MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 1, 2002

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THROUGH: Julie Beitz, M.D., Director
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TO: Jonathan K. Wilkin, M.D., Director
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SUBJECT: OPDRA Postmarketing Safety Review (PID020169)
Adverse Event: All Adverse Events
Drug: Lindane (6309, 10-718)

EXECUTIVE SUMMARY

This document summarizes all reports of adverse events associated with lindane use in the AERS database, and is prepared in response to a DDDDP and Environmental Protection Agency request for lindane risk assessment. We provide an overview of all AERS reports and a detailed review of serious[1] reports.

We searched the AERS database on April 1, 2002 for all adverse event reports associated with lindane use, and found 488 reports. There were 446 US, 23 foreign and 19 reports with an unknown country of origin. The most prevalent adverse event reported was "drug ineffective" (111), followed by convulsions (65), dermatitis (34) and dizziness (29). Fifteen additional reports described "grand mal convulsions".

A detailed review of 74 serious cases described 15 deaths, 46 hospitalizations, seven life threatening and six cases of congenital anomalies.

The elderly and the very young appear to be more susceptible to lindane's adverse effects. The adults who died[2] were older than the adults who were hospitalized[3] or who experienced life-

[1] Reports coded with an outcome of death, hospitalization, life threatening and/or congenital anomaly.
[2] Three of the adult death patients occurred in the "elderly" and in a patient aged 83 years
[3] Median age 58 years, n = 22

threatening[4] outcomes. Likewise, the children that died were younger[5] than the children that were hospitalized,[6] or the children who experienced life-threatening[7] outcomes. Lindane toxicity as determined by autopsy was the cause of death in a child, and was the means of a successful adult suicide. In the other cases, the direct cause of death was attributed to reasons other than lindane. Nine death cases (children and adult) reported the time of death from within 24 hours to 13 months, with a median of four days.

The appendix contains a tabular presentation of lindane indications for use, and exposure for 74 cases with a serious outcome. Of the 74 serious cases, 14 cases reported using lindane according to the label. These 14 cases reported no contraindications to use, or misuse and resulted in serious outcomes, including death. Forty-three (58%) cases described misuse of lindane. Misuse of lindane included uses exceeding label recommendation (34), oral ingestion (8), and prophylactic use (1). Five cases reported a contraindication to use. Ten cases reported confounders.

BACKGROUND INFORMATION

On February 13, 1995, the Division of Epidemiology and Surveillance, in response to a request by the National Pediculosis Association, reviewed all death and nervous system related adverse event reports associated with lindane (Kwell). A search of the SRS[8] database found 87 unduplicated reports, of which five were deaths, and 26 were serious. Two of the five deaths were central nervous system related. The majority of the nervous system adverse events found were seizures, and multiple neuromuscular complaints.

For this review, we searched the AERS database. 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, as well as the absence of information that does not have a coded field. In spite of known limitations, the spontaneous system has value. The system is sensitive to rare, unexpected events, and is simple to use, and relatively inexpensive.

LABELING

The following information is located in the ***Warnings Section*** of the label:

LINDANE PENETRATES HUMAN SKIN AND HAS THE POTENTIAL FOR CNS TOXICITY (SEE CLINICAL PHARMACOLOGY SECTION). LINDANE LOTION SHOULD BE USED ACCORDING TO RECOMMENDED DOSAGE (SEE DIRECTIONS FOR USE)

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[4] Median age 47, n = 4
[5] Median age 18 months, n = 4
[6] Median age 5 years, n = 20
[7] Median age 12.5 years, n = 2
[8] Spontaneous Reporting System

ESPECIALLY ON INFANTS, PREGNANT WOMEN AND NURSING MOTHERS. ANIMAL STUDIES INDICATE THAT POTENTIAL TOXIC EFFECTS OF TOPICALLY APPLIED LINDANE ARE GREATER IN THE YOUNG. SEIZURES AND, IN RARE INSTANCES, DEATHS HAVE BEEN REPORTED AFTER EXCESS DOSAGE, OVER-EXPOSURE, FREQUENT REA PPLICATIONS, AND ACCIDENTAL AND INTENTIONAL INGESTION OF LINDANE. THESE INSTANCES OF PATIENT MISUSE HAVE BEEN ASSOCIATED WITH LACK OF PATIENT UNDERSTANDING OF DIRECTIONS OF USE, PRESCRIBING OR DISPENSING EXCESSIVE QUANTITIES, AND IMPROPER REAPPLICATIONS. IN EXCEEDINGLY RARE CASES SEIZURES HAVE BEEN REPORTED WHEN USED ACCORDING TO DIRECTIONS. NO RESIDUAL EFFECTS OF LINDANE TREATMENT HAS BEEN DEMONSTRATED; THEREFORE, THIS PRODUCT SHOULD NOT BE USED TO WARD OFF A POSSIBLE INFESTATION.

