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QUALIFICATIONS

I, Richard A. Parent, PhD, DABT, RAC, ERT, am a board certified toxicologist with over 25 years' experience in the field of industrial toxicology and 17 years' experience in litigation support for both the plaintiff and defense. I have testified in local and federal courts as an expert in toxicology and have given expert testimony in the disciplines of toxicology and chemistry. During my career, I have spent 10 years in research on organic chemicals at American Cyanamid Company. In the field of toxicology, I have initiated and carried out an active program in product safety relating to toxicology for the Xerox Corporation. I have directed two contract toxicology laboratories: Food and Drug Research Laboratories, Inc. and Gulf South Research Institute, Life Sciences Division. In 1984 I established Consultox, Limited, a toxicology consulting firm, and have since consulted in product safety for various industries and have designed toxicology studies to assess the safety of materials being considered for use in various products. For litigants, I have provided toxicological support and have addressed causation issues for the plaintiff as well as the defense. I present myself to the Court as an expert in the fields of toxicology and chemistry. For the Court's information, I offer my curriculum vitae in Appendix A and a listing of my testimony in past depositions and trials in Appendix B.

INTRODUCTION

I begin this report with a list of materials I reviewed in preparation for my report, which includes a narrative relating to the sequence of events which involved the use of lindane for treating Ms. [redacted] scabies during her pregnancy and medical records of her daughter, Ms. [redacted]. This will be followed by a discussion of published peer-reviewed research describing the adverse effects of lindane on animals, fetuses, children, and adults. Although all aspects of lindane toxicity will be addressed initially, I will then focus on a more intense discussion of the neurological effects in man and animals with particular emphasis on fetal exposure to lindane and similar organochlorine compounds. I will conclude my report with a discussion of the causal relationship between [redacted] ([redacted]) exposure to lindane while pregnant and the resulting neurological problems being suffered by [redacted] as a result of her *in-utero* exposure to lindane.

MATERIALS REVIEWED

- Medical Records of [redacted] from March 20, 1987, to April 11, 1996.
- Medical Records from Dr. [redacted] relating to Judy Adams from July 16, 1986, to November 2, 1995.
- Deposition of Dr. [redacted] taken on December 7, 2000.

- Complaint: [redacted] Inc. and CVS Pharmacy, US District Court ND of Alabama; [redacted]
- Plaintiffs Answers to Interrogatories dated March 30, 2000.
- Handwritten account describing events from June 26, 1986, to July 16, 1986, presumably written by the plaintiff.
- FDA's Spontaneous Reporting System Report on Lindane dated May 19, 1994.
- FDA's Adverse Event Reporting System Report on Lindane dated October 18, 1999.
- All accessible literature relating to lindane and related subjects.

MEDICAL SEQUENCE RELATING TO MS. [redacted] LINDANE TREATMENT

- On June 26, 1986, [redacted] made an office visit to [redacted] a dermatologist, for a condition called "scabies" which is a mite infestation of the skin. At that time she was given Eurax (crotamiton) as a treatment and was told to apply it over her whole body on two consecutive nights. She also was given Synalar Cream (fluocinolone acetonide), a corticosteriod lotion. She and her husband showered and applied the lotions over their bodies for two consecutive nights. Dr. [redacted] office notes indicate that "[redacted] is 3 months pregnant." [redacted] applied these lotions to her body and her husband's without using gloves.
- On July 2, 1986, [redacted] called Dr. [redacted] office because she and her husband were still itching. We were told to use the Eurax and Synalar as before and also to apply a prescription called "Zone A Lotion" (hydrocortisone acetate). The lotions were again applied by hand without gloves after hot showers. Office notes indicate that the prescriptions were phoned in to Revco Bama Mall.
- On July 10, 1986, Ms. Adams again visited Dr. [redacted] office with continued itching from a "classical scabies". Dr. [redacted] prescribed 6% precipitated sulfur suspended in petrolatum to be applied nightly for three nights for her and 1% lindane lotion for her husband, the latter to be used overnight and washed off in the morning. Dr. [redacted] also provided Synalar samples to be used for the itching. Ms. Adams claims to have applied the lindane lotion to her husband's body without the use of gloves.
- On July 16, 1986, Ms [redacted] phoned Dr. [redacted] and indicated that she was still itching over her whole body. Dr. [redacted] prescribed a 1% lindane lotion to be applied over the whole body at night and washed off in the morning. In Dr. [redacted] office notes there is a hand-written entry indicating a risk-benefit discussion on lindane regarding its toxicity. Ms. [redacted] claims that Dr. [redacted] tampered with her medical records indicating that they never discussed risk-benefit related to lindane, nor did she recommend the use of rubber gloves to apply the lindane to her husband on July 10, or warn them about the increased lindane absorption after a hot bath. This was her last visit to Dr. [redacted]

