November 22, 2002

Public Information and Records Integrity Branch (PIRIB)
Information Resources and Services Division (7502C)
Office of Pesticide Programs (OPP)
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20640

**Re: Docket ID Number OPP-2002-0202**
**Lindane Reregistration Eligibility Decision (RED)**

The purpose of this letter is to comment on the EPA's Lindane Reregistration Eligibility Decision (RED), which was made available for public comment on September 23, 2002. The National Pediculosis Association®, Inc. (NPA) is a non-profit organization serving the public since 1983 and dedicated to protecting children from the misuse and abuse of potentially harmful lice and scabies pesticidal treatments.

The NPA urges the EPA to recognize the risks associated with the pharmaceutical use of lindane for the treatment of lice and scabies as part of the Agency's RED document. Consideration of the risks of pharmaceutical use of lindane is appropriate because the risks apply not only to the child or individual being treated, but also to the caregiver ("applicator"), the public at large and the environment.

The extent of exposure to lindane from pharmaceutical use is quite large. According to the National Prescription Audit**, 270,000 prescriptions** for 1% lindane lotions and **641,000 prescriptions** for 1% lindane shampoos were filled in 2001 for the treatment of scabies and lice, respectively. These numbers alone account for 0.35% of the U.S. population. However, lindane is also purchased in bulk quantities for treatment, as well as prophylaxis, for head lice, pubic lice, body lice and scabies in nursing homes, hospitals, jails, and shelters where it is common practice to treat not only residents but also contacts and staff. In addition, residential use of lindane can involve entire families and contacts (baby sitters, relatives and guests) when only one family member has symptoms of an infestation. Therefore, it is more likely that closer to 1% of the United States population (**2-3 million individuals**) is exposed to lindane in shampoos and lotions on an annual basis. This extensive pharmaceutical use, according to the EPA's own marketing research (EPA memorandum "Estimated concentrations of Lindane in surface water used as a source of drinking water from use and disposal of shampoo and lotion into household wastewater" April 25, 2002) amounted to 1914.6 kilograms (**over two**

**tons**) during 1999-2000, most of which ended up being flushed down the drain, contributing to pollution of the environment and our nation's waters.

**The NPA is concerned that the Agency's Lindane Reregistration Eligibility Decision only considered toxicology studies provided by lindane manufacturers in setting exposure limits.**

Lindane is a neurotoxin. In setting acute oral exposure limits in the Lindane RED document, the EPA used results from an acute neurotoxicity screening battery in rats (MRID #44769201–1999; see EPA memorandum "Revised HED Risk Assessment for Lindane" July 31, 2002), where the No Observed Adverse Effect Level (NOAEL) was 6 mg/kg/day (females) and the Lowest Observed Adverse Effect Level (LOAEL), based on increased grip strength and decreased motor activity, was 20 mg/kg/day (females).

In contrast, the Agency for Toxic Substances and Drug Registration (ATSDR) used a published study by Joy et al. (1982) to set acute oral exposure limits in their assessment of lindane (ATSDR's July 1999 report entitled "Toxicological Profile for Alpha-, Beta-, Gamma- and Delta-Hexachlorocyclohexane"). The study by Joy et al. examined kindling (the development of seizure with repeated application of initial subthreshold electrical stimuli) in rats, and reported a NOAEL of 1 mg/kg/day (males) and a LOAEL of 3 mg/kg/day.

The choice of the acute toxicology study used to set the NOAEL for lindane impacts the risk assessment for pharmaceutical use of lindane to treat lice and scabies. In the Lindane RED, the Agency uses a Margin of Exposure (MOE) approach to assess risk to humans, where the margin of exposure is the ratio of the NOAEL in acute toxicity studies to the actual exposure in humans. Margin of Exposure data for 1% lindane lotion is presented in Text Table 1. The MOE target is 100. **When the study by Joy et al (1982) is used to set the NOAEL, the MOE for the pharmaceutical use of lindane is between 0.7 and 2, on average 100 fold <u>less</u> than the desired safety margin for a product that has effective, alternative therapies on the market.**