Instructions for use:

Lotion: Shake well

This product can be poisonous if misused. Children must not be allowed to apply this drug without direct adult supervision. Use lotion for scabies only. **Apply only once**. 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. Do not leave on for more than 12 hours. Do not ingest. Keep away from mouth and eyes. Cover infants' hands and feet during treatment to prevent sucking and licking of lotion. Do not use if open wounds, cuts or sores are present, unless directed by your physician.

1. Apply this preparation to dry skin in a thin layer and rub in thoroughly.
2. Trim nails and apply under nails with toothbrush (throw away toothbrush after use).
3. If a warm bath is taken before application, allow the skin to dry and cool completely before applying the medication.
4. A total body application should be made from the neck down, including soles of feet, unless otherwise directed by your physician.
5. The lotion should be left on for 8 to 12 hours (usually overnight) and then removed by thorough washing (bath or shower).
6. Avoid unnecessary contact with your skin if you are applying to another person. If treating more than one person, person applying lotion (especially pregnant or nursing women) should wear rubber gloves.
7. All recently worn clothing, underwear and pajamas, and used sheets, pillow cases, and towels should be washed in very hot water or dry-cleaned.

After one application, itching will continue for several weeks. This is normal and does not require reapplication.

Shampoo (Shake Well):

This product can be poisonous if misused. Children must not be allowed to apply this drug without direct adult supervision. Use shampoo for head and pubic lice only. Do not use for scabies. Use only in amounts directed below. In no case should more than 2 ounces be used by

one person in one application. Do not ingest. Keep away from mouth and eyes. Do not use if open wounds, cuts or sores are present on scalp or groin, unless directed by your physician.

Avoid using oil treatments, oil based hair dressings or conditioners immediately before and after applying lindane shampoo.

1. Before applying lindane shampoo, use regular shampoo (without conditioners), rinse and completely dry hair.
2. Use 1 ounce (half of a 2 ounce bottle) for short hair; 1.5 ounces (three-quarters of a 2 ounce bottle) for medium length hair; and full 2 ounce bottle for long hair.
3. Apply shampoo directly to dry hair without adding water. Work thoroughly into the hair and allow to remain in place for 4 minutes only.
4. After 4 minutes, add small quantities of water to hair until a good lather forms.
5. Immediately rinse all lather away. Avoid unnecessary contact of lather with other body surfaces.
6. Towel briskly and remove nits with nit comb or tweezers.
7. Avoid unnecessary contact with your skin if you are applying shampoo to another person. If treating more than one person, person applying shampoo (especially pregnant and/or nursing women) should wear rubber gloves.

Re-treatment is usually not necessary, but presence of living lice in hair 7 days after treatment indicates that re-treatment may be necessary. Do not retreat without the advice of a physician.

CONTRAINDICATIONS

Lindane lotion is contraindicated for premature neonates because their skin may be more permeable than full term infants and their liver enzymes may not be sufficiently developed. It is also contraindicated for patients with Norwegian (crusted) scabies due to possible increased absorption. It is also contraindicated for patients with known seizure disorders and for individuals with a known sensitivity to the product or any of its components.

SELECTION AND SUMMARY OF CASES

On April 1, 2002, we searched the AERS database for all reports of adverse events that listed lindane as a suspect drug. We found 488 reports. Four hundred and forty-six reports were US, 23 were foreign, and 19 were of an unknown country of origin. There were 80 reports with an outcome of death, hospitalization, life threatening or congenital anomaly. For those reports submitting age information 46% were aged newborn to 16 years, 47% were aged 17 to 60 years, and 7% were aged 61 years and older. Since 1995, the FDA has received 63% of the adverse event reports. The remaining reports were submitted over several years, with the earliest submitted in 1974. Please keep in mind that these are reports and not patients, and duplicate reports may be submitted for the same patient. Duplicate reports may have included follow-up information from the manufacturer, or multiple reporters (e.g., family member, physician, pharmacist, nurse, etc.). Below is a demographic table of the reports.