MS. [redacted] PREGNANCY

- Ms. [redacted] became pregnant on or about April 21, 1986, and delivered her child, [redacted], on January 21, 1987.
- Within the first trimester of her pregnancy, [redacted] was treated with two known animal teratogens and lindane, a fetotoxic agent, a central nervous system toxin, and possibly a neuroteratogen. Both Synalar and Zone A Lotion are Category C drugs relative to pregnancy in that they are generally teratogenic in animals when administered systemically at very low dosages. "Drugs of those class should not be used extensively on pregnant patients, in large amounts or for prolonged periods of time".[1] There is also literature demonstrating that Synalar is fetotoxic in rabbits. Eurax (crotamiton) is also a Category C drug since animal tests apparently have not been carried out, and the potential for fetal harm is unknown.[1] References may be found in Appendix C.
- Her daughter, [redacted], was born on January 21, 1987, and was diagnosed with profound mental retardation, autistic-like behavior, hyperkinesis, static encephalopathy, and microencephaly with evidence of epileptogenic activity. There is a question about the presence of mild dysmorphic features.
- Available information discounts possible metabolic disorders or chromosomal abnormalities as etiologic factors for [redacted] condition.
- The information I have indicates that there is no family history of mental disease, retardation, or seizures.
- [redacted] was exposed to lindane in-utero at a time when her brain was in the process of developing and was most susceptible to exogenous chemical influences.

MEDICAL RECORDS OF MS. [redacted]

03/20/87 Tuscaloosa Health Department (THD): well baby; low birth weight; immunizations needed; additional visits from 5/20/87 to 9/1/87.
08/26/87 Dr. [redacted]: multiple visits to 1998.
09/17/87 State Crippled Children Service: 7mo Caucasian female product of 34yo female; developmental delay; child referred by Dr. [redacted]
10/15/87 Crippled Children Service: head circumference below normal; CT scan shows large right side ventricle about 3x normal; large also on left side which is about twice normal; Dr. [redacted]
11/05/87 Crippled Children Service visit: baby slow in physical development; Dr. [redacted]
11/09/87 Crippled Children Clinic visit: abnormal growth and development; CT scan showed increased ventricular sizes and some shift across the midline; otitis media.
10/28/87 Drs. [redacted]: normal female cytogenetic pattern.

01/06/88 State Crippled Children Service: delayed development syndrome; may be very mild CP; Dr. [redacted]
01/12/88 THD: missing brain tissue bilaterally; regular visits to Dr. [redacted]
02/11/88 Dr. [redacted] storage disorder?; Sandohoff's?? ; other autosomal recessive condition??
02/17/88 Cerebral Palsy unlikely; Dr. [redacted]
02/18/88 Dr. [redacted] no seizures.
04/26/88 Tests for amino acid metabolic problem, Tay Sachs/Sandohoff all negative; peripheral blood test normal.
07/08/88 Dr. [redacted]: [redacted] is getting better and developing more rapidly physically.
01/05/89 Test for Krabbe's Disease negative.
04/20/89 Dr. [redacted]: head circumference still below normal; no seizures.
08/07/89 Dr. [redacted] she has Krabbe's Deformitity to her anterior thoracic chest wall but it's not bad.
05/18/89 THD: child mentally retarded, brain damaged.
11/08/90 THD: frequent vomiting several months; refer to gastroenterologist.
09/01/91 Neuro Consults of Tuscaloosa, Dr. [redacted]: 5yo girl seen a year ago; [redacted] suffers from an unfortunate neonatal insult of undetermined etiology; she has had significant static encephalopathy with marked developmental delay; seen by Dr. [redacted] at the Genetics Department and tested for various diseases including GM-1, gangliosidosis, Sandohoff's disease, Tay-Sachs and various other illnesses; no obvious cause for her developmental delay; Past Medhx - vomiting controlled with Tagamet and Reglan; no Famhx of neurological diseases; lives with mother and two siblings; Impression - static encephalopathy with marked developmental delay of undetermined etiology.
02/24/93 Dr. [redacted] DCH Regional Med Ctr: Assessment - bronchitis, left otitis.
03/10/94 EEG report: 7yo with hx of episodes of staring, eyes twitching; Meds - Tagament, Reglan, chloral hydrate; Abnormal EEG - demonstrates ample evidence of epileptogenic activity emanating from the right temporal lobe area; Dr. [redacted]
10/19/94 Otitis media; Dr. [redacted] bilateral chronic otitis media with recurrent acute otitis media; r/o adenoid hypertrophy; DCH Regional Med Ctr - admit assessments indicates seizures based on EEG.
02/02/95 Letter Report by Dr. [redacted] Director, Columbia Hospital for Women: [redacted] exposed to lindane during her pregnancy; goes into detail on tox of lindane; no associated animal teratogenic effects in mice, rats, hamsters, rabbits, cows and pigs; increased chromosomal aberrations and SCEs; human genotoxicity not demonstrated; absence of consistent effects in studies of developing immune system in rodents; dermal absorption, placental transfer; compound may possess mild estrogenic properties or alter fetal steroid metabolism by inducing hepatic microsomal enzymes; despite 40 yrs. of use, no reports found; lindane is a testicular toxicant; concentrates in breast milk.

