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This submission addresses the Draft Risk Management Evaluation for Lindane (May 2007) prepared by the ad hoc working group on lindane of the Persistent Organic Pollutants Review Committee (POPRC), and responds to inaccurate statements made in a comment submitted on that draft by Pesticide Action Network North America (PANNA). [1] Morton Grove Pharmaceuticals is currently the sole supplier in the United States of lindane shampoo and lotion, prescription drugs indicated for the treatment of respectively, head and pubic lice (shampoo) and scabies (lotion). Lindane is in each case a second-line therapy, which the United States Food and Drug Administration (USFDA) has concluded should be available for patients who cannot tolerate or are not successfully treated by other therapies.

First, we commend the POPRC for recognizing in the draft report the public health concerns expressed by the United States and Canadian governments regarding an international ban of lindane that would also include a ban on the pharmaceutical applications of this chemical. Such a ban would leave many patients in the United States and elsewhere without effective treatment options for head lice, pubic lice or scabies. Indeed, these infectious diseases—two of which are sexually transmitted—affect tens of millions of Americans and hundreds of millions of people worldwide every year.[2] [3] Evidence further

[1] There has been considerable misinformation propagated by activist groups concerning lindane medications. Accurate information concerning these products, from governmental and other sources, may be found at www.lindane.com, a website sponsored by Morton Grove.

[2] Chosidow O. Scabies and pediculosis. *Lancet.* 2000;355:819-826.

[3] Guenther L, Maguiness S, Austin TW. Pediculosis. 2005. *Available at: http*://www.emedicine.com/med/topic1769.htm.

suggests that these diseases are a growing concern in the United States due to increased rates of resistance and treatment failure with widely used scabicidal and pediculicidal agents, reinforcing the need for second-line medications like lindane.[4] [5] Most recently, the USFDA and the United States Environmental Protection Agency (USEPA) commented to the POPRC that "In the United States, if lindane products were not available, approved treatment options for lice and scabies would be very limited. Cases of lice and scabies could remain untreated or harmful home remedies might be used."[6] Morton Grove also understands this to be the case based on communications with physician thought leaders and other healthcare experts who manage these diseases in both clinic and institutional settings. Nevertheless, the use of lindane as a medication has been the subject of attacks, often based on inaccurate or exaggerated claims, by several groups, including PANNA.

Second, we would like to respond to certain statements submitted by PANNA as comments to the draft report concerning the ban of lindane by the State of California and related issues. Such statements and legislative actions are, we believe, inconsistent with the conclusions and positions of the USEPA and the USFDA and unsupported by the weight of scientific evidence as detailed below.

1. Regarding Drinking Water Contamination

As part of the re-registration eligibility decision (RED) process for lindane, the USEPA conducted "down-the-drain" estimates of the amount of lindane reaching public water supplies from the use of prescription medications and noted that lindane levels from pharmaceutical sources were "extremely low" and not of concern.[7] In the 2002 RED report, the USEPA concluded that "[T]he Agency does not have risk concerns for concentrations of lindane in surface water used as a source of drinking water from consumer use for both lice and scabies treatment."[7] The USEPA further noted that a "conservative approach" was taken in its assessment, which was based in part on the reported concentration of lindane in discharged effluent from Publically Owned Treatment Works of the Sanitation District of Los Angeles, California.[7] More recently, special interest criticisms of the USEPA's environmental assessments of pharmaceutical lindane, including those from the California Sanitation District of Los Angeles (CSDLA) specifically, were refuted by the Agency in a memorandum published in July of 2006.[8]

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[4] Ko CK, Elston DM. Pediculosis. *J Am Acad Dermatol* 2004;50:1-12.

[5] Heukelbach J, Feldmeier H. Scabies. *Lancet.* 2006;367:1767-1774.

[6] POPRC. Draft risk management evaluation for Lindane. Annex F information provided by the United States of America. May 2007.

[7] USEPA. Lindane Reregistration Eligibility Decision (RED). 2002. *Available at:* http://www.epa.gov/espp/effects/lindane/attach-1.pdf.

[8] USEPA. Memorandum: Agency response to comments on the 2002 lindane RED. Public Docket for Lindane (FDMS Docket #OPP-2002-0202). July 24, 2006. *Available at:* www.lindane.com/EPA 2006_Response.pdf..