Part I: Overview of all AERS reports

Demographic Information for All Reports (n = 488)

Gender: Female (276), Males (124), NR[9] (88)

Age:
Newborn to 5 years (56)
6 years to 16 years (85)
17 years to 60 years (145)
61 + years (20)
NR (182)

Report Years:
1974 to 1979 (41)
1980 to 1984 (33)
1985 to 1989 (24)
1990 to 1994 (83)
1995 to 1999 (245)
2000 to 2002 (62)

Outcome: *Number of Reports before exclusion of duplicate reports*
Death (15)
Hospitalization (51)
Life Threatening (7)
Congenital Anomaly (7)
Other (408)

Reporter: Consumer (192), Health Care Provider (163), Foreign Regulatory (25), Literature (6), Not Reported (102)

Top Twenty Adverse Event Terms Reported:

A listing of the 20 most commonly reported adverse events is in the table below, along with the label status of the event. Of note, a report may contain unlimited adverse event terms. "Drug ineffective", found in 111 reports was the predominant adverse event reported. The second most prevalent term was convulsion (65), followed by dermatitis (34), and dizziness (29). Additionally, 15 reports described "grand mal convulsions". Five of the top 20 adverse event terms are present in the lindane label. Labeled events include convulsions, grand mal convulsions, dermatitis, dizziness and overdose.

Rank	Adverse Event Term	# of Reports	Label Status of Event
1	Drug Ineffective	111	Not Labeled
2	Convulsions Nos	65	Labeled[10]
3	Dermatitis Nos	34	Labeled[11]
4	Dizziness (Excl Vertigo)	29	Labeled[12]
5	Alopecia	26	Not Labeled

[9] NR = Not Reported
[10] Labeled for CNS stimulation ranging from dizziness to seizure activity
[11] Labeled for eczematous eruptions due to irritation
[12] Labeled for CNS stimulation ranging from dizziness to seizure activity

6	Headache Nos	23	Not Labeled
7	Urticaria Nos	23	Not Labeled
8	Pain Nos	22	Not Labeled
9	Paraesthesia	19	Not Labeled
10	Vomiting Nos	18	Not Labeled
11	Overdose Nos	16	"Labeled" – Overdose section
12	Grand Mal Convulsion	15	Labeled [13]
13	Pruritus Nos	15	Not Labeled
14	Dyspnoea Nos	12	Not Labeled
15	Diarrhea Nos	11	Not Labeled
16	Pyrexia	10	Not Labeled
17	Medication Error	9	Not Labeled
18	Myalgia	9	Not Labeled
19	Thinking Abnormal	9	Not Labeled
20	Tremor	9	Not Labeled

Part II: Detail Review of Death, Hospitalization, Life Threatening and Congenital Anomaly Reports (80 reports representing 74 cases)

We found 80 reports in the AERS database that had a serious outcome defined as death, hospitalization, life threatening, or congenital anomaly. We excluded eight cases. The eight excluded cases included five duplicate reports, one report of death in a cat, one incorrectly coded death, and one incorrectly coded congenital anomaly. We included two additional death cases. A single report from a nursing home facility described three deaths temporally associated with lindane. We reviewed 74 cases, which included 15 cases of death, 46 cases of hospitalization, seven cases of life-threatening outcome, and six cases of congenital anomaly. **The appendix contains a tabular presentation of indications for use, and lindane exposure for those cases with a serious outcome.**

Death Cases (15)

Fifteen cases of death included nine adults, five children, and one case with an unknown age. Nine death cases (children and adult) reported the onset of death from within 24 hours to 13 months, with a median onset of four days. Thirteen patients used lindane topically, one adult ingested lindane orally for suicide purposes, and one child was stillborn after maternal exposure. Scabies and head and/or pubic lice were the predominant indications for use. Lindane toxicity, verified by autopsy was the cause of one child's death, and was the means of death in a successful suicide. The direct causes of death for the other cases were attributed to reasons other than lindane. Detailed demographic information is listed in Tables 1 and 2.

Adults

Adult patients who died received a median of 2.5 applications of lindane per patient (range 1 – 240). The elapsed time between applications was reported in four cases (daily-2, seven days –

[13] Labeled for CNS stimulation ranging from dizziness to seizure activity

2). The onset of death occurred within 24 hours to 47 days for those cases reporting onset information.

