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Lindane Reregistration Eligibility Decision (RED)

Comments Submitted on Behalf of the Natural Resources Defense Council

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The Natural Resources Defense Council (NRDC), is submitting the following comments on the revised risk assessment for lindane on behalf of our over 500,000 members nationwide. Many of our members are pregnant or have children who may be disproportionately exposed and susceptible to the health effects of a neurotoxic and endocrine disrupting chemical such as lindane. Other members are physicians or health care professionals who receive questions about treatment of scabies or head lice, and who see children who may be affected by pesticides including lindane. We receive calls from our members, and members of the general public with questions related to exposure to lindane used for treatment of head lice or scabies. Our work has focused for decades on risks to infants and children from exposure to toxic chemicals, pesticides, and endocrine disruptors. We are therefore directly affected by EPA's risk assessment for lindane. NRDC has no financial interest in the manufacture or use of lindane or lindane-containing products.

We have reviewed the RED for lindane, the Revised HED Risk Assessment for Lindane, and the accompanying Memorandum entitled: "Lindane; Chemical No. 009001. Revised Assessment of Risk from Use of Lindane for Treatement of Lice and Scabies." While we are pleased that EPA has performed a risk assessment for pharmaceutical uses of lindane, we have identified several problems with the analysis done by the Agency. It is also clear that the Food Quality Protection Act (FQPA) requires EPA to include all uses, including the pharmaceutical uses of lindane, in the RED as part of the aggregate risk determination, yet the Agency has not yet taken this essential step. NRDC reminds the Agency that the persistent failure to include all uses of this chemical in the aggregate risk determination is illegal. In addition, we are distressed that EPA has continued to ignore thousands of comments from health groups, environmental groups, public agencies, and members of the public on the Lindane Preliminary Risk Assessment and the Revised Lindane Risk Assessment. EPA still fails to address two major concerns: (1) the Agency reduced the 10x child-protective factor to only 3x despite evidence of data gaps and of disproportionate susceptibility of fetuses and neonates to lindane toxicity; and (2) EPA fails to include consideration of the breast milk pathway in the exposure assessment.

Topical Use of Lindane for Lice and Scabies

While NRDC is pleased that the Agency heeded the thousands of comments from members of the public raising concerns about the pharmaceutical uses of lindane, we believe that the resulting risk assessment is incomplete. In addition, the risk assessment is not incorporated into the aggregate risk analysis in the RED. It makes no

sense, and is illegal, to go through the exercise of calculating risks related to the pharmaceutical uses of lindane and then to completely ignore the substantial risks uncovered by this assessment in the aggregate risk determination itself.

The FQPA amended the FFDCA to allow the EPA Administrator to establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if she determines that the tolerance is safe. FFDCA §408(b)(2)(A)(i)(emphasis added). A tolerance can only be considered safe if the Administrator determines "that there is a reasonable certainty, that no harm will result from the aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and *all other exposures for which there is reliable information*." (emphasis added) FQPA §408(b)(2)(A)(ii). In making these determinations, special consideration must be given to the unique effects these pesticide residues may have on infants and children. FFDCA §408(b)(2)(C). There is no exception in the FQPA for pesticides that are also used as pharmaceuticals. It is therefore obvious that EPA must include pharmaceutical uses in the aggregate risk determination. Any tolerance set without determining that aggregate exposures to children, including pharmaceutical exposures, are safe, is illegal under the law.

NRDC has several concerns about the Revised Assessment of Risk from Use of Lindane for Treatment of Lice or Scabies. NRDC is very concerned that EPA chooses an acute oral study performed on adult animals for the toxicity endpoint. EPA acknowledges that "use of a toxicity endpoint based on the acute study may underestimate risks to children who are exposed to lindane." This concern is well-justified. In fact, an acute endpoint that will be adequately protective of children should be selected, or an additional uncertainty factor should be added to the acute analysis to account for this problem. NRDC is alarmed by the MOE analysis of lindane use for scabies. Our concerns about risks to children appear to be amply justified by the low margins of exposure for toddlers, children, and young adults in the analysis. Even when the low dermal absorption figure of only 10% is used, MOEs range from 4 (if a high-end dose is applied to a toddler) to 12 (if a low-end dose is applied to an adult). These results are far from the target MOE of 100. It is clear that exposure reduction is essential not only for children, but also for those who have achieved adult stature. Even worse, these results use the short-term oral toxicity study in adult rats that fails to adequately protect children. Therefore the true risks to children are likely to be even greater.

