MEMORANDUM

Date:
From: Lisa L. Mathis, M.D., Medical Officer
Through: Jonathan Wilkin, M.D., Division Director, DDDDP
To: Lee Lemly

Part 1: Executive Summary

Lindane (also known as gamma-hexachlorocyclohexane) is an organochloride pesticide approved for topical treatment of pediculosis and scabies in patients "who have either failed to respond to adequate doses, or are intolerant of, other approved therapies." Lindane was labeled a second line therapy in 1995 because, while it is similar in action to other approved therapies, it 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.

There is limited systemic exposure data for lindane products ranging from pharmacokinetic studies using the topical formulations to blood levels that have been obtained after accidental ingestions in patients presenting to the emergency room.

There are documented cases of resistance to lindane and crotamitan[1] with scabies. While there does not appear to be information regarding resistance of scabies to permethrin, there is no reason to assume that this will not occur with sufficient time and selection pressure. With pediculosis, there are documented cases of resistance to all available therapies, and the "best" choice of scabicide or pediculocide must be made based on local resistance patterns.[2]

There are potential risks when using all of the approved medications for the treatment of scabies and lice. Because lindane has a smaller safety margin than the other treatments available, its use should be limited to those patients who have failed and/or who cannot tolerate other therapies. In addition, it is clear from animal studies that young organisms are more sensitive to the neurotoxic effects of lindane, and the use in patients who have not achieved adult stature should be discouraged. Efforts should be made to increase the patient's awareness of the potential dangers of misusing lindane, and the use of lindane should occur under informed conditions.

---

[1] Roth I. William (name correct?), "Scabies Resistant to Lindane 1% Lotion and Crotamiton 10% Cream," *J Am Acad Dermatol,* 1991;24: 502-503.
[2] Dodd, C. S., "Interventions for Treating Headlice (Cochrane Review)," in: *The Cochrane Library*, Issue 1, 2002, Oxford: Update Software.

Part 2: Introduction

Current Approved Uses:

The FDA approved lindane for topical treatment of pediculosis and scabies in 1947. The label was changed in 1995 to read "for the treatment of patients ... who have either failed to respond to adequate doses, or are intolerant of, other approved therapies." It is currently available by prescription in a 1% lotion for the indication of scabies and 1% shampoo for the indication of pediculosis. Lindane lotion and shampoo are both supplied from the manufacturer in a 2-ounce patient size bottle, and a pharmacy-only size pint (473 ml) bottle. The label directs pharmacists to dispense in a light-resistant, child-resistant container.

Contraindications to the use of lindane include: premature neonates, because their skin may be more permeable and their liver enzymes may not be sufficiently developed; patients with a known seizure disorder, because they may have a lower seizure threshold; and, individuals with a known sensitivity to the product or any of its components. The label warns in upper case letters that there is a serious potential for CNS toxicity if not used as labeled.

The labeled directions for the shampoo recommend washing the hair first, followed by complete drying. Apply 1 ounce for short hair, 1.5 ounces for medium length hair, and 2 ounces for long hair. The lindane is to remain in the hair for 4 minutes, and then small amounts of water are to be applied until there is lather. Finally, the patient is to rinse out lather and remove nits with a comb or tweezers. Treatment should be repeated if there are viable lice after 7 days.

The package insert for the lotion/cream instructs patients to apply a thin film to dry skin. The patient is instructed to use a toothbrush to apply under nails (throw away toothbrush after use), and to apply to the entire body from the neck down. The lotion should be left on for 8-12 hours and then removed by thorough washing. Although the label does not recommend bathing prior to treatment, it does state that if a hot bath is taken before treatment, the skin should be completely dried and cooled prior to application of lindane.

Drug Use Data:

The use of lindane has been declining for the last four years. According to drug usage data, there were [ ] prescriptions written for lindane in 2001; [ ] in 2000; and [ ] in 1999. In 2001, [ ] prescriptions were written for patients [ ], [ ] were written for patients [ ], [ ] were written for patients [ ], and [ ] were written for patients [ ]. The average milliliters dispensed per prescription in those three years ranged from [ ]. This data demonstrates that the average prescription results in the dispensation of enough lindane to treat 4 pediatric patients or 2 adult patients.

Previous Safety Reviews:

Concerns of the safe use of lindane have been raised in the past by the Environmental Protection Agency (EPA). The EPA published a notice in the Federal Register (FR) February 17, 1977 about their intention to not register lindane as a pesticide. This was based on animal data and human studies with technical-grade material that has higher toxicity than the pharmaceutical grade material assessed by the FDA.

