nutrition and quality of store-bought foods is often inferior to fresh local sources. As local hunting and gathering practices are discontinued, there is a loss of cultural knowledge and a loss of society. This results in a greater dependence on government agencies for food, and for the money to buy these resources. Many Alaska Natives attribute alcoholism, family abuse, and other social horrors to this decrease in self-sufficiency. There has been a groundswell of desire and effort to return to traditional ways and reclaim ties to the land and cultural values. However, this is stymied when Natives are unsure if the traditional foods are still safe. Much of Alaska Native cultural knowledge was lost during the early epidemics, and now precious cultural knowledge is slipping away as Natives avoid collecting and using wild foods.”

Murre and other seabird eggs

Murre eggs are harvested by people living in many Alaska coastal communities and comprise an integral part of the Alaska Native diet. Murres (Common, *Uria aalge*, and Thick-billed, *Uria lomvia*) are distributed throughout the Arctic and sub-Arctic, nest in large colonies, and feed at the same trophic level as marine mammals. The average household in the two villages of St. Lawrence Island in the northern Bering Sea consume between 60 and 104 murres and eggs per year. Another report found that Alaska Native people living in villages of the Yukon-Kuskokwim area consumed up to 28 murre eggs per year. In an analysis of persistent organic pollutants (POPs) in Alaskan murre eggs, researchers found β-HCH among the major POPs in concentrations ranging from 59-282 ng/g lipid mass.
Researchers collected and analyzed contaminant levels in murre eggs from several colonies in Alaska. They measured concentrations of various PCB congeners and chlorinated pesticides, including α-, β- and γ-HCH. Statistical analyses showed variation among colony locations for all compounds except β-HCH. Researchers found the following concentrations of HCH isomers (data are expressed in ng/g lipid weight), ⁵⁹ ⁶⁰

<table>
<thead>
<tr>
<th></th>
<th>A-HCH</th>
<th>β-HCH</th>
<th>Γ-HCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Amatuli</td>
<td>16.1±7.3</td>
<td></td>
<td>4.66±7.1</td>
</tr>
<tr>
<td>St. Lazaria</td>
<td>9.51±4.0</td>
<td>143±50</td>
<td>1.97±1.7</td>
</tr>
<tr>
<td>Bogoslof Island</td>
<td>22.3±7.2</td>
<td></td>
<td>6.27±1.3</td>
</tr>
<tr>
<td>St. George Island</td>
<td>11.0±4.5</td>
<td>161±64</td>
<td>2.63±2.5</td>
</tr>
<tr>
<td>Little Diomede</td>
<td>10.0±5.5</td>
<td>183±63</td>
<td>2.62±2.9</td>
</tr>
</tbody>
</table>

While most “legacy” organochlorine contaminants have significantly declined in Canadian Arctic biota from the 1970s to the 1990s, HCH levels have “remained relatively constant in most species and proportions of the toxic β-HCH isomer have actually increased in seabird eggs and in ringed seal blubber.” ⁶¹

**Seal species and seal oil**

The risk assessment must take into consideration the variations and additive effects of contaminant/HCH levels among the various northern seal species, including ringed, spotted, bearded, harbor, ribbon, and northern fur seals. Traditional diets among people in different coastal areas of Alaska vary considerably in the relative importance of the different seal species. Seal oil is an important component of the Alaska Native diet, yet little information exists on the levels of contaminants in this rendered food source. People also consume muscle, liver, heart, kidney, and flipper of seal species, and contaminant levels may be more concentrated in certain tissues. In a dietary survey of 151 people in villages in the Norton Sound region of Alaska, people consumed up to 288 pounds of seal oil per person/year with 80% of the people surveyed eating seal oil. ⁶² Thus, the estimates for seal consumption provided in the Dietary Profile seriously underestimate the importance of seal and seal oil in the traditional diet.