When EPA calculated the blood levels associated with scabies treatment and compared these numbers with those associated with observed toxicity in human children, the Agency rightly concluded that the margin of safety is inadequate. In fact, there is only a 4-5 fold difference between blood levels detected in treated humans and blood levels detected in children with symptoms of lindane poisoning. This assessment shows that lindane pharmaceutical uses are a highly significant health risk. Yet these numbers are not included in the aggregate risk assessment in the RED. Obviously the inclusion of pharmaceutical uses would significantly alter the conclusions of the aggregate risk assessment, and these must be included.

NRDC has serious concerns about the EPA assessment of lindane use for head lice. The Agency inexplicably fails to perform a risk assessment and MOE analysis for head lice although it does so for scabies. Using the EPA calculated dose of 420-530 mg of lindane from an application of 44-57 ml of 1% GBH shampoo (Revised Assessment of Risk from Use of Lindane for Treatment of Lice and Scabies, Table 5, p. 12), the table below can be calculated. This table is based on Table 6 on Page 18 of the RED. That table uses the same assumptions for scabies treatment that we reproduce below for head lice. We use the highly conservative 10% dermal absorption figure rather than the more health-protective 20% dermal absorption figure. It is obvious from this table that the MOE calculations are not sufficiently protective of health and fail to protect adults as well as children.

Assessment of Use of Lindane for Head Lice

Age Group	Oral NOAEL (mg/kg/day)	Applied Dose (mg)	Body Weight (kg)	Daily Dermal Dose (mg/kg/day)	Dermal absorption (%)	MOE	Target MOE
Young Adult	6	530 high end	60	8.8	10	6.8	100
Young Adult	6	420 low end	60	7	10	8.6	100
Child 4-6	6	530 high end	22	24	10	2.5	100
Child 4-6	6	420 low end	22	19	10	3.2	100
Toddler 1-3	6	530 high end	13	40.8	10	1.5	100
Toddler 1-3	6	420 low end	13	32	10	1.9	100

$$\text{MOE} = \frac{\text{Oral NOAEL (mg/kg/day)}}{\text{Daily dermal dose (mg/kg/day)} \times \text{dermal absorption factor (\%)}}$$

EPA's reliance only on a single human study with Kwell shampoo as a basis for the risk assessment for head lice raises several concerns. There is the immediate concern that use of this human study is in contravention of EPA's moratorium on the use of human testing. In fact, use of the 10% dermal absorption factor is also contrary to the moratorium. In addition, there are numerous concerns about the conduct of this study and the failure of the study to capture peak blood levels. EPA's decision to compare the results with levels that result in acute poisoning rather than to compare the results with a level that may be truly safe is another problem that results in a risk assessment that fails to protect health. EPA must include the full risk assessment for lindane use in the treatment of head lice and scabies in the RED as part of the aggregate risk assessment and must take steps to reduce exposure to this chemical because the risks are above EPA's level of concern for infants, children and adults.

EPA Must Retain the Full 10x Margin of Safety to Protect Children from Lindane

EPA's stated rationale for reducing the 10x FQPA margin of safety to 3x is deeply flawed. EPA gives six reasons for reducing the FQPA safety factor. Each of these reasons is either incorrect or irrelevant to the question before the Agency. They are discussed and refuted below:

1) *"The toxicology data base is complete"*

EPA repeatedly mentions that lindane has shown endocrine disrupting effects in numerous studies submitted to EPA and in the open literature. Rather than regulating lindane as an endocrine disruptor, however, EPA states the intention to require future studies on the endocrine disrupting effects of lindane through the Endocrine Disruptor Screening and Testing Program. This statement of intention amounts to an acknowledgement that there are significant data gaps in the toxicology database for lindane. If there were no data gaps, there would be no need for endocrine disruptor testing. In addition, as detailed below, EPA itself admits that lindane may be transformed in the environment into the even more toxic isomer, β-HCH, and the Agency asserts that the issue

is still unresolved (discussed in greater detail below). This is an extremely important data gap that must be addressed or filled by using the full 10x factor. Thus it is incorrect for EPA to say that the database is complete.