For context, the USEPA's assessment of the environmental impact of pharmaceutical lindane is based on a maximum water contaminant level (MCL) for lindane of 0.2 parts per billion (ppb).[9] California, on the other hand, applies a more stringent MCL standard for lindane of 19 parts per trillion (ppt)—a level that is more than 10 times lower than that applied to the rest of the nation and considered safe by the USEPA. Moreover, the California standard is based on an outdated 1988 national water quality criteria[10] and predicated upon the results of a flawed animal cancinogenicity study that the USEPA's Office of Pesticides no longer considers valid.[11] In fact, the USEPA more recently reported in 2003 on scientific justification for raising the MCL water standard for lindane to 1.0 ppb (more than 50 times higher than the California standard); however, the change was never implemented for practical reasons, as states had no apparent difficulty in maintaining levels within the 0.2 ppb safety standard previously set.[12]

In contrast, PANNA turns to information originating from the CSDLA to support its position on lindane, stating that "[A] single treatment for head lice when rinsed down the drain, contributed enough lindane to the water entering treatment facilities to bring 6 million gallons of water over the CTR [California Toxics Rule[13]] standard." However, follow up discussions with the CSDLA directly about this calculation reveals that it was not based on any research or study data but was instead described as a "back of the napkin" type of calculation. [14] Expert review of the calculation further shows an 8-fold mathematical error and no real-world practicality. Not only does the CSDLA contamination claim run counter to the conclusions of subject matter experts working with the USEPA (as noted above), but the point of reference is an outdated water quality standard for lindane that is no longer relevant.

To further clarify the issue, an unrealistic, worst-case scenario analysis of lindane medications was undertaken by toxicology expert Shayne Gad, PhD, DABT, ATS—adjunct professor of toxicology at Duke University Medical Center. What Dr. Gad's analysis shows is that even if lindane medications were dumped directly into drinking water reservoirs in a typical US location (vs. down the drain and into the sewage system as would normally occur), lindane levels would still be 67-times lower than the current MCL standard for lindane of 0.2 ppb and 333-times lower than the national recommended water criteria for lindane of 0.98 ppb. Specifically, this analysis was based on 2004 Albany, NY water supply data and lindane prescription data, and assumed proportional medication use across the state. The calculation is available at: http://www.lindane.com/safety/calculation/.

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[9] USEPA. Announcement of completion of EPA's review of existing drinking water standards. *Federal Register*. 68(138): July 18, 2003.

[10] The national recommended water quality criterion for lindane was revised in 2002 to 0.98 ppb. *Available at:* http://www.epa.gov/EPA-WATER/2002/December/Day-27/w32770.htm .

[11] Communication with USEPA's chemical review manager for lindane, Mark T. Howard, May 11, 2006.

[12] USEPA. Announcement of completion of EPA's review of existing drinking water standards. *Federal Register.* 68. (138): July 18, 2003.

[13] Note that California defines "contamination" using water standard for lindane that is 10-times lower than the USEPA standard applied to the rest of the nation and considered safe by the USEPA (19 ppt vs. 0.2 ppb).

[14] Communication with CSDLA, Preeti Ghuman, April 18, 2007.

2. Regarding Adverse Effects of Lindane Medications

Morton Grove also takes issue with PANNA's characterization of the safety of pharmaceutical lindane, which negatively distorts a well established profile. Lindane medications have been prescribed clinically in the United States for more than 50 years in tens of millions of patients, if not more, with a good record of safety. During this time, the numbers of reported serious adverse events have been relatively few, and have almost always resulted from product misuse. As noted in the May 2007 POPRC draft report, "Most of the side effects of lindane have been associated with chronic inhalation by seed treatment workers" and not healthcare uses. In the United States, lindane medications are available only by prescription and have been limited to small, single-use 2 oz. bottles since 2003 to minimize the potential for product misuse.

While it is true that serious adverse effects (e.g., seizure) have been reported when lindane medications have presumably been used according to directions, such events have been quantified as rare.[15] [16] In the most recent USFDA postmarketing safety analysis of lindane (published in 2003), the Agency noted a total of just 488 adverse events reported for lindane through their Adverse Events Reporting System database from 1951 through 2002 (first report received in 1974).[17] The vast majority (85%) of these reports were nonserious, while serious events most often resulted from product misuse—80% of serious cases. Thus, it is important to put into context PANNA's statement that "20% of those reporting serious events apparently used lindane according to the label directions," which in fact translates to just 14 case reports over a 50+ year period. During this same timeframe, just 3 deaths were confirmed related to lindane use, and all resulted from gross product misuse, including a suicidal ingestion. For perspective, we juxtapose these figures with the roughly 500 deaths associated with the use of acetaminophen and 400 deaths associated with the use of penicillin every year in the United States alone. [18] [19]

To date, Morton Grove has received just 15 safety-related complaints for lindane lotion and lindane shampoo combined since acquiring the products in 1995. Only 3 reports were considered to be of a more serious nature and all were associated with gross product misuse.

