EPA and CDER/FDA Approaches to Acceptable Exposure to Lindane 12 pm version 7/16/02 lindantech.doc

Approach or study	EPA Approach/Assumptions/Interpretation	FDA Approach/Interpretation	Uncertainties/Confounding factors
General approach	Therapeutic benefit is not considered A NOAEL is determined in the most sensitive species A quantitative risk assessment is conducted based on the NOAEL A reasonable certainty of no harm requires a target safety margin of exposure (MOE) of 100	Risk is evaluated with respect to the benefit obtained by the patient. This risk/therapeutic benefit is considered paramount. A quantitative risk assessment is not conducted.*see note 1. Other available therapies considered. *see note 2. Animal data should be from studies with the same route and duration of exposure Nonrodent also tested; most relevant species is used Human safety data supercede animal toxicity data Human exposure is determined under conditions of use with the clinical formulation. *see note 3. Thresholds for toxicity are considered Very large (>10x) safety factors are not generally used Minimal reversible toxicity could be considered acceptable	
Acute oral neurotoxicity in immature (4- to 5-wk old) rats	The NOAEL for behavioral effects is 6 mg/kg Assumes sensitivity of rats and humans to lindane effects is similar This value will be used for extrapolation to humans	Data were highly variable; 20 mg/kg could be considered the NOAEL for behavior, and effects were reversible; however 60 mg/kg caused convulsions, so for purposes of extrapolation 1/10 a convulsive dose could be used. The animals were immature (more sensitive to lindane) and not adult The exposure was by gavage and not dermal; The neurotoxic effects could be exaggerated when the entire dose is given once, yielding a higher Cmax, rather than over a multi-hour period A steep dose response exists between no effects and convulsions	Young animals exposed by gavage would probably result in a lower NOAEL than dermal exposure in adult animals .
Dietary multidose in rabbits (gestation day 6 through lactation day 10)	NOAEL for pup effects is 1.2 mg/kg/d maternal exposure NOAEL for maternal effects is 5.6 mg/kg/d Pup NOAEL could be used for extrapolation to humans	Pregnant women should not use lindane Multi-dose exposure increases toxicity Exposure is dietary and not dermal Exposure of pups to lindane is unknown and cannot be determined from maternal exposure Lindane could accumulate in fetus and pups would also be exposed in the milk. Higher conc of lindane in fetal blood than in maternal blood and in fetal tissue than in maternal fat.	Multi-dose studies will result in a lower NOAEL than single dose studies. Since pup exposure is not known, quantitative extrapolations not possible without further information. NOAEL in pups should not be used to determine risk in adults.

EPA and CDER/FDA Approaches to Acceptable Exposure to Lindane (b)

Approach or study	EPA Approach/Assumptions/Interpretation	FDA Approach/Interpretation	Uncertainties/ confounding factors
Single dermal exposure of 60 mg/kg in 1-kg weanling rabbits caused convulsions Lindane in blood 24 hr later at time of convulsions was 0.7-2.5 ug/ml		Immature animals more sensitive to lindane than young adult animals	Effects in weanling cannot be extrapolated quantitatively to effects in adults
13-week neurotoxicity study in rabbits		Lindane accumulates (10x) in the brain, as well as in adipose tissue	Plasma levels may not reflect brain levels
320 ng/ml plasma 4 hr after oral ingestion associated with convulsions in a child	This value could be compared to values after appropriate clinical use	Effects are in a child and not in an adult Effects may be attributed to higher than measured blood levels; 4 hours could be after the rapid distribution phase Effects would correlate with brain levels The highest no effect level is not known Other components in the product when ingested may lower the threshold for lindane toxicity	Children are more sensitive than adults Other components in the product when ingested may lower the threshold for lindane toxicity Plasma levels associated with causation of the toxic effects are not known. *See note 4
Dermal bioavailability of lindane lotion in monkeys after 24–hr exposure is 20%	The value of 20% could be used in extrapolation from an oral study to human dermal exposure	24-hr exposure exceeds labeled use of 8-12 hr.	20% dermal bioavailability estimate is probably on the high side; 8-10% is quoted from human studies that did not use the marketed formulation.
Dermal bioavailability of a pesticide formulation is 10% in humans		Dermal bioavailability of lindane lotion is unknown and depends on the formulation 10% could be considered a reasonable estimate	Dermal bioavailability of lindane lotion under conditions of use is unknown
Max Plasma level after whole body exposure to lotion for scabies is 64 ng/ml (mean is 29 ng/ml)	A 4x adjustment should be made because old labeling allows patients to use more than the amount used in the study	Application of the lotion was preceded by a warm bath that increased dermal bioavailability and which is counter to labeling Entire body was covered, so no adjustment is necessary Revised labeling will reduce the amount available for application	EPA estimate of human exposure under conditions of use may be higher than actual. *see note 5.