06/06/95 Medical Genetics Clinic, UA at Birmingham: saw on 4/27/95 - originally seen on 2/12/88 and 4/21/88 By Dr. [redacted]; Hx - describes lindane use twice; [redacted] is only child of her mother and father; mother has other children all from different fathers; no Famhx of mental retardation, learning problems, birth defects, or other medprobs; Exam - evidence of self stimulatory behavior with automations and constant hand fluttering and movement in front of her face, ataxic gait; Assessment - profound mental retardation, autistic-like behavior, mild dysmorphic features with microcephaly, hypotelorism, beaked appearing nose, thin vermilion border and brachydactyly; static encephalopathy with marked developmental delay of undetermined etiology, no metabolic abnorm, no genetic abnorm; mother has questions about lindane use at about 3mo gestation; did review of Repro Tox Database - animal studies have not associated lindane with teratogenic effects; in vitro tests have shown chromosomal aberrations and SCEs; can cross placenta; overexposure results in symptoms including: restlessness, muscle spasms, convulsions, and coma; Lindane is a potent neurotoxic insecticide; use during pregnancy or lactation is not advised; Mrs. [redacted] feels that lindane exposure is responsible for [redacted] problems; suggests possible Angleman's Syndrome; Look at Rett's syndrome.

08/17/95 Dr. [redacted]: UA genetics lab - Angelman Syndrome ruled out; normal chromosomal pattern; enzyme assay for GM2-gangliosidoses normal.

09/27/95 Dr. [redacted]: OV mother pregnancy; Meds - Mellaril, INH.

10/16/95 Dr. [redacted] MR Brain Scan: no structural abnorms seen; opinion, ventriculomegaly - ventricular enlargement is probably on the basis of atrophy rather than hydrocephalus.

11/08/95 Dr. [redacted]: 8yo girl, flup for behavioral problems; child extremely active; constantly running around; Meds - Tagamet; head circumference - 49 cm; moderate isotropy on both eyes; no facial asymmetry or cranial nerve abnorms; generalized decrease in muscle tone; Dx - mental retardation with some autistic features; hyperkinesis; etiol of mental retardation unclear; start on Clonidine.

02/29/96 Whatley Health Center: Meds - Mellaril, INH; developmental delay, possible autism; below 5 percentile on height and weight curves; Famhx - mother, thyroid disease, liver/gall bladder, spastic colon; grandfather, heart disease.

04/08/96 Dr. [redacted] - Brainstem Auditory Evoked Potential: normal study on left, delayed response marked on right, suggesting right sided peripheral problems.

04/11/96 Division of Autism Services, Alabama Autism Clinic; Glenwood Mental Health Services - 9 yrs, 3mo old Evaluation:
Dr. [redacted] global developmental delay, microcephaly, profound mental retardation, static encephalopathy of unclear etiology, myopia; normal chromosomes, normal brainstem auditory evoked responses; abnormal EEG suggestive of periodic epileptogenic activity without generalization within the right temporal lobe; MRI revealed symmetrical

ventriculomegaly, likely secondary to atrophy; CT revealed delayed myelinization with ventriculomegaly and atrophy noted in the MRI; physical history notable for: microcephaly, myopia, frequent otitis media, GI reflux, hyperkinesis, hyperflexibility, developmental delays severe in speech and language, social skills, motor skills, repetitive/restricted behaviors and interests; mother was 34yo at time of birth; most likely diagnosis consistent with DSM/IV is mental disorder NOS due to genetic, neurologic or toxic insult of unknown etiology.

Dr. [redacted]: Developmental Pediatric Review - 5lb 3oz product of term gestation to a 34yo female; pregnancy complicated by treatment with lindane for scabies for 2 days reportedly without evidence of intoxication at the third month of pregnancy; at 4-5 mo ultrasound revealed small fetus; various evaluations.

Dr. [redacted], medical geneticist: normal 46XX karyotype; delayed myelination with sl large ventricles.

Dr. [redacted], a pediatric neurologist: Dx Static Encephalopathy with marked developmental delay of undetermined etiology; trial with Clonidine and Mellaril = severe side effects.

Dr. [redacted], ophthalmologist: epicanthal folds noted otherwise normal.

Dr. [redacted]: no inborne error of metabolism; microcephaly and minor dysmorphic features; EEG done in 1994 showed epileptogenic activity from right temporal lobe.