In one study of organochlorine pesticides in the blubber of ringed seals, “wet mass sum HCH (Σ-HCH, sum of α-, β-, and γ-HCH) values for samples that included β-HCH measurements, ranged from 146 ng/g wet mass to 561 ng/g wet mass. Muir et.al. (1995) also measured variable Σ-HCH concentrations in ringed seal samples; 246 ± 231 ng/g in females and 274 ± 123 ng/g in males. Schanz et.al. (1996) reported γ-HCH values in ringed seals from Barrow and Nome, Alaska from 2.1 ± 0.01 ng/g to 633 ± 4 ng/g. For the samples in which all three HCHs were measured, α-HCH contributed the most to the Σ-HCHs, ranging from 59% of Σ-HCH in RGSL-047 [sample number] to 68% in RGSL-053.” ⁶³
In a study of northern fur seals, researchers concluded that the “overall toxic equivalency shows levels approaching and exceeding those levels recommended for human consumption at St. George Island and approaching those levels at St. Paul Island.” Although the researchers analyzed only for PCB congeners and DDT/metabolites, the study is indicative that contaminant levels may already exceed levels considered safe for consumption without the additional adverse effects that might be caused by HCH and other contaminants. The authors note that fur seals have higher levels of organochlorine contaminants than ringed seals. The researchers also conclude: “Northern fur seal pups, especially first-born, have a substantial exposure to organochlorine contaminants at a critical developmental stage.” Concentrations of organochlorine contaminants are likely a key factor in the precipitous declines of northern fur seals and Steller sea lions.

Steller sea lion

“Steller sea lion habitats and prey are contaminated with additional chemicals including mirex, endrin, dieldrin, HCH, dioxin compounds, cadmium, and lead…Ikonomou (2002) reported PBDEs had exponentially increased in ringed seals from the Canadian Arctic between 1981 and 2000 and that PBDEs may become the most prevalent POP in arctic ringed seals in the next 50 years. Thus, a significant data gap in our understanding is the potential for unmeasured contaminant exposure in Steller sea lions, many of which may be increasing.” Clearly, marine mammals are burdened with multiple chemical contaminants that may adversely affect the health of the animals and people who consume them—the risk assessment fails to consider additive and synergistic effects of multiple chemical exposures on wildlife and people.

Beluga whales

Data published in the Alaska Traditional Knowledge and Native Foods Database (www.nativeknowledge.org) show a range of HCH levels in beluga whale blubber in ng/g wet wt.:

<table>
<thead>
<tr>
<th>Sample site</th>
<th>HCH isomer</th>
<th>Sex</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point Hope</td>
<td>α</td>
<td>F (n=4)</td>
<td>162-180.3</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>F (n=2)</td>
<td>99.1-188.2</td>
</tr>
<tr>
<td></td>
<td>γ</td>
<td>F (n=4)</td>
<td>33.3-95.9</td>
</tr>
<tr>
<td>Point Lay</td>
<td>α</td>
<td>F (n=6)</td>
<td>43.9-186.9</td>
</tr>
<tr>
<td></td>
<td>α</td>
<td>M (n=18)</td>
<td>70.8-196.3</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>F (n=3)</td>
<td>22.3-144.1</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>M (n=9)</td>
<td>120-180.8</td>
</tr>
<tr>
<td></td>
<td>γ</td>
<td>F (n=6)</td>
<td>11.5-49.2</td>
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<tr>
<td></td>
<td>γ</td>
<td>M (n=18)</td>
<td>39.6-64.9</td>
</tr>
<tr>
<td></td>
<td>Sum-HCHs</td>
<td>F (n=3)</td>
<td>77.7-364.4</td>
</tr>
<tr>
<td></td>
<td>Sum-HCHs</td>
<td>M (n=8)</td>
<td>265.3-478.3</td>
</tr>
</tbody>
</table>
Bowhead whales