Four of the nine adults were elderly. Treatment of three elderly patients occurred during the same scabies outbreak, at the same nursing home facility. Within 24 hours of lindane application, two of the three elderly patients died from pulmonary edema, and chronic obstructive pulmonary disease. The third patient, in the same facility died of an unknown condition 41 days after use. Additionally the third patient experienced a seizure on the day of expiration. At a different nursing home facility, a fourth elderly patient died of an unknown condition within three hours of lindane use. The fourth patient had "very excoriated" skin.

A 28-year-old male with a history of renal transplantation died 2 days after lindane treatment. Two adult patients had contraindications to the use of lindane; one patient had a previous history of seizures, and one patient had Norwegian scabies.

Table 1: Death - Adult Cases (n = 9)

- Location: US (9)
- Age: Range 25 to 82 years, n = 6, Reported as "Elderly" = 3
- Gender: Male (4), Female (5)
- Indication: Scabies (5), Norwegian scabies (1), head lice (1), pubic lice (1), NR (1)
- Formulation: Lotion (1), Shampoo (3), Lindane Unspecified (5)
- Route of Administration: Topical (8), Oral (1)
- Number of Applications: Range 1 to 240, median = 2.5 applications, n = 8
- Elapsed time between applications: Daily (2), Every 7 days (2)
- Duration of application: Possibly 24 hours (3)[14]
- Time of death after lindane use: within 24 hours (3), 2 days (1), 41 days (1), 47 days (1), NR (3)
- Death due to:
  - Suicide (1)
  - Myocardial infarction with hypoxic brain damage (1)
  - Chronic obstructive pulmonary disease (1)
  - Pulmonary edema (1)
  - "Acute Illness" (1)
  - Malignant Brain Tumor (1)
  - Perianal Cancer (1)
  - Unspecified (2)
- Adverse Events:
  - Seizure (2)
  - Breathing Difficulties (1)
  - Myocardial infarction (1)
  - Malignant Brain tumor (1)

[14] All three were in the nursing home, treated during the same scabies outbreak.

  - Rash/allergy (1),
  - NR (3)
- Confounders (2): Serious Pre-existing Underlying Condition (2)
- Contraindications to use (2): Previous seizure history (1), Norwegian Scabies (1)
- Reporter: HCP[15] (4), [redacted] (3), National Pediculosis Association (2)

Children

Four of the children who died received a median of 19 applications of lindane per child (range 1 – 54), usually applied on a daily basis. Three cases reported the time of death from four days to 13 months, with a median time of three months. An autopsy report confirmed lindane toxicity as the cause of death in a six-month old child. A second child developed aplastic anemia and acute myelocytic leukemia some time after lindane exposure. The patient had been given lindane three times daily for a 2 ½ to 3 week time period. Case reports of lindane associated aplastic anemia have been cited in the medical literature.[16]

Table 2: Death – Children (n = 5)

- Location: US (5), Foreign (0)
- Age: Range: newborn to 9 years, median = 18 months, n = 4
- Gender: Male (3), Female (1), NR (1)
- Indication: Scabies (2), Lice (2), Exposure in utero (1)
- Formulation: Lotion (1), Shampoo (1), Lindane unspecified (3)
- Route of Administration: Topical (4), via mother in utero (1)
- Number of Applications: Range 1 to 54, median = 19 applications, n = 4
- Elapsed time between applications: Three times daily to daily, median = daily, n = 3
- Duration: One patient received lindane daily for 10 to 12 days each month for 3 months; an additional patient received lindane three times daily for a 2.5 to 3 week time period.
- Confounder (1): Acute myelocytic leukemia
- Time of Death: Range 4 days to 13 months, median = 3 months (n=3)
- Death due to:
  - Lindane toxicity by autopsy (1)
  - Death at birth (1)
  - RSV pneumonia three months after lindane exposure (1)
  - E. Coli sepsis following aplastic anemia + acute myelocytic leukemia after lindane exposure (1)
  - Beta cell lymphoma of the brain 11 months after lindane (1).
- Reporter: HCP (2), Consumer (2), Lawyer (1)

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[15] Health Care Professional

[16] Rauch AE, Kowalsky SF, Lesar TS, et al. Lindane (Kwell) – induced aplastic anemia. Arch Intern Med 1990 Nov;150(11): 2393-5.