Drs. [redacted] reported profound mental retardation and autistic like behaviors and suggested possible Angleman Syndrome - abnormal EEB, Ataxia and hand flapping movements - dismissed; Rett's Syndrome - dismissed.

Dr. [redacted] (continuing): [redacted] has always been delayed; she started walking at 5yo and her gait is wide and she loses her balance frequently; repetitive self stimulating activities, often flips her hands; no verbal; uses gestures; Physical Exam - head circumference is below 5th percentile; height and weight deviant from curve; also noted - hypotelorism, beaked nose with large tip, very small mouth, right single palmer crease, small hyperpigmented spot on dorsum of the right hand, high arched palate, mild torticollis; Neuro exam - poor muscle definition, reduced muscle strength; List of Problems - profound mental retardation, pre- and post-natal growth retardation, frequent vomiting and reflux, autistic features, ataxia, ventriculomegaly/brain atrophy; nonprogressive disease, prenatal exposure to lindane.

Dr. [redacted] Dir of Autism Services (summary): all test results were incongruous to a firm diagnosis; [redacted] meets the criteria for autism.

TOXICOLOGY AND CARCINOGENICITY OF LINDANE

General

Lindane is one of eight possible isomers of 1,2,3,4,5,6-hexachlorocyclohexane, usually referred to as HCH or mistakenly as benzene hexachloride (BHC).[2] The one particular isomer of interest, the gamma-isomer, also referred to as lindane, is the subject of this report. Lindane contains at least 99.9% of the gamma-HCH isomer.[3]

Lindane was first discovered as an insecticide in 1942 and has been used extensively in the past[4] as an insecticide on fruit, vegetables, and forest crops.[2] It also has been used in the United States and other countries to control head and body lice and scabies, a contagious skin disease caused by mites.[2] Although not produced in this country since 1976, lindane is still available by import as a dust, powder, liquid, or concentrate and is available also in formulations of lotions, creams, or shampoos to control scabies and head lice.[2] The US EPA classified lindane as a restricted use pesticide in 1985 based on its toxicity and possible carcinogenicity.[5]

Absorption into the Body

Lindane is readily absorbed into the body by dermal absorption, oral ingestion, or by inhalation of the dust or vapors.[4] As described below, oral ingestion of lindane can occur through contaminated food or water or by deliberate or accidental ingestion of formulations containing lindane.[2] Inhalation of lindane as either an aerosol or dust could certainly occur in the industrial environment during formulation or packaging of products or in field spraying operations. Another possible inhalation exposure source for lindane would be the inhalation of vapors from vaporizers which use lindane.[2]

Absorption through the Skin

Regarding the situation discussed herein, dermal absorption of lindane is by far the most pertinent route to discuss. Lindane is readily absorbed through the skin from various types of formulations.[6] Feldman and Maibach[7] examined the penetration of lindane through human skin using ^{14}C-labeled lindane. They applied the radiolabeled lindane to various areas of the skin, including the forearm, and measured ^{14}C in the urine of exposed subjects and found that 9% of the applied label was excreted during the observation period. They then compared other sites to the forearm and found that absorption from the neck, face, forehead, and scalp produced 2-6 times more absorption than the forearm.[7] Percutaneous absorption of lindane is thought to be greater when applied to the face, scalp, axillae, neck and scrotum[5] and simultaneous applications of lotions,

ointments or oils may enhance the absorption.[5] This absorption also is reported to increase after lotions are applied following a hot soapy bath.[5]

Of course, there are other studies which support the observations mentioned above.[6,7] In guinea pigs, when sufficient lindane is applied to the skin, the animals die.[4] In another guinea pig experiment, the amount of lindane found in the animal's brain after topical application of lindane increased with increased numbers of applications.[8] In a study of treated children, lindane was measured (from 2 to 48 hours) in the blood of young children who had been treated with 1% lindane. Concentrations in blood varied with weight and body surface area, but the lindane was almost totally absorbed.[9] It was pointed out that children do not absorb lindane faster than adults, but they do have a greater ratio of surface area to body mass than adults that results in a greater systemic dose of lindane.[10] There is also an indication that damaged skin may absorb lindane more efficiently than intact skin.[4,5,1]

Another study involved application of a 1% lindane cream (Kwell) according to label instructions to five male and four female volunteers, and after three days significant levels of lindane were found in circulating blood. The authors concluded that there is significant transcutaneous absorption of lindane which is consistent with neurological toxicity of lindane cream.[12] A study involving healthy volunteers and scabies patients has been reported where a 0.3% emulsion of lindane resulted in blood concentrations of around 3 ng/ml in the normal patients and about ten times that concentration in scabies patients.[11] In a similar study involving application of 30 grams of a 0.3% commercial lindane emulsion to the skin of healthy patients and scabies patients, after 5.5 hours healthy volunteers showed lindane levels of about 5 ng/ml in their blood while scabies patients showed concentrations about forty times higher.[13] A study done in 1983 and sponsored by a manufacturer of lindane shampoo and lotions reported on application of shampoo containing 1% lindane twice to nine children resulting in blood levels of 4.0 ng/ml lindane.[14] Thus, it appears clear that absorption of lindane through the skin has been well documented and occurs readily.

