UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Office of Prevention, Pesticides and Toxic Substances

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MEMORANDUM

SUBJECT: **Lindane**; Chemical No. 009001. Revised Assessment of Risk from Use of Lindane for Treatment of Lice and Scabies

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This provides HED's revised assessment of risk from use of lindane for treatment of scabies and lice. The revised assessment incorporates additional information and comments provided by the Food and Drug Administration (FDA).

1.0 ASSESSMENT OF RISK FROM USE OF LINDANE TO TREAT SCABIES

HED's assessment of risk from use of lindane to treat scabies uses data from both animal and human studies and provides a range of risk estimates. EPA conducted analyses using: 1) a Margin of Exposure (MOE) approach based on animal toxicity data, and 2) a comparison of lindane blood levels from one study which documents cases of accidental lindane ingestion by toddlers in which blood levels were determined after ingestion, and a second study which provides data on blood levels of lindane following application of lindane to treat scabies. HED based its assessment on directions provided in the current label for scabies treatment. It is important to note, however, that FDA is planning to make a number of changes to the label including statements that restrict the use to patients who have attained adult stature (i.e., $\geq$ 60 kg body weight). Therefore, HED also considered pending label changes in its assessment of lindane as a scabies treatment.

1.1 MOE Approach

Under this approach, an estimated MOE is calculated based on a toxicological endpoint recommended by HED's Hazard Identification and Assessment Committee (HIARC) and compared with the target MOE for short-term dermal exposure/risk to determine whether there is an exposure of concern. The MOE is the ratio of the appropriate No Observed Adverse Effect Level (NOAEL) to estimated exposure. For the short-term dermal endpoint, a NOAEL of 6 mg/kg/day was selected from an acute oral neurotoxicity study in rats. For residential exposures, uncertainty factors are used to determine target MOEs. The target MOE for exposure to lindane from pharmaceutical use is 100 based on uncertainty factors (UF) used to account for differences among humans (intraspecies variability - UF of 10), and for differences between the test animals and humans (interspecies extrapolation - UF of 10).

Since the NOAEL is based on an oral toxicity study, dermal absorption data are required to adjust the oral dose. Two different dermal absorption factors were used to calculate estimated exposure. One was taken from a 1989 article published in *Journal of Toxicological and Environmental Health*, which reported data from a dermal absorption study on rhesus monkeys to determine if lindane applied for treatment of lice and scabies is absorbed into the blood stream (1). A second was taken from a study in *Toxicology and Applied Pharmacology*, 1974, in which lindane was tested on human subjects to quantify dermal penetration (2).

The monkey study involved topical application of 1% lotion, at label prescribed rates, to the forehead, forearm, or forepaw of monkeys for 24 hours. Percent absorption was determined based on urinary excretion of ^{14}C-lindane. Study results indicated that 18, 34, and 54% of the applied dose was absorbed after application to the forearm, forehead, and palm, respectively. A weighted average of 20% was derived based on the body surface area corresponding to the applicable dermal absorption factor from the monkey study.

For the human study, C^{14}-labeled lindane was applied topically ($4\mu g/cm^2$) to the forearm and via the intravenous route ($1\mu Ci$). Excretion of the chemical was then monitored by collecting

and analyzing urine samples during the 5 day testing period. All results were calculated as percent of the injected or applied dose. Data from the IV dosing was used to correct the skin penetration data for incomplete urinary recovery. Lindane was shown to have a dermal penetration factor of 9.3% ± 3.7 (SD).

Results of the scabies MOE assessment for children and young adults using both monkey and human dermal absorption data are provided in Tables 1 and 2 respectively. The analysis indicates MOEs of concern (MOE<100) from both high and low-end treatment scenarios.