**Text Table 1: Risk assessment for use of 1% lindane lotions for treatment of scabies.**

| Age Group | Body Weight* (kg) | Dose* (mg) | Equivalent Oral Exposure (mg/kg/day, assuming 10% absorption) | MOE (using EPA's NOAEL = 6 mg/kg/day) | MOE (using ATSDR's NOAEL = 1 mg/kg/day) |
|---|---|---|---|---|---|
| Young Adult | 60 | 600 | 1.0 | **6** | **1** |
| Young Adult | 60 | 300 | 0.5 | **12** | **2** |
| Child (4-6 yrs) | 22 | 250 | 1.1 | **5.5** | **0.91** |
| Child (4-6 yrs) | 22 | 150 | 0.7 | **8.6** | **1.4** |
| Toddler (1-3 yrs) | 13 | 200 | 1.5 | **4** | **0.67** |
| Toddler (1-3 yrs) | 13 | 100 | 0.8 | **7.5** | **1.3** |

*Values of Body Weight and Dose are taken from the EPA memorandum of 7/31/02 "Revised Assessment of Risk from Use of Lindane for Treatment of Lice and Scabies."

The EPA and FDA both acknowledge that there is insufficient safety data following use of 1% lotions. The FDA has made labeling changes to address this issue.

**The NPA takes exception to the EPA's anticipation that pending label changes that restrict use to patients who have attained adult stature will eliminate risks to young children.** The underlying assumption is that the consumer will use the product in accordance with the revised label. More likely, the consumer will follow the common practice of treating everyone in the affected household (including children under 60 kg) with the product.

**The NPA is also concerned that the EPA doesn't acknowledge that the proposed FDA changes in the label for lotions containing 1% lindane will not eliminate the risks to young adults**. Studies of lindane as an anthelmintic for humans (summarized in the Handbook of Pesticide Toxicology, Academic Press, Wayland J. Hayes Jr. and Edward R. Laws, Jr., editors, 1991, Volume 2, p.805) suggest that ingestion of as little as 0.64 mg/kg/day x 3 days can lead to poisoning and convulsions in humans. Even with the revised labeling, young adults will have a MOE of less than six, which is an inadequate safety margin to ensure minimum risk of toxicity from lindane after application of the lotion.

**In addition, the NPA takes exception to the Agency's conclusion that lindane pharmaceutical products used for treatment of lice (1% lindane shampoos) do not pose acute human health risks when used in accordance with directions provided on the label.** The Agency based their conclusions on a comparison of mean peak blood levels following the use of Kwell® shampoo (maximum individual value 0.00613 micrograms/mL) and the peak blood level of 0.32 micrograms/mL reported for a single case of acute accidental ingestion which resulted in short-term adverse effects. The NPA respectfully suggests that the Agency consider the maximum blood levels following 1% lindane shampoo treatment when compared to those attained following 1% lindane lotion application (0.00613 micrograms/mL and 0.064 micrograms/mL, respectively) for their analysis. This data suggests 1% of the lindane in the shampoo is absorbed through the skin. The equivalent oral exposure from the shampoo (assuming 1% absorption) is approximately 0.1 mg/kg/day (see Text Table 2). If the ATSDR NOAEL is used for risk assessment, this analysis suggests that the amount of lindane absorbed from the shampoo is approximately 10 times the amount that would provide a MOE of 100.

**Text Table 2: Risk assessment for use of 1% lindane shampoo for treatment of lice.**

| Age Group | Body Weight* (kg) | Dose* (mg) | Equivalent Oral Exposure (mg/kg/day, assuming 1% absorption) | MOE (using EPA's NOAEL = 6 mg/kg/day) | MOE (using ATSDR's NOAEL = 1 mg/kg/day) |
|---|---|---|---|---|---|
| Young Adult | 60 | 600 | 0.1 | **60** | **10** |
| Young Adult | 60 | 300 | 0.05 | 120 | **20** |
| Child (4-6 yrs) | 22 | 250 | 0.11 | **55** | **9.1** |
| Child (4-6 yrs) | 22 | 150 | 0.07 | **86** | **14** |
| Toddler (1-3 yrs) | 13 | 200 | 0.15 | **40** | **6.7** |
| Toddler (1-3 yrs) | 13 | 100 | 0.08 | **75** | **13** |

*Values of Body Weight and Dose are taken from the EPA memorandum of 7/31/02 "Revised Assessment of Risk from Use of Lindane for Treatment of Lice and Scabies."