Toxicity of Lindane

There are numerous reports in the published literature relating to the toxicity of lindane, and many organ systems are involved. A major concern with lindane is its ability to produce blood dyscrasias, including aplastic anemia (APLA), a life-threatening disease. I will address most of this information below, but my focus will conclude on the central nervous system and, in particular, the ability of lindane when contacted by any route to stimulate seizure responses in exposed individuals and alter neurological development of the fetal and neonatal brain.

Symptomatology Related to Lindane Toxicity

Oral ingestion of lindane has been reported to result in lassitude, headache, vertigo, myalgia, intestinal colic, diarrhea, stomatis followed by central nervous system (CNS) effects including mental confusion, blindness, and convulsions.[4] Another report described rapid onset of nausea and vomiting, coma, seizures, respiratory failure, death, rhabdomyolysis, secondary renal failure, and aplastic anemia (APLA) related to the ingestion of lindane.[15] Others described similar symptomatology[4,10,16,17] and, in addition described various blood dyscrasias.[16] Lindane is reported to cross the placental barrier.[16] Inhalation exposure also results in some of the same symptomatology.[17]

Specific case reports of oral lindane toxicity describe similar patterns of symptomatology, but additional insights gained may warrant some discussion. After a patient drank a solution containing 20% lindane, he died 11 days later with seizures, coma, leukocytosis, and rhabdomylosis.[15] His autopsy showed widespread evidence of striatal muscle sclerosis, spongiform changes in white matter of the brain, steatosis, centrilobular necrosis, microabscesses of the liver with some evidence of renal tubular necrosis.[15] Acute renal insufficiency has been reported in another case.[18]

A two-month-old baby treated topically with lindane for two days was found dead, and high concentrations of lindane were found in his brain tissue.[19] A 29-year-old male who was involved in spraying animals with lindane developed symptoms that are consistent with peripheral neuropathy,[20] and field workers sprayed with lindane aerosol immediately experienced headaches, heavy perspiration, and loss of equilibrium and depth perception.[21] Another report of a lindane spraying in a house resulted in the usual signs of toxicity but included tremors of head and limbs, mental confusion, delirium, and blindness.[4,21]

Dogs treated orally with lindane exhibited diarrhea, hypothermia, sialorrhea, dacryorrhea, epitaxis, anorexia, oligodipsia, diuresis, proteinuria, and aciduria. Death was from respiratory failure. Autopsy findings included congestion of the meninges and capillary avenous vasodilation. In delayed deaths, fatty degeneration of the renal tubules and hepatic cells, degenerative hypovascular ulcers in the pylorys and small intestines, some inhibition of spermatogenesis and thymus gland atrophy were reported.[16]

Hematopoietic Effects

The potential for lindane-causing blood dyscrasias, particularly APLA has been well described[2] even by dermal exposure to lindane.[22-27] The effects of lindane on the blood-forming elements is an integral part of its toxicity, and various reports are briefly described here. About 30 cases of APLA have been reported to

have resulted from various routes of exposure including dermal exposure.[10] Various symptom patterns result from this progression to APLA including easy bruising,[25] petechial spots,[25] fatty bone marrow or panmyelophthisis,[28,29] depression of myeloid, erythroid and megakarycytes,[29] monocytosis,[30] eosinophilia,[30] granulocytopenia,[30] granulocytosis,[30] leukopenia,[30] leukocytosis,[30] pancytopenia,[31-33] severe anemia,[65] thrombocytopenia,[30,33] seizures,[34] pallor[34] and hypoplastic anemia.[34] Several other cases of APLA related to lindane have been reported.[3,10,23,29,31-38]

Cancer

Little information is available in the published literature that would allow one to draw many conclusions about the potential for lindane to cause cancer. In man, there is one report of twins developing leukemia.[39] There are some animal studies which described hepatomas in mice,[40,41] lymphoreticular tumors in Swiss mice,[41] and nodular hyperplasias and heptatocellular carcinomas in rats and mice that were fed lindane.[42] Although I have not conducted an exhaustive search on this subject, I find the available data to be equivocal.