Table 1. Assessment of Use of Lindane for Scabies - DAF from Product Specific Monkey Study

Age Group	Oral NOAEL (mg/kg/d)	Applied Dose (mg) [1]	Body Weight (kg) [2]	Daily Dermal Dose (mg/kg/d)	dermal absorption (%)	MOE	Target MOE [3]
Young Adult	6	600 high end (1 oz)	60	10	20	3	100
Young Adult	6	300 low end (2 oz)	60	5	20	6	100
Child 4-6	6	250 high end	22	11	20	3	100
Child 4-6	6	150 low end	22	7	20	4	100
Toddler 1-3	6	200 high end	13	15	20	2	100
Toddler 1-3	6	100 low end	13	8	20	4	100

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

where:

Daily Dermal Dose = applied dose (mg) ÷ body weight (kg)
Applied Dose = 20-60g of 1% lotion (high-end); 10-30 g of 1% lotion (low-end) depending on age group
Dermal Absorption Factor = 20% (weighted avg)

where:

Palm Dermal Absorption Factor = 54% -- DAF from monkey study; Used for hands which are assumed to be 6% of Dosed Body Surface Area based on % of Surface Area/Body Part from EPA Exposure Factor Handbook (EFH)Vol I
Forearm Dermal Absorption Factor = 18% -- DAF from monkey study; Used for 94% of Dosed Body Surface Area (all but hands) based on % of Total Surface Area/Body Part from EPA EFH Vol I
Dosed Body Surface Area = entire body from neck down

Table 2. Assessment of Lindane for Scabies - DAF from Pesticide Exposure in Human Study

Age Group	Oral NOAEL (mg/kg/d)	Applied Dose (mg)[1]	Body Weight (kg)[2]	Daily Dermal Dose (mg/kg/d)	dermal absorption (%)	MOE	Target MOE [3]
Young Adult	6	600 high end	60	10	10	6	100
Young Adult	6	300 low end	60	5	10	12	100
Child 4-6	6	250 high end	22	11	10	5	100
Child 4-6	6	150 low end	22	7	10	9	100
Toddler 1-3	6	200 high end	13	15	10	4	100
Toddler 1-3	6	100 low end	13	8	10	8	100

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

where:

Daily Dermal Dose = applied dose (mg) ÷ body weight (kg)
Applied Dose = 20-60 g of 1% lotion (high-end); 10-30 g of 1% lotion (low-end) depending on age group
Dermal Absorption Factor = 10% from human pesticide application dermal absorption study

[1] Application rates are based on pending label for young adults and current label/estimated body sizes for small children.
[2] Young adult BW is based on pending label changes. Child and toddler BW is avg from EPA EFH
[3] Does not include an FQPA safety factor which, if applied, would increase the Target MOE to 300 for infants and children

Uncertainties Associated with the MOE Assessment

Toxicity Endpoint - The toxicity endpoint used in the MOE assessment is based on an acute oral neurotoxicity study where the test material was administered by gavage. An oral gavage dose may be absorbed more rapidly than the dermal dose, producing a higher peak concentration of lindane in the blood and target tissues than a dermal dose. Use of a toxicity endpoint based on an oral dose (adjusted to reflect 10% or 20% dermal absorption) may therefore overestimate toxicity from a dermal dose.

Since adult animals were used in the acute oral study and children are more susceptible to exposure than adults, use of a toxicity endpoint based on the acute study may underestimate risks to children who are exposed to lindane.

Dermal Absorption - HED calculated MOEs assuming 20% and 10% dermal absorption. The 20% absorption value is derived from a study of the absorption of the scabies lotion applied to monkeys. The lotion was left on for 24 hours in the monkey assessment and therefore may overestimate dermal absorption for scabies treatment, which has a 12 hour exposure duration limit based on label restrictions. In addition, monkeys may not absorb the scabies lotion in the same manner as humans. The 10% absorption values is from a study of absorption of pesticides applied to humans. Humans may absorb the pesticide and lotion formulations at different rates. Since there are no data to evaluate the relative absorption of the scabies lotion by monkeys vs. humans or the relative absorption by humans of the pesticide vs. scabies lotion, it is not possible to assess whether these dermal absorption factors tend to overstate or understate potential risk. However, use of both studies provides a range of dermal absorption and probably provides an adequate bounding of potential exposure.