2) *"Available data provide no indication of increased susceptibility in rats from in utero exposure to lindane in the prenatal developmental study."*

This statement is incorrect. EPA uses three rat studies to assess fetal risk: a prenatal developmental study, a reproductive toxicity study, and a developmental neurotoxicity study. While it is true that there was no clear evidence of increased susceptibility in the first study, the other two both clearly show qualitative, and in one case, quantitative increased susceptibility in the fetus. If EPA is purporting to use a weight-of-evidence approach to assessing the scientific literature, the evidence clearly supports the disproportionate susceptibility of the fetus to the toxic effects of lindane. Furthermore, biologic plausibility also supports fetal susceptibility due to the various neurotoxic and endocrine disrupting modes of action of this chemical in the fetus and neonate. Finally, the one study that purported to fail to demonstrate increased fetal susceptibility – the rat developmental study – is the least sensitive of the studies at detecting functional abnormalities – the precise type of abnormalities caused by lindane. In addition, this supposedly negative study found increased skeletal malformations compared to controls at all doses tested. The fact that the study lacked statistical power to detect an effect on skeletal development, and that the study lacked the sensitivity to address functional (neurological) endpoints are not be sufficient reason to reduce the FQPA factor. Reducing the FQPA safety factor based on one study flies in the face of the weight of scientific evidence and the mode of action of this pesticide.

3) *"The offspring effects seen in the developmental neurotoxicity study were the same as those seen in the two-generation reproduction study."*

Even if it were true, this statement would be irrelevant to the question before the Agency. The more important issue is that both of these studies clearly showed disproportionate vulnerability in the fetus. In addition, this statement is incorrect. The developmental neurotoxicity study showed increased motor activity and decreased motor activity habituation as compared to controls. These endpoints are important because they are indicative of the same type of CNS stimulation seen in human children who have been exposed to lindane. Although full-blown seizures were not observed in this particular study, these effects are along the continuum of CNS kindling and behavioral alterations that have been observed in humans. These effects were seen in the offspring in the absence of maternal toxicity. It should go without saying that CNS hyperexcitability in the offspring at doses non-toxic to the mother is indicative of a serious and very disturbing risk to the fetus, infant, and child.

4) *"Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess food exposure and to provide a screening level drinking water exposure assessment."*

This rationale makes no sense in light of the examples presented in our comments showing that the Agency completely omits numerous exposure pathways from the risk assessment. The adequacy of the exposure data should be reconsidered after the agency evaluates and includes the data on exposure to lindane in breast milk, lindane in fish, and historical residues of lindane. In addition, the high risks shown in the pharmaceutical risk assessment require that the above statement be reconsidered and withdrawn.

5) *"Although the developmental toxicity study in rabbits was classified unacceptable, the HIARC concluded that a new study is not required."*

This rationale is also irrelevant to the decision about the 10x FQPA factor. Whether or not a new rabbit study is needed, there are obvious data gaps due to incomplete information about endocrine disrupting effects.

6) *"There are currently no residential uses."*

This is the strangest of the six reasons for abandoning the FQPA margin of safety. Most members of the public would consider direct application of lindane to a child's skin (or to the skin of a household pet) to be a residential use. Failure to acknowledge this use of lindane baffles logic. Clearly there are residential uses. EPA

must include them and must use the full 10x FQPA margin of safety because of these uses and because none of the six justifications for abandoning the 10x holds up to logic or scientific scrutiny.

The astonishing thing about the decision to reduce the FQPA margin of safety for lindane is that the Agency appears to be turning the statutory requirement on its head. Under the Food Quality Protection Act's precautionary approach to protecting children, EPA must maintain an additional 10-fold margin of safety in its risk assessments for individual pesticides to "take into account potential pre– and post–natal developmental toxicity and completeness of the data with respect to exposure and toxicity to infants and children." 21 U.S.C. § 346a(b)(2)(C). EPA can use a different margin of safety "only if, on the basis of reliable data, such margin will be safe for infants and children." *Id.* In the case of lindane, the Agency clearly states in the RED that there is scientific evidence that infants and children are likely to be more susceptible to lindane toxicity, yet inexplicably then concludes that it can reduce the presumptive 10-fold factor anyway. More specifically, EPA states:

> *In the reproductive toxicity study, both systemic and developmental LOAELs are 13 mg/kg; however a qualitative difference in maternal and offspring effects (reduced body weight of maternal animals and reduced viability and delayed maturation in pups) indicates an increased susceptibility to exposure. This is further corroborated by a developmental neurotoxicity study in which a qualitative and quantitative increase in susceptibility is seen.*
> *Revised HED Risk Assessment for Lindane, p. 3*

If EPA is required by law to use the full 10-fold child margin of safety when there are no data regarding child susceptibility, it is clearly inconsistent with the clear meaning and intent of the law to decrease the margin of safety in the face of affirmative scientific evidence clearly indicating both qualitative and quantitative increased susceptibility in offspring from the neurotoxic effects of lindane. In fact, it is precisely to protect children from chemicals such as lindane that the FQPA required EPA to include this additional margin of safety. EPA has not, and cannot, meet the standard of proof in FQPA that would allow reduction of the full 10-fold margin of safety. The FQPA standard requires that EPA can reduce the margin of safety "only if, on the basis of reliable data, such margin will be safe for infants and children." *Id.* A chemical that shows clear and incontrovertible evidence of neurological effects in developing animals at levels below those that cause effects in the mother is not likely to be safe for infants and children without a full 10-fold margin of safety.