Work related and environmental exposures to high and persistent concentrations of lindane initially led to concerns regarding the safety of this pesticide. In contrast to therapeutic use, exposures secondary to environmental use result in no direct benefit for the exposed persons. This risk of occupational/environmental exposure should be assessed separately and independent of the risk related to the therapeutic use of a medication to treat a medical condition where there is direct benefit to the patient.

Issues concerning lindane have also been presented to the FDA's Dermatologic Drugs Advisory Committee numerous times. In 1975, 1976, 1977, 1983, 1984, 1985, and 1993 the committee was consulted and conducted in-depth reviews and discussions on the safety of lindane.

The comments from the Advisory Committee were incorporated into labeling, and, in the June-July 1976 issue of the *FDA Drug Bulletin*[3], the agency highlighted some adverse events associated with the use of lindane.

[3] Gamma benzene hexachloride (Kwell and other products) alert. FDA Drug Bull. 1976;6:28

The following table briefly summarizes concerns and actions recommended by the FDA's Dermatologic Drugs Advisory Committee:

9/30/76	Concern was raised regarding adverse events such as seizure that had occurred with lindane use. There was also discussion regarding the duration of therapy. The AC discussed changing the label to include warnings about use during pregnancy and on very young children. They also discussed the need to minimize repeated use in the absence of viable organisms. Recommendations were made to consider a label at the next meeting.
12/16/76	Discussed adverse events and ongoing studies. Discussion was tabled until more data was available.
3/2/77	Discussed EPA's proposal to ban lindane that was published in the FR (Feb 17, 77). Discussed boxed warnings and decreased dosage in pediatrics as well as labeling for the amount to be used per application. The decision was reached to add "Do not exceed recommended dosage" to the label and to add stronger warnings in the Warning section regarding use in young patients
6/2/77	Again discussed labeling and made some recommendations regarding bathing prior to application, duration of application, and a warning regarding re-treatment when no viable lice were present.
9/30/77	Made minor changes to label as discussed in previous meetings. Removed the statement that Kwell was ovicidal in scabies, as there was only data for pediculosis.
6/13/83	The AC determined that lindane was safe when used in the manner labeled, and that it was important enough for the treatment of, especially, scabies to remain on the market. The committee agreed to further investigate changes that could be made in labeling to increase the safety of this product.
10/20/83	The committee reviewed recommendations to increase the safe use of lindane. The first suggestion was to remove the indication of head lice from the lotion and cream label. There was concern that the differential in time of treatment in the label would result in prolonged application time if the cream or lotion were used for lice. They also recommended contraindicating the use of lindane in infants, pregnant women, and in lactating women. This was decided against, as these patients may need to use this product as last resort. The decision was to contraindicate the product in premature infants and patients with a seizure history. Other recommendations were made regarding application safety, and the possibility of a patient package insert and unit dose packaging.
11/5/84	There was brief discussion regarding the patient package insert, the National Pediculosis Association provided copies of a handout that they currently give to parents regarding the safe application of lindane.
6/24/85	The National Pediculosis Association submitted a written statement regarding the importance of the patient package insert, and made the assertion that the handout previously provided by the NPA would serve as a model for this PPI.
5/6/93	There was extensive discussion of an article that suggested an association between lindane and childhood brain cancers. The committee noted there were several flaws in the data presented in the article, and that there was an unlikely association based on the data. The committee voted that lindane was safe when properly used, and that it should remain on the market.

In 1995, four Citizen's Petitions were filed with the FDA requesting that lindane be removed from the market because of concern regarding the safety of the product (from Consumers Union of the U.S., Ms. Kathlyne H. Bohuslaw, Cancer Prevention Coalition, Public Citizen). It was determined that the petitions were without merit, that lindane was safe and effective when used as directed, and that it should remain on the market as a treatment option.

The review of lindane that occurred secondary to the Citizen's Petitions did lead the Agency to believe that, while the directions for use were clearly presented in the label, there were still cases of adverse events secondary to misuse of the product. Language

was incorporated into labeling in 1995 making lindane a second line therapy for patients in whom other treatments were either ineffective or intolerable.

Since 1995, there have been additional reports of adverse events, both in the literature and in the spontaneous adverse event reporting to the FDA. This review will cover the new information regarding human exposure, adverse events, and efficacy of lindane, as well as the armamentarium currently available for the treatment of scabies and lice. All new information will be used to evaluate the risk versus benefit of lindane as a therapy for the treatment of scabies, pediculosis, and/or both.