Anticipated Label Changes - According to the FDA, the label for the 1% scabies treatment lotion will be revised to restrict use to, "patients who have attained adult stature, or approximately 60 kg". The label will also be revised to recommend only that a thin layer of lotion be applied. The current label prescribes the following; "*Use only enough to cover the body in a thin layer. 1 ounce (half a 2 ounce container) should be all that is needed for children under 6 years of age: 1-2 ounces for older children and adults*". HED conducted its scabies MOE assessment based on directions provided in the current label. Given anticipated label changes, use in accordance with the revised label would eliminate risks to young children (less than 60 kg). Also, according to FDA, pending label changes to the amount of lotion required should result in lower application rates for both older children and adults.

1.2 Blood Level Comparison in Children

HED also analyzed potential risk from lindane used as a scabies treatment based on data on lindane blood levels provided in two published literature studies. One study documents cases of accidental lindane ingestion by toddlers in which blood levels were determined after ingestion. The second study provides data on blood levels of lindane in children after application of 1%

lindane lotion to treat scabies. The blood level associated with acute accidental ingestion which resulted in short-term adverse effects according to the accidental ingestion case study is 0.32 ug/mL. The highest measured blood concentration from the clinical study of levels associated with prescribed uses of lindane to treat scabies was 0.064 ug/mL. The studies are described in more detail below.

Acute Accidental Lindane Ingestion

Case reports published in the November, 1995, edition of the *Annals of Emergency Medicine* provide data on blood levels, adverse effects, and time and level of recovery resulting from acute accidental lindane ingestion in toddlers.(3) As noted in the *Annals* publication, most cases reported in the literature involve dermal lindane toxicity; ingestion toxicity is infrequently documented and data on blood levels associated with ingestion are rare. The article presents three cases in which blood levels were obtained and documented after ingestion. The highest lindane blood concentrations documented in the case studies in which the patient exhibited full recovery was 0.32 ug/mL (Case 1). This case involved a 13 month old boy who accidently ingested part of the contents of a bottle of Kwell lotion. The following description of Case 1 is excerpted from the 1995 article.

> In this case, a 13 month old boy was brought to a local emergency department after being found with an open bottle of Kwell lotion. He was described as glassy eyed, he vomited twice, and had a generalized tonic-clonic seizure. The child was transported to the hospital where he was somnolent. Shortly after arrival, he had another seizure. He was treated and laboratory analyses were conducted.
>
> Blood lindane concentrations were determined with the method of Dale et al in accordance with Environmental Protection Agency procedures. The lindane level was 0.32 ug/mL (4 hours after ingestion) and 0.02 ug/mL (20 hours after ingestion). The child was transferred to a children's hospital ICU, where his mental status progressively improved. The next day the child had slightly decreased activity. During observation over the next 2 days his condition progressively improved, and he was discharged home.

The Physicians Desk Reference (PDR) provides the following statement on clinical pharmacology regarding 1% lindane cream, "Dale, et al reported a blood level of 290 ng/ml associated with convulsions following the accidental ingestion of a lindane containing product".

Lindane Blood Levels in Children Following Application of 1% Lotion for Scabies

A 1977 article in *The Journal of Pediatrics* provides data from a study conducted in the Acute Care Clinic of Children's Medical Center, Dallas, Texas which documents blood levels of lindane in infants and children who were treated with 1% lindane lotion for scabies. (4)

In this study, serum concentrations of lindane were determined in infants and children with and without scabies infection following application of 1% lindane lotion. Studies were performed in 20 infected and noninfected patients who averaged 33 to 64 months of age with average weights ranging from 13 to 17 kg. After a pretreatment blood sample was obtained, 1% lindane product was applied to the body surface area prescribed by the label. Twenty four hours after application of the lotion, all patients were given a warm soapy bath. The current label for lindane lotion applied for scabies specifies that the lotion should not be left on for more than 12 hours. This may result in an overestimation of blood concentrations, however, it is likely not relevant to the risk assessment since the blood level measured at 6 hours was used for risk assessment purposes. Specimens of blood for determination of lindane concentrations were obtained at 0, 2, 4, 6, 8, 12, 24, and 48 hours after topical application of 1% lotion. Patient characteristics are presented in Table 3 and results are presented in Table 4.