Death – US, Age Unknown
There was an additional poorly documented US report of death from a health care professional concerned about the possibility of dispensing errors with "Kwell" and "Kwelcof".[17] However, it is unclear if death occurred in a patient, or if the reporter checked the "death" category to emphasize the seriousness of a possible (or real) dispensing error.

Hospitalizations (46)

There were 46 hospitalizations, 25 in adults and 21 in children. Six of the adults hospitalized were aged 70 years and greater, and five of the hospitalized children were less than two years old. Although the majority of the patients used lindane topically, seven patients, two adults and five children, ingested lindane orally. One of the two adults who took lindane orally reported attempting suicide; the second adult reported oral ingestion without a reason. Two of the five children who took lindane orally reported accidental ingestion, and the other three cases did not provide an explanation of how the oral ingestion occurred.

Adults and children were treated primarily for scabies, and head and/or body lice. The adverse effects seen in children and adults were primarily central nervous system in origin, including seizures, a dystonic reaction, and unspecified central nervous system involvement. There were two cases of hepatotoxicity, one occurring concomitantly with aplastic anemia. Some of the cases presented with acute respiratory distress prior to the onset of additional symptoms.

There were several confounding factors, and contraindications to use. Two patients with a previous medical history of seizure activity and one patient with Norwegian scabies experienced seizures with lindane use. One patient with a previous history of psychosis experienced a psychotic reaction. An additional patient with an occupational exposure to fiberglass and insulation developed aplastic anemia, and another patient who had a seizure, was later found to have a left temporal parietal tumor.

The adult hospitalized patients were administered a median of two applications of lindane per patient (range 1 – 60), over multiple days, with the elapsed time of application as long as seven days. The children received a median of one application of lindane per child (range 1 to14) with an elapsed time of application as long as one month (range daily to one month). Hospitalization occurred in ten children after use of a single dose. Three of the ten children reporting single dose use took the drug orally. The fourth child hospitalized after oral use did not report the number of doses or the amount of lindane taken. An additional hospitalized child took lindane orally, and used it topically for multiple doses.

Table 3: Hospitalization - Adult Cases (n = 25)

- Location: US (19), Foreign (6)
- Age: 18 – 86 years, median = 58, n = 22
- Female (18), Males (7)

[17] Kwelcof – cough preparation containing guaifenesin and hydrocodone

- Indications: Scabies (14), Head or Body Lice (3), Misdiagnosed scabies (1), Flea infestation (1), Norwegian Scabies (1), Suspicious leg rash (1), Suicide attempt (1), Not reported (3)
- Route of administration: Topical (21), Oral (2), Not reported (2)
- Confounders (8); medication (1); possible exposure to occupational toxins (1); pre-existing underlying illness (6)
- Contraindication (3): Previous seizure history (2), Norwegian Scabies (1)
- Adverse Events: Seizures (11), aplastic anemia (1), general systemic effects with CNS involvement[18] (7), rash (2), hepatotoxicity (1),
- Elapsed time between applications: Twice daily (1), Daily (3), every 2 days (1), every 5 days (1), every 7 days (3)
- Number of applications: range 1 to 60 applications, median = 2, n = 18
- Reporter: HCP (16), Consumer (5), Lawyer (2), National Pediculosis Association (1), Regulatory Agency (1)

Table 4: Hospitalization - Children (n = 21)

- Location: US (17), Foreign (3), NR (1)
- Age: 3 months to 17 years, median = 5 years , n = 20
- Female (11), Male (9), NR (1)
- Indications: Scabies (11), Head lice (5), Mother used – exposed when pregnant (1), Misdiagnosed scabies (1), NR (3)
- Route of Administration: Topical (16), Oral (4), Oral + topical (1)
- Elapsed time between applications: Daily (3), Every 2 days (1), Every 7 days (3), Every Month (1), Single Application (10), NR (3)
- Number of applications: range 1 to 14, median = 1, n = 19
- Adverse Events: Seizures (11); Dystonic reaction (1), Loss of appetite[19] (3), drug intoxication (1), kidney dysfunction (1), respiratory arrest (1), acute lymphocytic leukemia (1), lung surgery (1), "low consciousness" (1)
- Concomitant Scabicides (4): Rid (1), Nix (1), Rid + Nix (1), Scabicide Furniture Spray (1)
- Reporter: Consumer (7), HCP (7), National Pediculosis Association (2), Lawyer (2), Literature (1), Other (2)

Life-Threatening (7)

There were seven cases with a life-threatening outcome, four adults and three children. Five of the seven cases were reported from the same household address and described an unspecified amount of use over a two year period, resulting in depression and other local and systemic adverse effects. Two additional patients respectively reported Hodgkin's disease, and brain tumor. There was no oral use of lindane and no confounders reported in this group of patients. All seven patients reported multiple applications of lindane.