Part 3: Public Health Benefit

Incidence and Manifestations of Scabies and Lice:

Scabies is an infestation with the mite *Sarcoptes scabiei*. The global incidence of scabies infestations is 300 million[4]. The infestation can involve the entire body from the neck down (except in very young patients where the head may also be involved) and manifests as an intensely pruritic, erythematous, papular eruption caused by burrowing adult mites in the epidermis. In severe cases (Crusted scabies), the lesions can develop thick crusting and can cause the patient great discomfort. The itching and papular reactions can persist for weeks to months after treatment. Cutaneous secondary bacterial infection can occur, caused most commonly by *Streptococcus pyogenes* and *Staphylococcus aureus*.

Pediculosis capitis and pubis are infestations with lice that affect the hair on the head and the anogenital area. Pediculosis is among the most common medical problems in the U.S. Head lice infest 6-12 million persons every year[5]. Itching is the most common symptom, although many patients will not complain until the infestation becomes heavy. In most cases, failure to treat a light infestation will lead to a heavier infestation resulting in excoriation and possible secondary infection of the skin. Social attitudes to head lice infestation vary greatly between societies, but in western societies, parents are often ashamed if their children have lice because of the mistaken perception that it is an indication of uncleanliness. Schools do not allow students to attend if they have adult lice and/or nits.

Although not life threatening, both scabies and pediculosis pose significant problems, including severe itching and secondary infections, for those who are infested. There is no question that the standard of care for these patients is to administer scabicidal and pediculocidal treatment for their infestation.

---

[4] Walker GJA, Johnstone PW. "Interventions for treating scabies (Cochrane Review)". In the Cochrane Library, Issue 1, 2002. Oxford: Update Software

[5] Atkinson L, Clore ER, Kisel BE, Posch I. "Internal and external parasites" Pediatrics 1986;1:1-7

Available Therapies:

Treatments used for scabies include permethrin cream, 5% (Acticin and Elimite), lindane lotion 1%, crotamiton cream (Eurax), and precipitated sulfur ointment, 5-10%. 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.

Available treatments for head/pubic lice include lindane shampoo, 1% (Kwell), and malathion lotion 0.5% (Ovide) available by prescription only. Over-the-counter treatments in the U.S. include pyrethrum 0.33% with piperonyl butoxide shampoo and cream rinse (Rid), and permethrin cream rinse, 1% (Nix). Malathion lotion (Ovide) is only approved for the indication of head lice.

Although there are several agents available to treat both scabies and lice, there is evidence that scabies and lice have developed resistance to different therapies. This resistance is difficult to adequately document, and is due to several factors including poor application technique, noncompliance, reinfestation, overuse, and true genetic mutation of lice and scabies. There are documented cases of resistance to all available therapies, and the "best" choice of scabicide or pediculocide must be made based on local resistance patterns.[6]

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.

Part 4: Assessment of Safety and Potential Risks

The safety information for lindane comes largely from the spontaneous adverse event reporting system and current literature reports. The safety and potential for adverse events are related to the local and systemic exposure that results from topical application of lindane.

The most common adverse events associated with the topical treatment are skin irritation and central nervous system stimulation ranging from dizziness to seizures. The majority of adverse events occurred because of misuse of the product – either ingestion or daily

---

[6] Eichenfield LF, Francisco CF "Treatment of Head Lice" Ped Inf Disease 1998;17:419-420
Chesney PJ, Burgess IF "Lice: Resistance and Treatment" Contemp Pediatr 1998;15:3-9
Boix V, Sanchez-Paya J, Portilla J, Merino E "Nosocomial outbreak of scabies clinically resistant to lindane" Ann J Ind Med. 1998 Jan;33(1):82-87
Berry D, Brewster M, Rodney W, Neuberg R "Untoward effects Associated with Lindane Abuse" AJDC 1987;141:125

application for a prolonged period, but some have occurred when the product was used as recommended. Some reports associate lindane exposure to aplastic anemia, although this has largely occurred with exposure to agricultural or veterinarian formulations (higher concentrations than the formulation approved for human application).

Spontaneous Adverse Event Reports:

A post-marketing safety review conducted by the Division of Drug Risk Evaluation revealed 488 reports of adverse events related to the use of lindane in the AERS database as of April 1, 2002. Although these are the adverse events that have been reported since approval in 1947, the first report date in the existing databank is 1974.