TABLE 3. Characteristics of Scabies Treatment Patients

	Infected	Non-Infected
No. patients	12	8
Mean Age (months)	33	64
Mean Weight (kg)	13	17
Dose of 1% lotion (mg)	44	57

TABLE 4. Blood Concentrations of Lindane After Scabies Treatment

Concentrations of Lindane in Blood (ug/ml)				
Time (hr)	Infected		Noninfected	
	Avg	Range	Avg	Range
2	0.013	0.005-0.038	0.007	0.001-0.017
4	0.025	0.007-0.048	0.013	0.008-0.027
6	0.028	0.013-0.039	0.024	0.007-0.064
8	0.026	0.010-0.037	0.019	0.009-0.040
12	0.023	0.002-0.043	0.015	0.002-0.033
24	0.010	0.003-0.019	0.013	0.006-0.024
36	0.008	0.002-0.012	0.009	0.004-0.018
48	0.006	0.001-0.021	0.005	0.002-0.008
Blood half-life	17.9 hr		21.4 hr	

Discussion of Uncertainties Associated with Blood Level Analysis

Allowable Blood Level in Children (i.e., non-exceedance levels based on evidence of adverse effects) - It is uncertain whether the levels of 320 ng/ mL and 290 ng/mL represent the maximum levels of lindane in the subjects' blood. Given that the measured level of 320 ng/mL in the cited clinical study was taken at least 4 hours after ingestion, it is likely that initial blood levels were higher. It is also uncertain what blood level is associated with the effects observed in the case study patient. To the extent that observed effects are attributable to higher than measured lindane blood levels, the assessment tends to overstate potential risk. To the extent that adverse effects may be associated with lindane blood levels lower than 320 ng/mL, the assessment may tend to underestimate risk.

The subjects in the clinical study received a bath with warm soapy water prior to application of the lindane lotion. Wet skin tends to exhibit greater dermal absorption than dry skin. Use of the blood levels from the study may therefore overstate potential exposure for individuals who have dry skin at the time of application.

In the clinical study, the lindane lotion was left on for 24 hours after application. The current label for scabies treatment specifies that the lotion should not be left on for more than 12 hours. This prolonged exposure may result in an overestimation of blood concentrations seen after 12 hours. However, it should not effect the 6 hour peak level used in the risk assessment.

The potential contribution of other lotion components to observed effects is not known.

Anticipated Label Changes - Based on the average age, the clinical scabies study looked only at infants and small children (up to 8 yrs old). Average amounts of lindane applied in the study were 129-158 mg. Given that the current label prescribes up to 300 mg (1 oz) for infants and up to 600 mg (2 oz) for children 6 and older, the amount of product applied in the study was 2-4 times less than the currently allowable amount. However, the label for the 1% scabies lotion will be revised to prescribe against use of the product for small children (i.e., children less than 60 kg). Given anticipated label changes, use in accordance with the revised label would eliminate risks to young children (<60 kg). Also, according to FDA, pending label changes on the amount of lotion required should result in lower application rates for both older children and adults. Although there is insufficient data to indicate a correlation between amount applied dermally and corresponding blood levels, it is reasonable to assume that use of a lower amount of product will produce lower lindane blood levels. Finally, the new label will direct that lindane be applied to dry skin which will reduce the amount of lindane absorbed into the blood stream.

Children vs. Adults - The blood level comparison analysis pertains and is applicable only to small children. HED has no data on blood levels associated with adverse effects in adults nor do we have data on blood levels associated with prescribed use of lindane to treat scabies in adults. Based on available toxicity data, children are more sensitive than adults. Therefore adverse effects would occur at higher blood levels in adults and older children than in young children. In addition, blood levels associated with prescribed use (under both current and revised labels) would be lower in older children and adults due to differences in weight to body surface area ratios between young children and adults/young adults.