Bowhead whales (n=72) in the vicinity of Barrow, Alaska had concentrations of Σ-HCH of 203 ng/g (geometric mean, wet weight). “The partitioning of HCH isomers between the lower- and higher-latitude marine environments (i.e. the north Pacific versus Arctic Oceans) has been observed in biota. The relative abundance of β-HCH was significantly greater than the α-HCH isomer in pinnipeds from 40-60°N in the western Pacific Ocean. As well, β-HCH is the most dominant isomer in blubber tissues from minke whales from the north Pacific. However, α-HCH is the dominant isomer in ringed seals and low trophic level biota from the high Canadian Arctic. The bowhead whales harvested during the spring migration were recently occupying waters with higher β-HCH relative to the Beaufort Sea which may explain the PC1 results.”60

Polar bears

Levels of Σ-HCH in Chukchi and Bering Sea polar bears are among the highest reported in the circumpolar Arctic. Σ-HCH concentrations were highest in Alaska male polar bear fat samples (geometric mean 593, with 95% confidence limits 363-909 ng/g lipid weight). “Σ-HCH concentrations showed the steepest negative west-east gradient across the populations studied. Σ-HCH concentrations were significantly highest in Alaska bears compared to Western Hudson Bay and to populations east of Lancaster Sound/Jones Sound (Tukey’s test; p<0.02), and lowest in bears from Svalbard (Tukey’s test p<0.001). There was a six-fold difference in age-adjusted mean Σ-HCH concentrations between bears from Alaska and Svalbard. Muir and Norstrom (2000) and Norstrom et.al. (1988) also reported the highest Σ-HCH concentrations in polar bear fat samples from Alaska (Bering/Chukchi Sea). This may indicate an ongoing contribution of HCHs from China, southeastern Asia, and North America. The west-east geographical trend for Σ-HCH was in general agreement with results of polar bears spanning the regions of Svalbard eastwards to the Chukchi Sea, measurements of HCHs in seawater, and results of ringed seals from the Canadian Arctic eastwards to the Russian Arctic. Furthermore, latitude was negatively correlated with the α-HCH: Σ-HCH ratio and was the most pronounced latitudinal gradient measured in this study. No correlation was found between longitude and the α-HCH: Σ-HCH ratio. The contribution of the more water-soluble α-HCH to Σ-HCH, relative to β-HCH, was thus highest at the southernmost populations of the distribution range of the polar bear.” In Alaska polar bears, the concentrations of Σ-HCH in male bears ranged from 398 up to 1269 ng/g lipid weight and in female bears the concentrations ranged from 332 up to 550 ng/g lipid weight.67

In another study, researchers also found that polar bears from the Chukchi Sea had the highest levels of α-HCH and β-HCH. In all the bears, Σ-HCHs was dominated by β-HCH. Concentrations (ng/g lipid weight) in the blood of adult female polar bears (age >5) in the Chukchi Sea ranged from 108-353 for α-HCH and 193-830 for β-HCH.68 The Σ-HCH distributions in ringed seals were dominated by α-HCH, while β-HCH was the major isomer in polar bears.

Polar bears are eaten (primarily muscle tissue) in the communities along the Bering, Chukchi, and Beaufort Sea coasts and may be an important source of exposure to HCH and other contaminants.
HCH in people of the Arctic

Relative to numerous studies in Canada, there have been few analyses of persistent organic pollutants in people of the Alaskan Arctic and sub-Arctic. One study identified “widespread Alaska Native exposure to organochlorines that originated outside the Arctic, a finding also seen in other studies.” The mean level of HCH in blood serum of Alaska Native women by geographical area was reported as follows:69

HCH mean (standard deviation) in ng/mL or ppb
Southcentral (n=47) 0.28 (0.40)
Northwestern (n=28) 0.43 (0.54)
Southwestern (n=50) 0.32 (0.42)
Interior (n=6) 0.20 (0.43)

A later study evaluated maternal plasma concentrations of β-HCH in women of the Aleutian and Pribilof Islands in Alaska compared with women in other areas of the circumpolar Arctic (1994-1996 geometric means, ppb lipid)70:

<table>
<thead>
<tr>
<th>Aleutian/</th>
<th>Pribilof Is.</th>
<th>Canada</th>
<th>Greenland</th>
<th>Sweden</th>
<th>Norway</th>
<th>Iceland</th>
<th>Russia</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=40</td>
<td>N=67</td>
<td>N=117</td>
<td>N=40</td>
<td>N=40</td>
<td>N=40</td>
<td>N=40</td>
<td>N=51</td>
</tr>
<tr>
<td>24.7</td>
<td>9.3</td>
<td>18.5</td>
<td>9.2</td>
<td>8.1</td>
<td>32.1</td>
<td>222.5</td>
<td></td>
</tr>
</tbody>
</table>

In addition to HCH, the study measured other organochlorine pesticides and PCBs. Levels of p,p’-DDE in Aleutian and Pribilof Island women were the highest in the circumpolar Arctic with a geometric mean of 503 ppb lipid (N=40).

Data concerning HCH isomers in the blood serum of Yupik people from St. Lawrence Island71 revealed the following lipid-adjusted average and maximum concentrations in ppb:

<table>
<thead>
<tr>
<th></th>
<th>α-HCH</th>
<th>γ-HCH (Lindane)</th>
<th>Delta-HCH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>246</td>
<td>21</td>
</tr>
</tbody>
</table>

β-HCH was not detected in these analyses. The study also showed elevated levels of oxychlordane and trans-nonachlor compared with levels in people of the lower-48 states.

E - Liver Effects

Both the cancer and non-cancer endpoints selected for exposure to α- and β-HCH are based on liver effects. Therefore, exposures to α- and β-HCH may be additive. Moreover, the chronic non-cancer endpoint for exposure to lindane, the gamma isomer, is also based on liver effects. The Agency is inviting comment. (p.50)
The scientific literature regarding the cancer and non-cancer effects of HCH supports EPA's expressed concern that exposures to HCH isomers may be additive. HCH “mixed isomer” liver effects from chronic exposure include: increase in the enzymes lactate dehydrogenase, leucine aminopeptidase and gamma-glutamyl transpeptidase (Ryan & Terri, 1996), as well as liver cell changes (Philip et. al, 1989) and induction of oxidative enzymes (Gosselin et. al, 1984).\(^7\)

Accumulation data of lindane residues in the liver and other organs suggest the concurrent presence of multiple isomers in the liver and provide a basis for the supposition of additive effects. In a study designed to assess the accumulation of residues,\(^7\) groups of five female Swiss mice were given diets containing lindane (purity, 99.8%) at a concentration providing a dose of 1.5 mg/kg bw per day for 4 weeks, 1 mg/kg bw per day for 6 weeks or 3.1 mg/kg bw per day for 2, 4 or 6 weeks. Lindane was measured in whole brain, ovary, adrenal gland, liver, kidney, abdominal fat and femoral muscle. The accumulation of lindane residues in tissues displayed a time- and dose-related increase in all treated groups. For all treatment groups, the highest lindane content was in fat, followed by brain, kidney, muscle, liver, adrenal and ovary.

**Tumor-initiating activity of HCH isomers**

The following are highlights of studies that document and compare the tumor-inducing impacts of the various HCH isomers:

- **A study testing for tumor initiating activity of HCH using the appearance of phenotypically altered foci in female rat liver as an end point**\(^7\) reached the following conclusion: “Based on daily doses the three HCH isomers were approximately equipotent; based on concentrations in liver or adipose tissue, \(\gamma\)-HCH was several-fold more effective than \(\alpha\)- and \(\beta\)-HCH. Thirdly, size and DNA and monoxygenase activities of the liver were determined. All three parameters were enhanced by HCH isomers and PB. However, no strict correlations were found. Rather, at the highest doses tested PB was the most effective inducer of monoxygenases, \(\alpha\)-HCH was the most potent inducer of liver growth, and all three HCHs were more potent than PB as inducers of focal expansion. Thus, induction of liver growth appears to be associated with foci expansion (tumor promotion); however, neither liver growth nor monoxygenase induction can be used for quantitative predictions of foci expansion by chemical compounds”.