There were 60 reports in the AERS database that had an outcome of death, hospitalization, life threatening condition, or congenital anomaly. There were 15 cases of death, 46 cases of hospitalization, seven cases of life-threatening outcomes, and 6 cases of congenital anomalies. Only 16 of these cases occurred with lindane shampoo (one of the 16 was listed only as lindane for lice and was from 1977, and it is assumed that it was shampoo), four of the 16 were oral ingestion.

Deaths: There were 15 deaths, 9 in adults and 5 in children, and one was a stillborn infant exposed during pregnancy. Thirteen of the patients were treated topically and one patient ingested lindane for suicide purposes. Five of the adult cases reported confounding factors: elderly (4), and renal transplantation (1). Three patients in one nursing home died after lindane application. Two of the 3 patients died within 24 hours of treatment, one from pulmonary edema, and the other from chronic obstructive pulmonary disease. The third patient died 41 days after treatment and had a seizure on the day of death. A fourth elderly patient in another nursing home died of an unreported condition on the day of lindane treatment. Three of these 4 adult patients had contraindications to the use of lindane.

The deaths in pediatric patients included one 22-month old patient who died of gram negative sepsis. She was diagnosed with myelocytic leukemia and aplastic anemia "some time after lindane use." Nonlymphocytic leukemia accounts for 20% of all childhood cancers, and aplastic anemia often occurs secondary to replacement of functional bone marrow with leukemic cells. Two of the deaths were secondary to other causes, Respiratory Syncytial Virus infection and lymphoma of the brain. The fifth child, a six-month-old male was determined to have died from lindane toxicity at autopsy. The adverse event report form stated that application occurred up to 4 times over four days. This would suggest that the child received multiple treatments on consecutive days.

Hospitalizations: There were 46 hospitalizations, 25 in adults and 21 in children. Six of the hospitalized adults were aged 70 years and older, and five of the pediatric patients were less than 2 years. Two adults and four children ingested the lindane; the other hospitalized patients used lindane topically. The adverse events leading to hospitalization were primarily central nervous system events, such as seizures and dystonic reactions, and unspecified CNS involvement. Of the pediatric patients hospitalized, there were 11 patients with adverse events most likely secondary to lindane;

one with a dystonic reaction, one with respiratory arrest, and 9 with seizures. Of note, most of these patients had the lindane applied repeatedly, not as labeled. One patient less than 2 years of age had a temperature of 103 degrees at the time of the seizure, suggesting the possibility of a febrile seizure not causally associated with lindane.

In all age groups, adverse events occurred mainly in patients who appeared to have misapplied or orally ingested lindane.

The congenital anomalies in infants possibly exposed in utero did not fit a characteristic pattern. The defects included neural tube defects (acrania, holoprosencephaly), another was born "handicapped" with rash that recurred, one had a bronchogenic cyst, two were "retarded," and there was one case of a full term stillborn child.

Literature Reports:

A MEDLINE search using the MeSH linking of "Lindane, adverse events, toxicity" and limited to animal and human reports from 1995-2002 yielded 182 reports. The previous major safety review of lindane reviewed all articles prior to 1995. The majority of the reports were animal and human exposures in the laboratory and in agriculture. Because of the lack of relevance of many reports to the therapeutic use of lindane, only some of these reports are included in this review. Some information from the literature published prior to 1995 was included in the systemic exposure section of this review because of relevant information.

There are 3 reports each with 3 children who ingested lindane and presented to the emergency room for treatment. Of note, one of these articles reports blood levels of these children and attempts to correlate blood levels with clinical presentation. It should also be noted that in all of these cases, the young children were able to access an ample quantity of lindane to result in acute neurologic symptoms ranging from irritability to seizures leading to respiratory collapse[7].

There is one case report of a 14-year old male who had been diagnosed with scabies and had open lesions on his entire body. He self-applied lindane to his entire body for 48-hour applications on at least 8 occasions. He developed pancytopenia, but recovered fully 2 months after exposure[8]. There have not been other reports of this event following use of 1 % lindane lotion, cream, or shampoo[9].

---

[7] Schmutz JL, Barbaud A, Trechot P. "Acute lindane intoxication in three children" Ann dermatol Venereol. 2001 Jun-Jul; 128(6-7):799
Nordt SP, Chew G "Acute lindane poisoning in three children" J Emerg Med. 2000 Jan;18(1):51-53
Aks SE, Krantz A, Hryhrczuk DO, Wagner S, Mock J "Acute accidental lindane ingestion in toddlers" Ann Emerg med. 1995 Nov;26(5):647-51

[8] Berry D, Brewster M, Rodney W, Neuberg R "Untoward effects Associated with Lindane Abuse" AJDC 1987;141:125

[9] American Hospital Formulary Service Drug-Information 2002. Bethesda, MD: American Society Hospital Pharmacists, 2002.