1.3 HED Conclusions

HED's analysis using the MOE approach indicates MOEs of concern from both high and low-end treatment scenarios for all ages assessed using either monkey or human dermal absorption data. For the blood concentration analysis, HED compared blood concentrations from the scabies study with the blood concentration associated with short-term adverse effects in children. HED is concerned that there is an inadequate margin of safety between the blood levels associated with scabies treatment (0.064 ug/mL) and the blood levels resulting in short term

effects in children (0.29 - 0.32 ug/mL). Given variability of responses in humans, an uncertainty factor of 10 is considered reasonable for this risk assessment. There is a 4-5 fold difference between blood levels in treated patients and allowable blood levels identified based on evidence of adverse effects. While this assessment does consider mitigation efforts being undertaken by FDA, it is important to note that it does not consider the medical benefits of scabies treatment.

1.4 FDA Assessment and Conclusions

FDA will approve a drug that it finds is safe and effective for a specific population with a specific condition when the drug is used in accordance with its proposed labeling.
Safe and effective does not mean without risks, it means that the benefit of the treatment outweighs the risk for the patient group specified in the label. As described below, FDA conducted a risk/benefit analysis of the use of lindane as second line prescription medication for scabies and concluded, based on that analysis, that lindane is safe and effective for treatment of scabies when used in a manner consistent with its labeling. Second line therapy is defined as a product that should be used only if another treatment has already failed, or if the patient cannot tolerate another available therapy.

Risks

Lindane has been on the market since 1947, but was labeled a second line therapy in 1995 after review by the FDA. It is similar in action to other approved therapies, but has a higher percutaneous absorption than other approved scabicides and pediculocides. This greater systemic exposure may translate to a greater potential for serious adverse events, such as seizure. This systemic exposure can be exaggerated in patients with an immature or compromised cutaneous barrier. Animal data have demonstrated that the young are more sensitive to the neurotoxic effects of lindane.

FDA assessed the safety and potential risks from use of lindane as a drug based on safety information from the spontaneous adverse event reporting system (AERS) and current literature. The AERS database is a collection of spontaneous, voluntarily submitted reports of adverse events associated with drug products submitted by consumers, healthcare professionals, manufacturers, and others. One of the limitations of a voluntary system of reporting is a substantial amount of under-reporting. FDA estimates that between one and 10% of all adverse events are reported to FDA. Other limitations include the variability in the quality and quantity of information reported. In spite of known limitations, the spontaneous system has value. The system is sensitive to rare, unexpected events, is simple to use, and is relatively inexpensive. However, the AERS database does not include the total number of patients who have been treated, with or without adverse events. Because of this, it is not possible to quantify the percentage of patients who have had adverse events. Most of the serious adverse events in the AERs database occurred in patients who had already labeled contraindications to the use of lindane, who used lindane in excessive amounts, or who ingested lindane.

Moreover, even though there appears to be a narrow therapeutic index, there isn't much evidence that labeled use leads to serious adverse events. The 290 ng/ml plasma level in the Physician's Desk Reference (PDR) and the 320 ng/ml plasma level from the Aks article are plasma levels that were obtained several hours after acute ingestion of the lindane product. The two levels are from pediatric patients who ingested lindane and had seizures. This information is helpful to a physician in determining if the patient's seizure was secondary to lindane ingestion, or if there is another etiology. The plasma levels may provide a tool to determine the etiology of a patient's seizure upon presentation to the Emergency Room but are not a "No observed adverse event level (NOAEL)."

The data for lindane indicate that there is a two-compartment pharmacokinetic model. After ingestion, there is a steep rise in the serum level, followed by a rapid decline during the disposition phase when some lindane distributes to lipid tissues and some is excreted. The disposition phase is followed by a prolonged beta elimination phase. Based on this model, it is probable that the patients'symptoms (seizure) occurred at a higher serum level than those levels obtained 4 hours after the initial ingestion. In addition, the marketed formulation contains other ingredients that may contribute to the toxicity in acute ingestions. Ingredients for lotion include: glycerol monostearate, cetyl alcohol, stearic acid, trolamine, carrageenan, 2-amino-2-methyl-1-propanol, methylparaben, butylparaben, perfume and water. Ingredients for shampoo include: trolamine lauryl sulfate, polysorbate 60, acetone and water

It is important to emphasize that the blood levels listed in the PDR and the article by Aks are single cases following ingestion by toddlers of an unknown quantity of lindane. The young do appear to be more sensitive to the neurotoxic effects of lindane, as seen in studies across species. The serum lindane level that may lead to a seizure in a small child is most likely lower than the level that would cause an equal effect in an adult. The labeling is being changed to reflect this concern, indicating that lindane should be used only in patients who have achieved adult stature, or approximately 60 kilograms.