Target Organs

I have already shown in some detail that the brain and the blood clearly represent the major target organs for lindane. In consideration of this subject, secondary target organs should include the liver (fatty infiltration, enlargement,[4,43] centrilobular necrosis, microabsesses),[15] the kidney (congestion and renal tubular necrosis),[15,43] the muscle (rhabdomyolysis, striatal muscle sclerosis),[15] and the heart (subepicardial hemorrhages).[43]

NEUROTOXICOLOGY OF LINDANE (central nervous system effects)

As early as 1976, the US Food and Drug Administration (FDA) warned of the neurotoxicity of lindane and noted its facile penetration of the skin resulting in systemic circulation. One FDA study demonstrated the fact that lindane produces convulsions and death in weanlings but not in adult rabbits, and the authors state "The veterinary literature contains numerous reports of deaths of young animals dipped in the insecticide.[44]

Lindane Goes to the Brain

There are numerous animal and human studies which demonstrate that lindane, once absorbed into systemic circulation, concentrates in the brain as exemplified by a reported guinea pig study showing brain concentrations of lindane as being ten times blood concentrations.[8] One study in rats not only demonstrates that

the concentration of lindane is dose dependent, but also that the resulting tonic convulsions correlate with concentration of lindane in brain tissue.[45] Other studies show similar findings.[46,47] Studies using radioactive labeled lindane showed brain concentrations of lindane correlating with the onset of convulsions and lindane being distributed to the white matter and myelinated structures of the rat brain.[48] Another study involving iv infusion of lindane emulsion given to dogs resulted in convulsive seizures and widespread distribution of lindane in both white and grey matter.[49] White matter, however, has 3-4 times the lipid content as grey matter, and lindane, being lipophilic, is preferentially distributed to the white matter.[50] An autoradiographic study of female rats dosed by intraperitoneal injection confirmed the latter finding.[51] Another study involving labeled lindane administered orally to male Wistar rats resulted in a concentration of lindane in the cerebellum of 5.1 μg/g, 18.5 minutes after dosing.[52] Histopathological changes in brains and meninges of rats also have been noted in response to lindane.[53]

Human studies also have demonstrated the affinity of lindane for brain tissue. It is said that "Lindane has a propensity to accumulate in the brain...".[5] A case report involving application of 1% lindane lotion to a 2-month-old, 4.5 kg infant resulting in death showed concentrations as high as 110 ppb of lindane in brain tissue, three times the level in blood.[19] Again, preferential storage of lindane in white matter is noted.[4] In one study supported by the manufacturer of Kwell products containing 1% lindane, the authors concluded that lindane accumulates in the brain after topical application, persists there for a period of up to two weeks and that the drug causes seizures especially in young children.[35]

Although an indirect measure of the ability of lindane to reach the brains of exposed humans, numerous reports have been published on adults and children exhibiting seizures, EEG abnormalities, convulsions, and even death after being exposed to 1% lindane shampoos and lotions.[19,35,54-64] In addition, similar effects are reported in poisonings involving oral ingestion of lindane preparations.[15,18,43,65-71] Some of this material is discussed in more detail below.

Seizures from Oral Ingestion in Man

There are a number of cases involving accidental ingestion of lindane which resulted in seizures.[15] One involved a 2.5-year-old girl who ingested lindane, became irritable, and quickly had grand mal seizures and cyanosis.[66] Eight cases of grand mal seizures secondary to ingestion of food grain contaminated with lindane also have been reported.[68] It is important to note that there is very little time (a few days maximum and sometimes just minutes or hours) between the contact with the toxicant and the development of the seizures. While another person survived drinking a lindane-containing fluid, she began having seizures at frequent intervals shortly thereafter.[43] A case involving a 16-year-old retarded

boy who ingested 1% lindane shampoo has been described wherein he developed status epilepticus with no prior history of seizures.[19] Yet another case involving a 35-year-old man who ingested food contaminated with lindane was reported to result in grand mal seizures and severe acidemia, both of which developed rapidly.[67] A patient who drank 20% lindane had seizures that followed rapidly, numerous other symptoms, and death 11 days later.[15] Of 50 adults who ate food contaminated with lindane, 20 experienced grand mal seizures.[18]

Seizures from Dermal Absorption in Man

Thirteen cases of seizures related to the proper use of a 1% lindane shampoo called Kwell were reported in one publication.[35] A total of 37 incidences of lindane-associated cases were described in that publication.[35] Individual case reports include three cases of seizures in elderly patients who were treated with 1% lindane following a hot bath with another hot bath 24 hours later. Seizures occurred 4-5 days after lindane application. None of the patients had any prior history of seizures.[56] In another report, a 3-year-old boy was treated with a single dose of 1% lindane cream, and 15 minutes later he developed nausea, vomiting, twitching of eyelids, and fluttering of eyes. Two hours after treatment, he experienced epileptiform convulsions and muscular spasms. He had no family history of seizures.[57] Another case involved a premature, malnourished 4-month-old infant who arrived at the hospital with scabies. The child was treated with 1% lindane lotion over his entire body, was bathed at 24 hours post application, and shortly thereafter was diagnosed with clinical seizures.[60] A nine-month-old female treated topically with lindane twice daily for one month developed seizures;[58] and an eight-year-old girl received lindane over her body for 22 days, six weeks later received another series of treatments, and then promptly developed seizures.[54] A seven-year-old child was treated with lindane lotion that was left on the body for 36-40 hours, and within 48 hours he developed seizures; he had no prior history of seizures.[54] A 13-month-old boy exhibited grand mal seizures after a two-week application of 1% lindane lotion.[54]