Factors influencing systemic exposure:

The potential for any topically applied agent to have systemic effects depends on absorption and systemic exposure. Absorption of topical medications is dependant on several factors, including molecular size, charge and partition coefficient of the active drug ingredient, concentration of ingredients, solvents used in the marketed substances, duration of application, amount of body surface area treated, degree of inflammation of skin (i.e. integrity of barrier to percutaneous penetration), and occlusion of site treated. The treatment of scabies requires application to the entire body from the neck down for 8-12 hours, followed by washing, which may occur in a warm bath. Treatment of head lice calls for application of the shampoo for 4 minutes, followed by and washing.

In the case of lindane, hydration of the stratum corneum may be a factor in increased systemic exposure, especially if patients are instructed to bathe and/or wash hair prior to application. It is conceivable that full drying of the hair does not usually occur prior to application of the shampoo, and that having the patient wash prior to application may result in a longer period before the patient is again bathed to remove the lindane.

Age may also be involved in increased absorption of lindane in young and elder patients. Young children have a high surface area to volume ratio, and consequently have a disproportionate potential for systemic exposure. In the elderly, the skin undergoes changes, mostly degenerative, which affect epidermal barrier function[10]. It is at these extremes of age that the risk of systemic absorption and exposure of lindane seems to increase.

Laboratory data:

The current label has some pharmacokinetic data as follows: "Dale et al reported a blood level of 290 ng/mL associated with convulsions following the accidental ingestion of a lindane containing product. Analysis of blood taken from subjects before and after the use of lindane shampoo showed a mean peak blood level of only 3 ng/mL which appeared at six hours and disappeared at eight hours after the shampoo was applied"

Most of the published literature demonstrating percutaneous absorption was performed to attempt to quantify the potential systemic exposure of workers to lindane. Chronic symptoms are seen in lindane-exposed workers with blood levels of 0.02 μg/mL. It should be noted that lindane is very lipophilic and may accumulate in fatty tissues (i.e. stratum corneum, brain, liver) with chronic exposure. In chronic exposure, there may be more CNS effect at lower serum levels because the drug may be distributed into the brain at higher than serum levels. This information may be relevant to patients who receive multiple applications because of misuse of the product.

[10] Tenenbein M. "Seizures after lindane therapy" J Am Geriatr Soc 1991;39:394-395

Maibach and Feldmann performed studies using lindane in acetone[11] applied to the forearms of healthy male volunteers and reported a bioavailability of 9.3 %. While this study is important especially for occupational exposures, it is difficult to extrapolate these results to the currently marketed formulations of lindane that do not contain pure acetone and have a much lower concentration of lindane.

Another study was performed to assess the percutaneous absorption of lindane in 8 healthy volunteers[12]. This study used high concentrations of lindane (120mg/mL or 12 % of lindane in pure acetone and 3 mg/ml or 0.33% of lindane in a white spirit). The acetone was used as a control because of previous studies that used acetone, and the white spirit was used because it is a wood preservative and is relevant to industrial exposure. The application solution (1 ml) was applied, and the sites were covered with a non-occlusive dressing for 8 hours. Peak plasma concentrations occurred at 4 hours for patients in the acetone group (range 0.79-1.15 ng/ml) and 6.5 hours for patients in the white spirit group (range 0.19 ng/ml-0.81 ng/ml).

Lange, et al, applied 50g of 0.3% lindane scabicide (a different formulation than that of the lindane lotion available in the U.S.) to the entire body of 2 male patients with scabies on three consecutive days and obtained peak plasma levels of 6.25 ng/ml (0.0625 μg/mL) at 6 hours[13]. The maximal blood level in one male patient with severe scabies was 0.425μg/ml.

Ginsburg et al performed a study of serum concentrations of lindane in pediatric patients with scabies treated with lindane, and used their apparently non-infested siblings who were also treated, as controls[14]. This study enrolled 20 patients. The infested children were actually younger, smaller and had inflamed skin. This study was performed on pediatric patients who had a warm soapy bath prior to application which may have increased systemic absorption. Specimens of blood were obtained at 2, 4, 6, 8, 12, 24, and 48 hours after application of 1% lindane lotion. Peak blood levels were observed at 6 hours for both groups, and the half-life of the lindane in the blood averaged 17.9 hours in the infested group and 21.4 in the non-infested. There were no adverse events reported in this series of patients.