[18] Included, but not limited to difficulty breathing, difficulty swallowing, cardiopulmonary and respiratory arrest, concentration impairment, headaches, depression, dizziness, palpitations, nausea, diarrhea, neck pain, ataxia, vertigo, nystagmus, unspecified neurologic symptoms, loss of appetite, weakness,

[19] One child lost 23 pounds in two months following exposure and a second child had a NG tube placed.

Table 5: Life-Threatening -Adult (n = 4)

- Location: US (4)
- Age: Range 18 to 48, median = 47, n = 4
- Gender: Female (2), Male (2)
- Indication: Body Lice (1), NR (3)
- Route of Administration: Topical (4)
- Elapsed time between applications: Unspecified amount of time over 2 years (3); One patient had 15 applications over 6 days over a 3 month time period (minimum interval between applications 4 days).
- Number of applications: 15 (n = 1), Multiple (3)
- Adverse events: Hodgkin's disease + cognitive dysfunction (1); severe eczema + depression + other local and systemic effects (3)[20]
- Reporter: Consumer (4)

Table 6: Life-Threatening - Children (n = 3)

- Location: US (3)
- Age: Range: 12 – 13 years, median = 12.5 years, n = 2
- Gender: Male (1), Female (2)
- Indication: Recurrent Head Lice (1), NR (2)
- Formulation: Lindane unspecified (3)
- Route of administration: Topical (2)
- Number of Applications: Multiple times (3)
- Elapsed time between applications: Multiple times over 2 years (2); Multiple times over 6 years (1)
- Adverse Events: Brain tumor (1), severe eczema + depression + other local and systemic effects (2)
- Concomitant Scabicide(1): Rid (1)
- Reporter: Consumer (2), National Pediculosis Association (1)

Congenital Anomalies (n = 6)

There were six cases of congenital anomalies temporally associated with lindane use. Five cases were maternal exposure, and one case was paternal exposure. Three parents used lindane for scabies, one parent used lindane for lice, and one parent used lindane on a prophylactic basis. The sixth parent did not report the reason for lindane use. Five of the six parents described multiple applications of topical lindane over time. The most profound case describes multiple congenital anomalies in an aborted fetus. The mother had actively treated her daughter, and had then prophylactically used lindane and an OTC lice medication on herself throughout pregnancy. The pathology report of the aborted fetus described a 17-week-old stillborn child with multiple malformations including acrania, holoprosencephaly, and omphalocele.

Other congenital anomalies reported included developmental delay (1), retardation (1), retardation and multiple disabilities (1), severe eczema (1), and osteoporosis and an eye condition (1). Four cases reported the concomitant use of other scabicides.

[20] These three reports were from the same address

Table 7: Congenital Anomalies (n = 6)

- Location: US (6)
- Exposure through: Mother (5), Father (1)
- Mother's Indication: Scabies (3), Lice (1), Prophylaxis/Prevention (1), NR (1)
- Formulation: Lotion (2), Shampoo (1), Lindane unspecified (3)
- Route of Administration for mother: Topical (6)
- Number of applications described as follows:
  - Ongoing (1)
  - Multiple times throughout pregnancy (1)
  - Multiple times over a six- month period (1)
  - Used several times (1)
  - Two applications, 6 days apart (1)
  - Not specified (1)
- Events Seen:
  - Acrania with iniencephaly (fusion of the cervical vertebral bodies), holoprosencephaly with disorganized cerebral tissue and apparent absence of cerebral tissues, rachischisis of the cervical spine to the thoracic level, lack of normal lung lobation, ruptured omphalocele sac containing the majority of the abdominal content, malformed left hand with absent first and second digits and metacarpals, bilateral clubbed feet, low-set ears, short neck with webbing and the head appears connected directly to the shoulders (1)
  - Developmental delay (1)
  - Retardation (1)
  - Retardation + multiple disabilities (1)
  - Severe eczema with bleeding dry skin (1)
  - Handicapped, osteoporosis, eye condition (1)
- Concomitant Treatments: Nix (1), Lindane Shampoo (1), Rid (1), Eurax (1)
- Reporter: Consumer (4), Lawyer (1), National Pediculosis Association (1)