There are additional case reports which describe related symptoms from dermal exposure to 1% lindane preparations. A 4-month old showed marked mental and motor retardation two days after being treated with Kwell lotion for 24 hours,[58] while a 10-year-old who received a thick layer of lindane lotion applied at bedtime could not be aroused 8-10 hours later.[54] A 37-year-old man was treated three times at 12-hour intervals with lindane and developed dizziness and amblyopia; and a mother who shampooed herself and her kids with lindane shampoo experienced nervousness, irritability, anxiety, insomnia, and on rechallenge with lindane, the symptoms reappeared.[54] A 24-year-old woman who used 1% lindane shampoo was reported to have experienced uncontrolled motor activity two hours after treatment.[55] Also, a 23-year-old man with scabies

covered his trunk and limbs with 1% lindane lotion, and 12 hours later he felt tired, weak, dizzy, vomited, had difficulty with balance and slurred speech. After an additional application one week later, he lost consciousness.

Seizures from Inhalation Exposure in Man

Lindane can be inhaled as a dust during manufacturing or formulation operations, as an aerosol while spraying crops or farm animals, or as a vapor when it is used in a vaporizer, as has been the case. One case of the latter involved a 2.5-year-old boy who experienced seizures, pallor and hypoplastic anemia after inhaling vapors from a home vaporizer.[34] Another possible vapor or aerosol exposure resulted from the treatment of the interior of a house with lindane where 79 people were affected, but only one patient developed tonic/clonic convulsions and died 4 days after being admitted to the hospital.[4,21] Two workers occupationally exposed to lindane experienced epileptic fits after lindane exposure with no history of epilepsy.[72] Thirty-seven men employed at a fertilizer plant were exposed to lindane for almost two years and reportedly showed clinical signs that included muscle jerking, myoclonia, emotional changes, and EEG changes suggestive of seizures.[72]

Seizures in Treated Animals

Obviously, studies in animals are highly controlled compared to those case reports in humans. Dose-response curves relating to neurotoxic effects in rats have been described,[46] and numerous studies showing myoclonic and myoclonic-tonic convulsions in rats treated with lindane have been reported.[45-47,52,73-75] It has been observed that younger animals are able to store lindane for longer periods in adipose tissue,[4] and that neonatal Wistar rats are about twice as sensitive to the convulsive effects of lindane as are adult rats, suggesting an increased sensitivity to lindane in children.[47] Dogs also demonstrate convulsive behavior after exposure to lindane.[50] Both dietary[76] and intravenous administration[49] of lindane to dogs has resulted in convulsive seizures. Weanling rabbits treated topically with 1% lindane in a single application developed hyperexcitability and convulsions.[77]

Lindane and Brain Pathology

Although it appears obvious from the information presented above that there is a causal connection between exposure to lindane and seizures, it would seem appropriate to look at the pathological effects that lindane has on the brain, both in man via autopsy material and in animal models.

Studies in rats have shown a correlation between exposure to lindane with resulting convulsions and the concentration of lindane in the brains of rats.[45]

Animals treated with lindane consistently show multiple small brain hemorrhages and, as mentioned above, a preferential storage of lindane in the white versus the grey matter of the brain[4,48,50] The distribution to the white matter in rats is very rapid after dosing.[48] Autopsy findings in a patient who died from lindane poisoning showed spongiform changes in the white matter,[15] multiple small brain hemorrhages with necrosis of small vessels,[4] and brain congestion after oral ingestion and death.[43] Pesticide workers exposed to lindane reportedly show abnormal EEG patterns[4,72] while ingestion of contaminated wheat resulted in myoclonic jerks, generalized tonic/clonic convulsions, loss of consciousness, and EEG changes including excess slow waves, spike activity, and paroxysmal delta wave bursts of short duration.[78] When lindane powder was sprayed into homes, 79 people involved in the exposure situation displayed spasmodic manifestations, cerebellar signs including ataxia, adiadochokinesia, asynergia, tremor, mental confusion, delirium, tonic/clonic convulsions, and death.[21]

Behavioral Changes Produced by Lindane Exposure

Unfortunately, there are few studies of human behavioral effects related to lindane. It would appear, however, that young children and animals are most susceptible to the neurotoxic effects of lindane,[44] and warnings have appeared regarding the use of lindane on very small infants.[10] Marked mental and motor retardation was reported two days after treatment of a 4-month-old child with 1% lindane lotion.[5,58,63]