---

[11] Maibach HI, Feldmann R. "Systemic absorption of pesticides through the skin of man" In: Occupational exposure to pesticides: Report to the Federal Working Group on Occupational Exposure to Pesticides, Appendix B, US Government Printing office, Washington D.C., 1975, pp 120-177

[12] Dick IP, Blain PG, Williams FM "The percutaneous absorption and skin distribution of lindane in man. I. In vivo studies" Hum Exp. Toxicol. 1997 Nov;16(11):652-657.

[13] Lange M, Nitzsche K, Zesch A "Percutaneous absorption of lindane in healthy volunteers and scabies patients" Archives of Dermatological Research 1981; 271:387-399

[14] Ginsburg CM, Lowry W, Reisch JS "Absorption of Lindane (gamma benzene hexachloride) in infants and children" J Pediatrics. 1977;91:998-1000

Blood concentrations of lindane (from Ginsburg):

Time	Mean concentration in blood (µg/mL)	
	Infected (n=12)	Non- Infected (n=8)
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 – 0.012)	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)

In a report by Aks S et al, lindane levels were obtained on children presenting to an emergency room after ingesting lindane[15]. The first case reported was a 13-month-old boy who suffered 2 seizures and required intubation, the second case was a 2-year-old boy who suffered a seizure, and the third case was a 16-month-old boy who was drowsy upon presentation, but was otherwise asymptomatic. All children received gastric lavage and activated charcoal, so they may not be true measures of systemic exposure. All children recovered from their poisonings. Additional case reports of lindane ingestion where serum levels were available were also included in this review:

Peak lindane levels after ingestion (from other case reports)[16]:

Author	Age (yrs)	Blood level µg/mL	Time since ingestion (hrs)	Clinical Manifestations
Roa	43	1.3 µg/mL	12	Seizure, rhabdomyolysis, DIC, death
Starr	2.5	0.84 µg/mL	2	Seizure
Davies	16	0.206 µg/mL	Approx 2	Seizure, coma
Munk	35	0.6 µg/mL	NA	Seizure, myonecrosis, pancreatitis
Daerr	16	0.25 µg/mL	Unknown	Lethargy, resting tremor
Dale	NA	0.29 µg/mL	6	Seizure
Kurt	41	1.3 µg/mL	"day one"	Death
Burton	32	0.13 µg/mL	<2 hrs	Emesis, seizure (pt taking phenytoin)

The author has postulated that levels can be roughly correlated with the symptoms using these case reports. The following correlates were proposed:

Seizure and coma	0.20 µg/mL
Seizure and coma in patients with underlying seizure disorders	0.13 µg/mL
Sedation	0.12 µg/mL

In addition to the data summarized above, Davies et al[17] also described a premature infant who had received 3 consecutive applications of lindane topically for scabies. These treatments were applied following a hot bath. The last application (the accounts of the

[15] Aks SE, Krantz A, Hryhrczuk DO, Wagner S, Mock J "Acute accidental lindane ingestion in toddlers" Ann Emerg med. 1995 Nov;26(5):647-51

[16] See references 19-26

[17] Davies JE, Dedhia HV, Morgade C, et al "Lindane poisonings" Arch Dermatol 1983;119:142-144

first two applications do not contain details of duration of therapy) was left on the infant's skin for 18 hours. The infant died 24 hours after this application. Heart blood contained 0.33 μg/ml of lindane.

The systemic levels obtained after acute ingestions are helpful to physicians in emergency rooms and cannot be considered the lowest observed effect level. 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.

Peak serum concentrations of lindane occur at approximately six hours in all studies. This data suggests that a dose-ranging study would be helpful in determining the shortest duration of treatment that provides acceptable efficacy rather than 8-12 hours – especially for small children and for the elderly.

Part 5: Conclusions

There are potential risks to using all of the medications approved for the treatment of scabies and lice. 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 failure 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.

Unfortunately, the information obtained from the spontaneous adverse event reports and the published literature suggests that some patients may not use lindane according to the labeled directions, leading to adverse events. The majority of these occurred in patients with contraindications to the use of lindane, who used the medication in excessive amounts, or ingested the lindane.

While there are other therapies available for first-line use in the treatment of scabies, it is in the best interest of the public health to have several alternatives available. Lindane should be prescribed for scabies only if medically indicated, and a limited quantity of lindane should be prescribed cautiously and under close monitoring.