DISCUSSION/CONCLUSION

Lindane is used both as a pharmaceutical agent, and as a broad-spectrum insecticide for agricultural use. As a pharmaceutical agent, lindane is approved as second line therapy for the treatment of scabies, pediculosis capitis, and pediculosis pubis. Lindane is contraindicated in premature neonates, patients with Norwegian scabies, and patients with a known seizure disorder, or hypersensitivity to the product.

Overall, there were 488 AERS reports of adverse events associated with lindane use, with the most prevalent adverse events after "drug ineffective" involving the central nervous system and dermatitis. Five of the top twenty adverse events associated with lindane are labeled. There were two cases of aplastic anemia, an event that has been reported in the medical literature. We reviewed, in detail, 74 cases of death, hospitalization, life threatening and congenital anomalies. One death, verified by autopsy was attributed to lindane use, and one successful suicide occurred after oral ingestion of lindane. For those cases reporting the cause of death, the direct causes were attributed to reasons other than lindane toxicity.

Forty-six percent of the AERS reports with age information, were received for children aged newborn to 16 years, 47% were received for adults 17 years to 60 years, and 7% were received for adults 61 years old and older.

Nine death cases (children and adult) reported the onset of death from within 24 hours to 13 months, with a median onset of four days. The elderly and the very young appear to be more susceptible to lindane's adverse effects. The adults who died were older than the hospitalized adults, or the adults who experienced life-threatening outcomes. Likewise, the children that died were younger than the hospitalized children, or the children who experienced life-threatening outcomes.

Of the 74 serious cases, 14 reported using lindane according to the label. A substantial number of cases (43, 58%) reported misuse of lindane. Misuse was reported in children and adults, and included oral ingestion, use exceeding label recommendations, and prophylactic use. Five cases reported a contraindication to use, and ten cases were confounded.

Overall adults and children received a median of two applications of lindane, with a range for the adults of one to 240 applications (n = 31), and a range for the children of one to 54 applications (n = 24). However, the adults and children that died received more frequent lindane administrations. The adults who died received a median of 2.5 applications, and the children who died received a median of 19. Additionally, the children received lindane with less elapsed time between applications than did the adults. Children received lindane on a daily basis, in contrast to the adults who received lindane on a weekly basis.

Three cases of congenital anomaly described developmental delay, or retardation. One case of an aborted fetus described significant malformations, and two additional cases respectively described severe eczema, and osteoporosis with an eye condition.

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Concur,

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cc:

NDA: 6309, 10718

Electronic only cc:
HFD-400/Seligman
HFD-430/Beitz/Karwoski/Guinn/Lindane (Drug File)
HFD-540/Mathis/Walker/Kozma-Fornaro

Appendix 1

Table 1: Indication for Lindane Use Stratified by Serious Outcome

Indication	Death	Hospitalization	Life-Threatening	Congenital Anomaly
Scabies	7	25	0	3
Lice	4	9	2	1
Other	4	12	5	2
Total # of Patients*	15	46	7	6

- *Two patients had both scabies, and head or body lice. These two patients were classified as the more serious scabies, and were counted only one time.

Table 2: Lindane Exposure Stratified by Serious Outcome

Exposure	Death	Hospitalization	Life-Threatening	Congenital Anomaly
Labeled Use	2	12		
Exceeded Label Use	7	16	7	4
Oral	1	7		
Contraindicated	2	3		
Misdiagnosis		3		
Prophylaxis				1
Unknown	3	5		1
Total # of Patients	15	46	7	6

- Ten patients used other concomitant scabies/lice products including RID, Nix, Eurax and/or the lindane lotion + shampoo.

- One patient described hot bath, and excoriated skin, conditions that can contribute to increased lindane absorption.

- The "Exceeded Label Use" category include duration of application for more than 12 hours for the lotion, and more than 4 minutes for the shampoo, as well as multiple doses per day, and multiple applications without sufficient elapsed time between applications.