Benefits

FDA recognizes that all drugs have associated risks. Therefore, FDA must determine if the potential risks of adverse side effects associated with a drug treatment outweigh the overall health benefits of treating the condition. Although not life threatening, scabies can pose significant problems if left untreated, including severe itching and secondary infections. In underdeveloped areas of the world where treatments are not available or medical care is inaccessible, scabies can be pandemic and accounts for significant morbidity. FDA has concluded that there is no question that the standard of care for these patients is to administer scabicidal treatment for their infestation.

FDA considers alternative therapies when evaluating the benefit of a drug. Although the FDA has determined that there are other products for the treatment of scabies that may have less risk and should be used first in a patient, FDA also recognizes that there are patients "who have

either failed to respond to adequate doses, or are intolerant of, other approved therapies." These patients would have documented failed prior treatment with other approved products, or documented reactions – either local or systemic, to those products or drugs that would be expected to cross-react with those products. Although there are other therapies available for first-line use in the treatment of scabies, FDA believes it is in the best interest of public health to have several alternatives available for this subset of patients. The approved treatment options for scabies are limited. They are:

- permethrin cream, 5% (Acticin and Elimite),
- lindane cream 1% (not marketed in the U.S.), lindane lotion 1%, and
- crotamiton cream (Eurax).
- Precipitated sulfur ointment, 5-10%, is occasionally compounded and used for scabies. For safety reasons, crotamiton and precipitated sulfur ointment are reasonable options for young children and pregnant women, but the efficacy of these products is much lower than other products, and re-treatment is frequently necessary. There is information available on the internet about other alternative treatments that include soaking in borax. The efficacy of these therapies is unknown.

Resistance to products must also be considered when evaluating drugs. There are currently only three approved treatments for scabies, and as mentioned earlier, crotamiton is not as effective as lindane or permethrin. Lindane is labeled for second line therapy and should only be used in the event that there is treatment failure or if the patient is intolerant to the other two treatments. If a patient has persistent infestation after one form of treatment, there should first be an assessment for appropriate use, and if it is determined that the failure wasn't due to misuse, then the patient should be retreated with an alternative agent. There is a public health benefit to having several treatment options for a condition where a patient may require re-treatment with a different therapy, especially when there may be emerging or transient resistance.

Lindane has been available since 1947, and there are some case reports that the scabies mite has recently developed resistance to it. A literature search did not reveal any reports of scabies mite resistance to permethrin, but it has been on the market for a much shorter period of time than lindane. There is one case report in the literature of resistance to crotamiton. It is not unreasonable to expect that resistance to permethrin will develop over time. If this resistance does occur, and lindane is not available, physicians would not have alternative approved and effective therapies for patients infested with scabies.

Conclusions

FDA has concluded that lindane is safe and effective for treatment of scabies when used in a manner consistent with its labeling. Although lindane is already labeled as a second line therapy, the current label is being revised to indicate that lindane is for use only in patients who have attained adult stature (approximately 60 kilograms). This emphasizes that it should not be used in young pediatric patients, and that patients should be post-pubescent. In addition, physicians are

instructed to use caution when they are prescribing this product to patients who have underlying conditions (HIV/AIDS) or are on medications that may result in a lowered seizure threshold, and patients who have skin conditions that may allow enhanced absorption.

Extensive information will be provided for the physician and the patient regarding the potential risk of applying the product more than once. The new label also includes a medication guide that must, by law, be given to each patient with the lindane prescription. This medication guide explains in plain language the potential for harm if the lindane is used other than as instructed. It also includes clear instructions for use. The high volume container sizes are being discontinued to limit the amount per prescription. It is anticipated that this will decrease over-use the product.