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[15] Lindane lotion, USP, 1% prescribing information. Updated March 28, 2003. *Available at:* http://www.fda.gov/cder/foi/label/2003/006309lotionlbl.pdf.

[16] Lindane shampoo, USP, 1% prescribing information. Updated March 28, 2003. *Available at:* http://www.fda.gov/cder/foi/label/2003/006309shampoolbl.pdf.

[17] U.S. Food and Drug Administration (FDA). Lindane Post Marketing Safety Review. Posted 2003. *Available at:* http://www.fda.gov/cder/drug/infopage/lindane/lindaneaeredacted.pdf.

[18] American Association for the Study of Liver Diseases. Acetaminophen use and liver injury. Updated October 2005. *Available at:* https://www.aasld.org/eweb/DynamicPage.aspx?webcode=FastFacts_Acetaminop

[19] Neugut AL, Ghatak AT, Miller RL. Anaphylaxis in the United States: An investigation into its epidemiology. *Archives of Internal Medicine*. 61 (1): 15-21. 2001.

The safety of pharmaceutical lindane is also supported by the results of one of the largest postmakreting safety studies of head lice treatments, which involved more than 34,000 patients and 37 local US health departments.[20] In this study, just 0.4% of patients treated with lindane shampoo reported an adverse event of any kind—none were serious. Moreover, there was no difference in the number of events classified as "medically significant" for patients treated with lindane compared with patients treated with permethrin–the most commonly prescribed first-line treatment for lice in the United States.

Lastly, we report on the findings of an analysis of unintentional lindane ingestions conducted by the United States Centers for Disease Control and Prevention (USCDC) in collaboration with the USFDA and USEPA to further underscore the relative safety of lindane medications.[21] The analysis identified 870 symptomatic cases of accidental oral ingestions of lindane shampoo or lotion between 1998 and 2003. The vast majority of symptoms reported were nonserious, such as nausea and vomiting. Just 3% were associated with seizure, and only 1 % resulted in an outcome classified as "highly serious." None resulted in death. Again, these effects occurred following oral ingestion of lindane and not with topical application as prescribed for medical use. In addition, this analysis was conducted before lindane medications were limited to small single-use 2 oz. bottles, which has dramatically minimized the risk for product misuse (ie, repeat or excessive applications) and accidental ingestion of large quantities of lindane.

3. Regarding Lindane Medications and Brain Cancer in Children

Consistent with the USFDA and other subject matter experts, Morton Grove disagrees with PANNA's claim that "Research shows a significant association between the incidences of brain tumors in children with the use of lindane-containing lice shampoos." First and foremost, the publication of these study results by Davis et al. triggered a special review by the USFDA's Dermatologic Advisory Committee that was convened on May 6, 1993 and concluded: "Based on the epidemiologic, biochemical and toxicology evidence presented, the committee voted that it was unlikely that the data in the Davis et al. study established any link between increased incidence of childhood brain cancer and the use of lindane 1% (Kwell) shampoo, and that there was no need to make any changes in the current labeling for Kwell."[22]

Further, the Davis study was not prospectively designed to evaluate lindane medications specifically but rather a variety of pesticides used in the home, including no pest strips and flea collars. In fact, there were only 7 cases where lindane was reportedly used for the treatment of head lice—findings that were based on participant recall of events dating back up to 10 years. For this and other reasons, the Davis study has been widely criticized for its lack of scientific rigor. For example, Duffy et al. notes that

[20] Andrews EB, Joseph MC, Magenheim MJ, et al. Postmarketing surveillance study permethrin crème rinse. *Am J Public Health*. 1992;82(6):857-861.

[21] USCDC. Unitentional topical lindane ingestions—United States, 1998-2003. *MMWR Weekly*. 2005;54:533-534.

[22] Duffy LC, Cole P, Lamm SH. Letter to the editor. *Arch Environ Contam Tox*. 1994;26:130-131.

"[T]he report suffers from major flaws in the epidemiologic design and lacks sufficient power to detect risks for appropriate age-matched subclassifications of exposure based on histologic type and exposure history."[22] These same experts further state that the study was "biased towards a positive association" with lindane shampoo. Even the study investigators note that "Given the large number of comparisons in the study, several of the significant findings may be due to chance alone."[23]

In contrast, Friedman et al. published in 1997 their findings of a large epidemiologic study that evaluated the carcinogenic risks of lindane medications, concluding that "There is still no persuasive evidence from studies of humans that lindane, as ordinarily used clinically, is carcinogenic in humans."[24] This study was conducted at Kaiser Permanente Medical Programme—a 50-year-old health maintenance organization in Oakland, California—and based on a 143,494-patient database with up to 21 years of patient follow up.