In the U.S., the NPA received, within a two-year period, over 1100 reports of the harmful side effects of head lice and scabies treatments containing pesticides; 500 of these reports related specifically to lindane preparations, most commonly known as Kwell®. It is generally accepted there is significant under-reporting of adverse effects. The NPA's data would support this and testifies to reporting as one of the most serious weaknesses in fair assessment of risk to the environment and human health. A single application of Kwell® to nineteen geriatric inpatients because of an outbreak of scabies resulted in seizures in three of them (Tenenbein, M., 1990.Vet. Hum. Toxicol. 32:363).

The NPA urges the EPA not to overlook the shampoo as a health concern, particularly since there are other, safer treatments that are effective for lice. For example, the FDA has approved medical devices for combing that provide cost effective, ecological, self sufficient and a feasible technique for the diagnosis and treatment of head lice (DeMaeseneer, J. et al. 2000. BMJ. 321.1187). Populations such as children, the elderly, and pregnant or nursing mothers, who are at higher risk of having adverse effects to lindane shampoo, should be encouraged to use combing as the method of choice in the treatment of head lice infestations. Combing has the additional benefit of preventing the predictable development of lice resistance that comes with pesticide reliance alone. An emphasis on safer alternatives is consistent with legal requirements outlined in the Massachusetts Commonwealth Chapter 85 Acts of 2000 to take every available opportunity to protect children from pesticides in school and childcare settings. The NPA urges the EPA to take a similar stance in the Agency's Lindane RED and emphasize the strong preference to avoid using lindane pharmaceuticals when possible.

**Finally, the NPA is also concerned about the impact of pharmaceutical use on pollution to the environment.** According to the Agency's own memorandum (dated April 25, 2002), over **two tons** of lindane are used pharmaceutically for the treatment of scabies and head lice, most of which ends up down the drain and contributing to chronic exposure levels in water and the food chain. The Agency argued, on the basis of their risk assessment, that the chronic exposure to lindane in the diet is not a concern because exposure estimates were significantly below the agencies assessment of the chronic Population Adjusted Dose (cPAD) that would present a dietary risk to man. The Agency used a NOAEL of 0.47 mg/kg/day based on a chronic dietary feeding study in rats where the lowest observed adverse effect level (LOAEL) for periacinar hepatocyte hypertrophy, increased liver and spleen weights, and decreased platelets was 4.8 mg/kg/day. The Agency then calculated the cPAD by multiplying the NOAEL by 100, the uncertainty factor (UF: 10X for inter-species variation and 10X for intra-species variation) and again by 3, the Food Quality Protection Act Safety Factor (FQPA SF). The Agency did not consider any studies evaluating the effects of lindane on immunological function in their toxicological assessment. In contrast, ASTDR did consider immunological effects and set the minimum risk level at 0.000012 mg/kg/day based a study where the LOAEL for changes in cell- and humoral-mediated immune function in mice was 0.012 mg/kg/day and serious adverse effects (necrosis of the thymus) were observed at 1.2 mg/kg/day (Meera et al., 1992).

The choice of study for setting the cPAD has profound consequences in terms of calculating the health risk of consuming lindane in the food supply. As illustrated in Text Table 3, the Agency's decision to use chronic hepatic toxicity as an end-point results in the conclusion that the amount of lindane currently in the diet poses no health risk to humans. If the Agency were to have considered immunological function as an end-point, as did ASTDR, their conclusion would have been very different.

**Text Table 3. Impact of choice of chronic toxicity study for determining cPAD for lindane exposure on estimated dietary risk to man.**

| Population Subgroup | Chronic Exposure* (mg/kg/day) | EPA NOAEL = 0.47 mg/kg/day UF = 100; FQPA SF = 3 cPAD = 0.0016 mg/kg/day | ATSDR LOAEL = 0.012 mg/kg/day UF = 100; FQPA SF =10 cPAD = 0.000012 mg/kg/day |
|---|---|---|---|
| | | % cPAD | % cPAD |
| U.S. Population | 0.000054 | 3 | **450** |
| All infants (<1 yr) | 0.000072 | 5 | **600** |
| Children (1-6 yrs) | 0.000173 | 11 | **1442** |

*Taken from the Agency's Lindane RED

**The NPA urges the Agency to reconsider the toxicology studies of the Lindane Reregistration Eligibility Decision (RED) and to include the ATSDR criteria and all other available scientific data in order to obtain the most thorough assessment and to provide for the greatest margin of safety to protect the public and the environment.**

Respectfully submitted,

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The National Pediculosis Association acknowledges BethAnn Friedman Ph.D., Arlington, MA for her assistance in preparing this document.

(signature on document submitted with original)