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Approach or study	EPA Approach/Assumptions/Interpretation	FDA Approach/Interpretation	Uncertainties/ confounding factors
Production volume of lindane pharmaceutical formulations = at least 50, 000 gallons per year		The number of persons using lindane for scabies is unknown and can only be estimated within an order of magnitude	
Adverse Event Reporting: Most effects associated with misuse or nonlabeled use		Most persons have no detectable serious effects Limited product size, revised labeling and increased warnings plans were conveyed to generic companies to further reduce risk. Dose-ranging studies are proposed to determine if lower dose and duration of application for scabies would still be effective	EPA used current labeling and considered effects on children *see note 6 and 7

Note 1: The Food and Drug Administration approves drugs based on a risk/benefit analysis. A drug must be determined to be safe and effective for a specific population with a specific condition at the dose described in the label. The FDA recognizes that all drugs have associated risks, and determines if the risk is acceptable when compared to non-treatment of the condition. The FDA has determined that there are other therapies for the treatment of head lice and scabies that may have less risk associated with them, and thus, the label states that lindane should be reserved for 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. For the indication of scabies, alternative therapies are limited.

Note 2: Resistance to products must be considered when evaluating pesticides. At this time, there is documented resistance to Lindane, which has been available since 1947. It should be noted that there is not resistance to permethrin noted in the literature to date for permethrin, but with increased usage, there is a likely possibility that this will occur. In addition, there are documented cases of resistance to all treatments that are currently indicated for the treatment of head lice.

Note 3: The human exposure from the Ginsburg study is per labeled instructions. This study was performed on pediatric patients who had a warm soapy bath prior to application which may have increased systemic absorption.

Note 4: It is important to note that the 320 ng/ml plasma level from the Aks article, as well as the 290 ng/ml plasma level in the PDR, are plasma levels that were obtained several hours after acute ingestion of the lindane product. The plasma levels provide a tool to determine the etiology of a patient's seizure upon presentation to the Emergency Room but are not a NOAEL. 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 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 patient's symptoms (seizure) occurred at a higher serum level than those levels obtained 4 hours after the initial ingestion.

The marketed formulation has 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: glycerol monostearate, cetyl alcohol, stearic acid, trolamine, carrageenan, 2-amino-2-methyl-1-propanol, methylparaben, butylparaben, perfume and water.

Note 5: Current labeling includes the following information regarding amount of lindane to be applied, "USE ONLY ENOUGH TO COVER THE BODY IN A THIN LAYER. 1 OUNCE (HALF OF A 2 OUNCE CONTAINER) SHOULD BE ALL THAT IS NEEDED FOR CHILDREN UNDER 6 YEARS OF AGE; 1 TO 2 OUNCES FOR OLDER CHILDREN AND ADULTS." The new labeling will exclude the volume to be applied and will describe application as a thin layer. In addition, only 1-ounce bottles of lindane will be available. For adult patients, physicians will have to write a prescription for two 1-ounce bottles to be dispensed, and the pharmacist will dispense two 1-ounce bottles.

Note 6: New labeling will restrict the use to "patients who have attained adult stature, or approximately 60 kg." This emphasizes that it should not be used in young pediatric patients and that patients should be post-pubescent.

Note 7: 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 includes a substantial amount of under-reporting. The FDA estimates that between one and 10% of all adverse events are reported to the 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. In addition, 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.