Indeed, the most recent expert assessments of lindane carcinogenic potential by the USEPA Cancer Assessment Review Committee, published in 2001,[25] and the Joint Committee on Pesticide Residues (JMPR) of the World Health Organization and the Food and Agricultural Organization of the United Nations, published in 2004[26], both concluded that the scientific evidence did not warrant additional cancer risk assessments of lindane in humans. Quoting JMPR specifically, "In the absence of genotoxicity and on the basis of the weight of the evidence from the studies of carcinogenicity, JMPR has concluded that lindane is not likely to pose a carcinogenic risk to humans."[26] To date, there has been no established link between the use of lindane medications and cancer in humans (adults or children), despite over 50 years of clinical use for the treatment of scabies, head lice and pubic lice.[24]

4. Regarding Treatment Alternatives for Scabies and Lice

As discussed previously and noted in the POPRC draft report on lindane, effective treatment options for scabies, head lice and pubic lice are very limited in the United States. Moreover, the increased rate of resistance to available medications further restricts the ability of healthcare providers to effectively manage these diseases, necessitating the need for a range of treatment options, which includes lindane. Consistently, the USFDA has maintained that lindane medications have important public health benefits that outweigh potential risks when used as directed; petitions to ban their use have been repeatedly rejected and determined to be without merit by experts working with this regulatory Agency.[27]

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[23] Davis JR, Brownson RC, Garcia R, et al. Family pesticide use and childhood brain cancer. *Arch Environ Contam Tox.* 1993;24:87-92.

[24] Friedman GD. Lindane and cancer in humans: A false alarm? *Pharmacoepidemiol and Drug Saf.* 1997;6:129-134.

[25] USEPA. Evaluation of the Carcinogenic Potential of Lindane, PC. Code: 009001. 2001. *Available at:* http://www.lindane.com/pdf/EPA_Cancer_Assessment_of_Lindane2001.pdf.

[26] World Health Organization. Lindane in Drinking Water: Background Document for Development of WHO Guidelines for Drinking-Water Quality. 2004. Available at: http://www.who.int/water_sanitation_health/dwq/chemicals/lindane/en/print.html.

[27] USFDA. Lindane Assessment Memorandum. 2002. Available at: http://www.fda.gov/cder/drug/infopage/lindane/lindanememoassessment.pdf.

Similarly, the USCDC continues to include lindane medications in their *Sexually Transmitted Disease Guidelines* for the treatment of scabies and pubic lice as second-line interventions.[28]

While PANNA describes a range of nonchemical and mechanical remedies for head lice, in particular, evidence of efficacy for those remedies is generally considered to be lacking. Specifically, PANNA states that "A study in the U.K. suggests that a treatment protocol of wet combing was more effective than pesticidal treatment." However, this statement is refuted by the results of a rigorous head-to-head clinical study published in *Lancet* by Roberts et al. in 2000 that showed manual removal of head lice with a commercial combing kit to be less than half as effective as treatment with a prescription pediculicide.[29] In fact, the most current Cochrane Systematic Review of head lice treatments (an independent, authoritative analysis of evidence-based research) commented that "The results of the trial by Roberts et al (2000) indicate that physical control methods, such as combing/'BugBusting' are ineffective as a means of curing head lice infections. This type of method of intervention is very labor intensive and requires a certain level of skill to be effective, which makes the treatment inappropriate as a primary treatment against head louse infestation."[30] Similarly, both the USCDC and the American Academy of Pediatrics designate pediculicidal medications as the preferred approach over manual removal with special combs for the treatment of head lice.[31] [32]

To conclude, we thank the POPRC in advance for their consideration of the facts presented and for the opportunity to submit this response to what we believe to be inaccurate statements in a comment to your committee.

Sincerely,

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Cc: Janice Jensen, USEPA

[28] U.S. Centers for Disease Control and Prevention (CDC). Ectoparasitic infections. Sexually transmitted diseases treatment guidelines 2006. Available at: http://www.cdc.gov/std/treatment/default.htm#tg2006

[29] Roberts RJ, Casey D, Morgan DA, et al. Comparison of wet combing with malathion for treatment of head lice in the UK: a pragmatic randomised controlled trial. *Lancet.* 2000;356:540-544.

[30] Dodd CS. Interventions for treating headlice. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD001165. DOI: 10.1002/14651858.CD001165.

[31] Frankowski BL, Weiner LB. Head lice: Guidance for the clinician in rendering pediatric care. *Pediatrics*. 2002;110;638-643.

[32]USCDC. Parasitic Disease Information: Head Lice Fact Sheet. 2005. Available at: http://www.cdc.gov/ncidod/dpd/parasites/lice/factsht_head_lice_treating.htm