2.0 ASSESSMENT OF RISK FROM USE OF LINDANE TO TREAT LICE

HED's assessment of risk from use of lindane to treat head lice relies on data provided in two published literature studies. One study documents cases of accidental lindane ingestion by toddlers in which blood levels were determined after ingestion. The second study provides data on blood levels of lindane in children and young adults following application of Kwell Shampoo to treat head lice.

2.1 Blood Level Comparison in Children

Acute Accidental Lindane Ingestion in Toddlers

See case study and PDR data described above for scabies assessment. (3)

Absorption of Lindane Following Application of Kwell Shampoo to Treat Lice

EPA has a published study on blood levels of lindane in children and young adults following standard application of Kwell Shampoo. An 1983 article in *Pediatric Dermatology* provides data from a study conducted in the Outpatient Clinic of Children's Medical Center, Dallas, Texas. (4)

In this study, serum concentrations of lindane were determined in children with pediculosis capititis following application of 1% Kwell shampoo. Studies were performed in 9 patients who were from 3.5 to 18 years of age with weights ranging from 13.6 to 35 kg, and heights ranging from 99 to 163 cm. After a pretreatment blood sample was obtained, 1% lindane product was applied to dry hair using a sufficient amount of medication to thoroughly saturate the hair and scalp. After 10 minutes, small quantities of water were added until a lather formed. Shampooing was continued for an additional 4 minutes after which the hair was rinsed and blown dry with a hair dryer. The current label for Kwell shampoo specifies that the shampoo should remain in place on dry hair for 4 minutes only before water is added to form lather. Consequently, the study may result in higher absorption than would occur following label directions. Four patients were

retreated because of persistence of living lice after 5 days. Specimens of blood were obtained at 0, 2, 4, 6, and 24 hours after topical application of Kwell shampoo. Patient characteristics are presented in Table 5 and results are presented in Table 6.

TABLE 5. Characteristics of the Lice Patients		
	Initial Treatment	Retreatmemt
No. patients	8	4
Mean Age (years)	7.8	8.1
Mean Weight (kg)	27	29
Mean Height (cm)	122	124
Dose of 1% GBH Shampoo (mL)	44	57
Calculated Dose of lindane (mg)	420	530

TABLE 6. Blood Concentrations of Lindane After Lice Treatment				
Mean Concentrations of Lindane in Blood (ng/mL)				
Time (hr)	Initial Treatment		Retreatment	
	Avg	Range	Avg	Range
0	0		0.29	0.25-0.3
2	1.4	0.43-2.53	3.6	3.26-3.88
4	0.96	0.38-1.52	3.3	1.75-6.13
6	0.72	0.29-1.05	2.1	1.64-2.64
24	0.41	0.26-0.69	1.1	0.81-1.33

Discussion of Uncertainties Associated with Blood Level Analysis

It is uncertain whether the levels of 320 ng/mL and 290 ng/mL represent the maximum levels of lindane in the subjects' blood. Given that the measured level of 320 ng/mL in the cited clinical study was taken at least 4 hours after ingestion, it is likely that initial blood levels were higher. It is uncertain what blood level is associated with the effects observed in the case study patient. To the extent that observed effects are attributable to higher than measured lindane blood levels, the assessment tends to overstate potential risk. To the extent that adverse effects may be associated with lindane blood levels of 320 ng/mL or lower, the assessment may tend to underestimate risk.

The current label for Kwell shampoo specifies that the shampoo should remain in place on dry hair for 4 minutes only before water is added to form lather. In the clinical study, the shampoo was left in place for 10 minutes before water was added. Consequently, the study may result in higher absorption than would occur following label directions.

2.2 HED Conclusions

The highest measured blood concentration obtained following single and double treatments of head lice at label rates but at longer than label specified treatment durations was 0.00613 ug/mL. This is significantly lower than 0.32 ug/mL, the blood level associated with acute accidental ingestion which resulted in short-term adverse effects according to the cited case study

article. Therefore, HED does not believe that lindane pharmaceutical products used for treatment of lice pose human health risks of concern when used in accordance with directions provided on the label.

2.3 FDA Assessment

Based on its assessment of safety and potential risks from use of lindane as a prescription medication for scabies and lice, FDA has concluded that lindane is safe and effective for treatment of lice when used as labeled.

References

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