EPA Fails to Include Exposure to b-HCH

EPA continues to fail to adequately address serious concerns about the isomerization of lindane into the more toxic and persistent β-HCH. In the Revised HED Risk Assessment for Lindane, EPA states that, "lindane can possibly transform to the alpha and beta isomers of hexachlorocyclohexane by biological and phototransformation, although this issue remains to be conclusively resolved." (p. 9) The Agency must address this issue in light of the evidence in the peer-reviewed scientific literature.[1] [2] Resolution of this question is of substantial public health and environmental importance. The beta-isomer of HCH is the most persistent and bioaccumulative form. As much as 90 percent of HCH detected in human tissues and breast milk is the β form of HCH.[1] In addition, the Agency points out that technical grade HCH "may induce some mutagenic activity"

[1] Deo PG, Karanth NG, Karanth NG. Biodegradation of hexachlorocyclohexane isomers in soil and food environment. Crit Rev Microbiol 1994;20(1):57-78.
[2] Deo PG, Hasan SB, Majumder SK. Interconversions and toxicity changes in hexachlorocyclohexane isomers on dispersion in water. J Environ Sci Health B 1981;16(6):691-701.

(id, p. 11). EPA must reconsider its position in light of the available evidence and the major implications of isomerization, and should include a risk assessment for β-HCH exposures as a result of lindane use. If the Agency feels that it is unable to make a decision about whether or not to include β-HCH, then it must acknowledge this problem as a major source of uncertainty in the risk assessment and account for the data gap by requiring data collection to address this important question, and increasing the FQPA safety factor to the full 10x.

Failure to Include Breast Milk Exposures

EPA completely failed to address a major concern raised in our previous comments: the fact that the Agency omitted consideration of the breast milk pathway in the exposure assessment. We are deeply concerned that EPA failed to include exposures to breastfeeding infants in the RED. It is not acceptable to completely ignore public comments, and even less acceptable to fail to include a major exposure pathway to children as required under the FQPA.

EPA admits that a review of the open literature shows that breast milk is an important exposure pathway, saying: "These studies show that exposure to lindane, both transplacental and via mother's milk, is possible and that such exposure may result in adverse developmental effects on human offspring." *Revised HED Risk Assessment for Lindane, p. 14*. It is strange that this admission is followed by a complete failure to even consider this exposure pathway in the risk assessment or the RED, including in the assessment of risks to the Indigenous Peoples of the Arctic. This omission is particularly egregious because lindane is known to bioaccumulate to higher levels in breast milk, and because the nursing infant is at higher risk from the neurotoxic and endocrine disrupting effects of this chemical. Failure to include the breast milk exposure pathway is a violation of §408(b)(2)(D)(vi) of the FFDCA.

Worker Risks are High and Underestimated

NRDC is deeply concerned that workers (including pregnant and lactating women) are predicted to be exposed to dangerous levels of this chemical from use in seed treatment. Mitigation measures must bring levels of exposure low enough that workers who inhale this chemical and get it on their skin are still protected from health effects. 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."[2] We believe that seed treatment poses unacceptable health risks to workers, and that the EPA risk assessment demonstrates a serious health risk that must be addressed.

NRDC is incorporates by reference our comments on the Lindane Draft Risk Assessment dated October 29, 2001, and on the Lindane Revised Risk Assessment dated April 1, 2002, as we believe that EPA has failed to adequately address our concerns in the RED. On reviewing the literature on lindane's persistence, bioaccumulation in the environment and in human tissues, and toxicity, we do not believe that this chemical can safely be registered for use in the United States. We are particularly concerned about the disproportionate risks to certain subpopulations, including fetuses, breastfeeding infants, subsistence fishing communities, and workers.

[1] Jensen, A.A. and S.A. Slorach, Chemical Contaminants in Human Milk. 1991, Boca Raton Ann Arbor Boston: CRC Press, Inc.
[2] Ministry of Agriculture, Fisheries and Food, 1999. News Release: Review of the Pesticide Lindane (206/99) June 18.