There were far fewer cases of serious adverse events related to the use of lindane shampoo for pediculosis. This may be because the area where the lindane is applied is smaller and the treatment duration is shorter for lice than it is for scabies. While pediculosis does not pose a significant health risk, the current standard of care is to treat patients who are infested. Because of the magnitude of the problem of pediculosis, and the need to have alternatives available when treatment fails or cannot be tolerated in a patient, it is in the best interest of the public health to have lindane shampoo, 1%, available by prescription.

The literature and the spontaneous adverse event reports did not provide new information regarding unknown risks of using lindane. There is data, although limited as discussed in the review, that the safety margin for lindane in the treatment of scabies is small. While the directions for use are clearly presented in the label, there continues to be cases of adverse events secondary to misuse of the product.

Lindane, available in a pharmacy-only size bottle, may be dispensed to consumers in any volume. Given the number of ingestions where an open and empty bottle is found next to toddlers, it is likely that this product is being dispensed without child-resistant containers. In addition, labeling placed on transfer bottles may be insufficient, stating only to "use as directed." The use of transfer bottles may not adequately communicate the proper usage and the risks associated with misuse[18]. In addition, according to the IMS data, the quantity dispensed in one bottle averages [ ]. This quantity may predispose to over use.

The FDA has considered the benefit-risk analysis of lindane several times over the last 20 years. Currently, the FDA believes there is a public health benefit in having lindane available on the market as a second line therapy for the treatment of scabies and lice; however, increased information to physicians and patients in the label and limitations in the quantity of lindane dispensed per prescription are needed to reduce the potential adverse events that may result from the misuse of lindane products.

---

[18] Sitowitz J, Roberts SB. "Danger of "as directed" instructions." Am J Health Sys Pharm. 2001 Sep 1;58(17): 1657

Part 6: Recommendations

Lindane shampoo, 1%, should be available by prescription for the treatment of lice in patients who cannot tolerate or have failed therapy with other pediculocides. Lindane lotion, 1%, should be available by prescription for the treatment of scabies in patients who cannot tolerate or have failed therapy with other scabicides.

While the adverse events that occur from this product are largely the result of misuse, it is clear that the misuse continues despite attempts to clarify risks in the label. The following recommendations may increase the safe use of lindane:

1. Given the increased sensitivity to the nuerotoxic effects of lindane in young organisms, the use of this product should be limited to second line therapy in patients who have attained adult stature (approximately 60 kilograms).

2. The manufacturer should make only single dose units of the shampoo, lotion, and cream available (1-ounce packages, 1 to be dispensed to a child and two 1-ounce single-units for adults). Refills should occur only after contact with the physician.

3. A medication guide should be included with every prescription of lindane that not only provide application instructions to patients, but also provides a clear definition of a second line therapy and a full disclosure regarding the serious adverse event sthat may result if the product is misused.
4. Suggested label changes:
   - A list of medications known to lower the seizure threshold should be included, and patients who are taking the drug should be instructed that they may be a greater risk of adverse events if they use lindane.
   - Physicians should be informed to use lindane with caution in patients with extensive skin disease or underlying medical conditions that may lower the seizure threshold (HIV/AIDS).
   - Bathing and washing of hair should not occur prior to treatment. Instructions should be given to completely rinse out lindane shampoo (not just "rinse out lather") after use using luke-warm water.
   - Because there are animal reproduction studies that demonstrate an adverse effect on the fetus and there are no well-controlled studies performed on pregnant women, this drug should be changed from pregnancy category B to category C.

5. Studies have evaluated shorter application times of lindane for the treatment of scabies in pediatric patients. Because of the altered epidermal barrier in both extremes of age, the application time could be shortened in these patients. This is supported by the serum blood level data, and by several investigators who report that the initial treatment duration was purely empiric and that they have data that a 6-hour treatment is as effective as an 8-12 hour application.[19]

[19] Attributed to Dr. Charles Ginsberg in the summary minutes of the Advisory Committee, Eighth Meeting, December 16, 1976. Attach