- **IPCS-Inchem’s Lindane comments**\(^7\) concluded that technical grade \(\alpha\)- and \(\beta\)-HCH and \(\gamma\) isomer (lindane) produced liver tumors in mice when administered orally; the technical grade also produced lymphoreticular neoplasms. In two studies in rats, an increased incidence of liver tumors was observed with the \(\gamma\) isomer, and in one study in rats a few thyroid tumors were observed with the \(\gamma\) isomer; other studies were considered to be inadequate. Technical grade HCH and the \(\gamma\) isomer were cancer tested inadequately by skin application in mice. \(\alpha\)-HCH enhanced the incidence of liver neoplasms induced in rats by N-nitrosodiethylamine (IARC, 1979; IARC, 1984).
Young and elderly particularly susceptible to HCH liver effects

ATSDR’s 2005 toxicological profile on HCH found that “A susceptible population will exhibit a different or enhanced response to HCH than will most persons exposed to the same level of HCH in the environment. Reasons include genetic makeup, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults.”

In a 1991 study, rats of mixed ages were fed β- and γ-HCH isomers for two weeks and effects of this dietary treatment on body and organ weights were observed and compared with a control group. Researchers found that the observable health impacts produced by dietary HCH isomers are dependent on the age of the animals for a given dosage. “It appears that for a given dose and duration of HCH treatment, young animals are uniquely susceptible. The difference in response during early life may be a consequence of the relative insufficiency of various metabolic and excretory pathways, the greater susceptibility of certain organs, and immaturity of the blood-brain barrier.” In the study, liver weights were increased by dietary HCH isomers in rats of all ages. This increase in liver weights produced by HCH isomers was higher in younger rats as compared to aged rats. The liver weight increase caused by β-HCH over the corresponding controls was 99, 67, 44, 41 and 24% respectively in rats of age groups: 5 weeks, 10 weeks, 16 weeks, 32 weeks and 16 months. Similarly, the liver weight increase caused by γ- HCH over the corresponding controls was 40, 40, 31, 18 and 13% respectively in the rats of age groups: 5 weeks, 10 weeks, 16 weeks, 32 weeks and 16 months. Liver total fat expressed per g tissue was significantly higher in rats of 5 weeks and 10 weeks age groups consequent to either β or γ-HCH treatment. The hepatic fat content was not altered by these HCH isomers in rats of higher ages. Hepatic cholesterol was also not altered by HCH isomers treatment in rats of any of the age groups. Thus, increase in liver weights caused by HCH treatment is higher in younger animals as compared to older ones. Fatty changes in liver is one of the several toxicological manifestations induced by HCH isomers in their spectrum of hepatotoxic effects (Srinivasan and Radhakrishnamurty 1989). The increase in liver fat content is seen here only in the rats of 5 weeks and 10 weeks age and possibly the dosage and duration of HCH treatment used in this study has produced hepatomegaly and hepatotoxicity in only these younger age groups.

Additional HCH liver effects data

Participants in a 2002 meeting on pesticide residues in food sponsored by the Food and Agriculture Organization and the World Health Organization commented that lindane was toxic to the liver after administration orally, dermally or by inhalation in short-term and long-term studies of toxicity and studies of reproductive toxicity in rats. Their comment was based on the fact that hepatocellular hypertrophy was observed in a number of studies in mice, rats and rabbits...
and was reversed only partially after recovery periods of up to 6 weeks. In a 2-year study of toxicity and carcinogenicity in rats, the NOAEL was 10 ppm in the diet (equal to 0.47 mg/kg bw per day) on the basis of increased liver weight, hepatocellular hypertrophy, increased spleen weight and deaths at 100 ppm (equal to 4.7 mg/kg bw per day).\textsuperscript{78}