Part 6: References

1. Gamma benzene hexachloride (Kwell and other products) alert. FDA Drug Bull. 1976;6:28
2. Walker GJA, Johnstone PW. "Interventions for treating scabies (Cochrane Review)". In the Cochrane Library, Issue 1, 2002. Oxford: Update Software
3. Atkinson L, Clore ER, Kisel BE, Posch I. "Internal and external parasites" Pediatrics 1986;1:1-7
4. Eichenfield LF, Francisco CF "Treatment of Head Lice" Ped Inf Disease 1998;17:419-420
5. Chesney PJ, Burgess IF "Lice: Resistance and Treatment" Contemp Pediatr 1998;15:3-9
6. Boix V, Sanchez-Paya J, Portilla J, Merino E "Nosocomial outbreak of scabies clinically resistant to lindane" Ann J Ind Med. 1998 Jan;33(1):82-87
7. Berry D, Brewster M, Rodney W, Neuberg R "Untoward effects Associated with Lindane Abuse" AJDC 1987;141:125
8. Schmutz JL, Barbaud A, Trechot P. "Acute lindane intoxication in three children" Ann dermatol Venereol. 2001 Jun-Jul; 128(6-7):799
9. Nordt SP, Chew G "Acute lindane poisoning in three children" J Emerg Med. 2000 Jan;18(1):51-53
10. Aks SE, Krantz A, Hryhrczuk DO, Wagner S, Mock J "Acute accidental lindane ingestion in toddlers" Ann Emerg med. 1995 Nov;26(5):647-51
11. Berry D, Brewster M, Rodney W, Neuberg R "Untoward effects Associated with Lindane Abuse" AJDC 1987;141:125
12. American Hospital Formulary Service Drug-Information 2002. Bethesda, MD: American Society Hospital Pharmacists, 2002.
13. Tenenbein M. "Seizures after lindane therapy" J Am Geriatr Soc 1991;39:394-395
14. Maibach HI, Feldmann R. "Systemic absorption of pesticides through the skin of man" In: Occupational exposure to pesticides: Report to the Federal Working Group on Occupational Exposure to Pesticides, Appendix B, US Government Printing office, Washington D.C., 1975, pp 120-177
15. Dick IP, Blain PG, Williams FM "The percutaneous absorption and skin distribution of lindane in man. I. In vivo studies" Hum Exp. Toxicol. 1997 Nov;16(11):652-657.
16. Lange M, Nitzsche K, Zesch A "Percutaneous absorption of lindane in healthy volunteers and scabies patients" Archives of Dermatological Research 1981; 271:387-399
17. Ginsburg CM, Lowry W, Reisch JS "Absorption of Lindane (gamma benzene hexachloride) in infants and children" J Pediatrics. 1977;91:998-1000
18. Aks SE, Krantz A, Hryhrczuk DO, Wagner S, Mock J "Acute accidental lindane ingestion in toddlers" Ann Emerg med. 1995 Nov;26(5):647-51
19. Roa CVS, Shreenivas R, Singh V "Disseminated intravascular coagulation in a case of fatal lindane poisoning" Vet hum Toxicol 1988;30:132-134

Pramanik AK, Hansen Rc "Transcutaneous Gamma Benzene hexachloride Absorption and Toxicity in Infants and children" Arch Dermatol, 1979; 115:1224-1225

20. Starr HG, Clifford NJ "Acute lindane intoxication" Arch Environ Health 1972;25:374-375
21. Davies JE, Dedhia HV, Morgade C, et al "Lindane poisonings" Arch Dermatol 1983;119:142-144
22. Munk ZM, Nantel A "Acute lindane poisoning with development of muscle necrosis" Can Med Assoc J 1977;117:1050-1054
23. Daerr W, Kaukel E, Schmoldt A "Haemoperfusion: A therapeutic alternative for early treatment of acute lindane poisoning" Dtsch med Wochenscher 1985;110:1253-1255
24. Dale WE, Curely A, Cueto C "Hexane extractable chlorinated insecticides in human blood" Life Sci 1966;5:47-54
25. Kurt TL, Bost R, Gilliland M, et al "Accidental Kwell Ingestions" Vet Hum Toxicol;1986;28:569-571
26. Burton BT, Will VK, Brunett PH, et al "Seizure following lindane ingestion in a patient pre treated with phenytoin" Vet Hum Toxicol;1991;31:391
27. Sitowitz J, Roberts SB. "Danger of "as directed" instructions." Am J Health Sys Pharm. 2001 Sep 1;58(17): 1657
28. Attributed to Dr. Charles Ginsberg in the summary minutes of the Advisory Committee, Eighth Meeting, December 16, 1976. Attach
29. Pramanik AK, Hansen RC "Transcutaneous Gamma Benzene hexachloride Absorption and Toxicity in Infants and children" Arch Dermatol, 1979; 115:1224-1225