In its 2005 update on the toxicological profile for HCH, the Agency for Toxic Substances and Disease Registry (ATSDR)\textsuperscript{79} commented that in the liver, \(\gamma\)-HCH is thought to function by interfering with hepatic oxidative capacity and glutathione metabolism (Barros et al. 1988, 1991; Srinivasan and Radhakrishnamurty 1988; Videla et al. 1991). Another possible mechanism for hepatic toxicity is the increased lipid metabolism. Inhibition of Mg\(^{2+}\)ATPase activity has been observed in rat liver tissue, suggesting an ATPase enzyme sensitivity to the action of \(\gamma\)-HCH. The researchers suggested that some toxic effects appearing in mammals as a result of \(\gamma\)-HCH exposure may arise from its influence on this ATPase activity (ATSDR, 1994).\textsuperscript{80}

Lindane induces a number of metabolizing enzymes, including the cytochrome P450 system, glutathione-S-transferase and UDP-glucuronosyl transferase. In contrast, it inhibits, for example, epoxide hydrolysis at concentrations of 100 ppm and more.\textsuperscript{81} According to ATSDR, statistically significant increases in blood levels of the enzymes lactate dehydrogenase, leucine aminopeptidase, and gamma-glutamyl transpeptidase were reported in 19 individuals occupationally exposed to technical-grade HCH for approximately 10 years in an HCH-formulating plant (Kashyap 1986); exposure concentrations were not reported. Both inhalation and dermal exposure probably occurred.\textsuperscript{82}

Acute oral studies in animals have reported hepatic effects in the mouse (Oesch et al. 1982). Intermediate-duration oral studies have been performed in animals regarding hepatic effects (Desi 1974; Dikshith et al. 1991a; Fitzhugh et al. 1950; Hanada et al. 1973; Ito et al. 1973; Oesch et al. 1982; Ortega et al. 1957; Ravinder et al. 1989; Van Velsen et al. 1986).\textsuperscript{83}

Studies on oral exposure to HCH isomers by mice concluded that a variety of morphological and biochemical lesions are produced in the liver during continued dietary intake of \(\beta\)- and \(\gamma\)-isomers of HCH by young rats (Srinivasan and Radhakrishnamurty 1988, 1989; Srinivasan et al 1988; Ravinder et al 1989). “The hepatotoxic effects produced by these HCH isomers in experimental animals include hepatomegaly, fatty metamorphosis of the liver, hyperlipemia, elevated levels of serum aminotransferases and alkaline phosphatase with associated lowerings of hepatic cytoplasmic enzymes. The hepatomegaly resulting from HCH isomers treatment has been shown to be predominantly due to hypertrophy.” (Srinivasan et al 1988)

“The development of an oxidative stress condition in the liver by lindane intoxication is another possible hepatotoxic mechanism of the insecticide. Lindane is metabolized by liver microsomal enzymes to a variety of metabolites, which are susceptible of conjugation for proper elimination. In addition, the interaction of lindane with the liver tissue results in the induction of the microsomal cytochrome P-450 system, together with enhanced rates of superoxide radical generation and a significant increase in indicators of lipid peroxidation. Concomitantly, lindane intoxication induces a derangement of some antioxidant mechanisms of the liver cell, including decreased superoxide dismutase and catalase activities and alterations in reduced glutathione content leading to depressed GSH/GSSG ratios.”\textsuperscript{84}
Summaries of additional studies of HCH liver effects are included below:

- A study on dietary HCH exposure\(^{85}\) including \(\gamma\)-HCH produced significant increase in liver weights of mice. Elevated levels of alanine and aspartate aminotransferases and of alkaline phosphatase in the blood of these animals suggested hepatotoxicity. Hepatic soluble enzymes—aspartate aminotransferase and lactate dehydrogenase—were markedly lowered. Among the hepatic lysosomal enzymes, acid phosphatase and acid cathepsin were increased in the experimental animals. Hepatic glucose-6-phosphatase was lowered by HCH while aldolase activity was increased. Hydrolytic enzymes in small intestine, viz., disaccharidases, lipase, amylase, dipeptidase and phosphatases, were also affected by dietary HCH and \(\gamma\)-HCH. The results suggested cellular toxicity in hepatocytes of HCH and \(\gamma\)-HCH fed animals, and also interference in gastrointestinal absorption.

- In a 28-day range-finding study, groups of 15 Wistar rats of each sex received diets containing lindane (purity, 99.5\%) at a concentration of 0, 1, 10, 100 or 400 ppm and were observed twice daily for clinical signs of toxicity or death. Individual body weights, food consumption and food use efficiency were assessed at the beginning of the study and weekly thereafter. Haematological and clinical chemical parameters were evaluated only at the end of the study. At the highest concentration, males and females had increased absolute and relative weights of the liver and females had an increase in the relative spleen weight.\(^{86}\)

- Videla, L.A. et al (1991) found that lindane resulted in marked changes in hepatic oxidative capacity and glutathione metabolism among rats, which condition the production of oxidative stress in the liver at different times of intoxication.\(^{87}\)

- Simon-Giavorrotti et. al (2002) concluded that “Lindane hepatotoxicity in hyperthyroid state, comprises an enhancement in the oxidative stress status of the liver”.\(^{88}\)

- In a study in which lindane (60 mg/kg) was administered orally to rats it was found that lindane oral exposure “increased liver cytochrome P-450 content and superoxide radical (O2-) generation 24 h after treatment, while formation of thiobarbituric acid reactants and NADPH/ADP-supported microsomal chemiluminescence were significantly increased 4 h after treatment. 2. Hepatic superoxide dismutase (SOD) and catalase decreased 6 h after lindane treatment and SOD/O2- ratio progressively decreased during 4 to 24 h after lindane treatment. 3. Morphological evidence of hepatic cell injury after lindane treatment was seen at all times studied, and appeared to increase with time. 4. Lindane administration results in time-dependent oxidative stress in liver which involves an early component (4-6 h) related to the reductive metabolism of lindane, and a late component (24 h) associated with the induction of cytochrome P-450; the biochemical changes correlated with the observed morphological lesions.”\(^{89}\)
Risk Reduction Opportunities

As is noted in the North American Regional Action Plan (NARAP) on Lindane/HCH, and in the EPA Assessment of Lindane and Other HCH Isomers, 6-10 tons of waste isomers are produced for every ton of lindane. This massive quantity of persistent and toxic waste poses threats to workers, local communities, and globally through atmospheric transport of the HCH isomers produced. The NARAP calls for projects in China and India that will reduce use and emissions that result in long-range transport of lindane and its waste isomers. It does not address, however, production issues in Romania—the source of all imports to the U.S. The U.S. should agree to stop purchasing lindane from all sources in an effort to halt production of lindane and its waste isomers.

Eliminating the production of lindane is the only way to prevent sources of contamination that cause unnecessary harm to the health of wildlife and people of the Arctic. Given the fact that lindane is banned in 52 countries throughout the world and is now nominated as a chemical for listing in Annex A of the Stockholm Convention, it is unconscionable that the U.S. delay action to eliminate this dangerous chemical. The EPA Assessment of Lindane and Other HCH Isomers clearly demonstrates that the ecological and human health risks justify elimination of all uses. The U.S. must also take positive action by ratifying the 1998 Aarhus Protocol of the Convention on Long Range Transboundary Air Pollution, the Rotterdam Convention, and the Stockholm Convention.

The Agency must follow the example of other countries that have banned lindane and replaced it with less harmful alternatives that do not threaten public health and the environment.

Sincerely,

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