There are animal studies which report behavioral alterations relating to lindane exposure.[79] A study of lindane exposure in adult Fisher 344 rats examined not only the effects of lindane exposure on seizure response, but also its effect on avoidance response using two-way shuttle box techniques. The authors concluded that lindane treatment at nonconvulsive doses significantly reduced the animals ability to acquire and use new information and the number of correct avoidance responses. These effects were thought to be mediated by gamma-aminobutyric acid (GABA).[80] A study involving chronic exposure of Wistar rats to hexachlorocyclohexane containing 24% lindane was reported to have resulted in altered behavioral activities including motor and grooming activities suggesting that the treatment induced impairment of the enzymes involved in synaptic activity and consequent behavioral alterations.[81] Other effects that have been reported include convulsions in dogs dosed with lindane by intravenous injection;[20] tremors, ataxia, weakness and paralysis in rabbits, guinea pigs, and mice following dietary lindane;[20] convulsions in rabbits treated dermally with lindane;[77] effects on locomotor activity, induced seizures and death in treated mice;[82] altered motor activity and neuromuscular reflexes in rat pups dosed orally,[83] and increased geotaxis, decreased motor activity, altered EEGs, and increased GABA brain levels in chronically dosed rats.[84]

Studies done in young animals also have been reported. Oral treatment of suckling pigs at age 10-13 days with lindane resulted in increased anxiogenic effects thought to be mediated through the action of lindane on the benzodiazepine-$GABA_A$ receptor-chloride channel complex[85] (see discussion below). Treatment of rat pups with lindane at 15 days postnatal age produced behavioral alterations including altered avoidance responses which were thought to be due to an imbalance of the central monoaminergic systems and lindane-induced GABAergic blockade.[86] Yet another rat study involving male and female offspring of Wistar rats treated with nonconvulsive doses of lindane on postnatal Days 1 and 2 resulted in positive responses in relation to effects on neuromotor reflexes including surface righting, cliff avoidance, and tail hang reflex.[83]

In addition to the many studies cited above which show behavioral changes in children and animals exposed postnatally to lindane, three additional rat studies by Rivera *et al*. should be noted. The first study[83] reported that rats exposed postnatally to lindane during the first or second week after birth showed increased locomotor activity and increased neuromotor responses. The second[85] demonstrated altered suckling behavior similar to that observed with benzodiazepines, and the third[86] reported altered passive avoidance and motor activity after postnatal treatment with lindane.

Lindane and the Fetus

In a review paper published in 1981, the following statement appeared: "Several physicians have suggested that Kwell be used with extreme caution, if at all, in pregnant women, very small infants and people with massively excoriated skin".[10] Kwell products contain 1% lindane. Another study published in 1982 concludes that lindane should not be used to treat pregnant women, small infants, or individuals with skin problems.[61] In 1986, "The Centers for Disease Control (CDC) currently states that lindane is not recommended for use in pregnant or nursing women".[5] In the report of a study sponsored by the manufacturers of Kwell shampoo and lotions containing 1% lindane showing dermal absorption of lindane in children, the following statement appears: "Because of this and the putative teratogenic effects of the drug, its seems prudent that GBH [i.e., lindane] in any form, should be used with caution during pregnancy."[14]

It should be clear from the above discussion, that lindane is easily absorbed through the skin and enters systemic circulation readily. What should be clear also is that lindane, when in systemic circulation, tends to concentrate in the brain thereby dismissing any "blood-brain barrier" concept for lindane.[87] What is not clear at this point, is whether or not lindane crosses the "placental barrier". Since lindane is lipophilic, the answer to the question should be an obvious yes, it does cross the placental barrier,[87] and it enters systemic circulation in the fetus

and concentrates in the fetal brain. Indeed, lindane crosses the human placenta,[3,88] is excreted in human breast milk, and is thought to be fetotoxic.[5] "During pregnancy, higher concentrations [of lindane] have been found in fetal blood and fetal tissue as well as placenta and amniotic fluid compared to maternal fat tissue".[5]

Animal studies also support both the placental transfer of lindane to the fetal brain and subsequent fetotoxicity. Pregnant rabbits treated orally with lindane have been reported to have produced offspring containing high levels of lindane in liver, brain and gastric contents.[89] Treatment of pregnant albino Wistar rats with lindane and subsequent analysis of fetal brains for lindane showed significant concentrations of lindane.[90] Endrin and lindane are reported to have caused fetotoxic effects in two strains of mice[91,92] while another study demonstrated dose dependency of the effect.[93] Embryotoxicity in rats, hamsters, and rabbits has been reported[94] as well as observations of significantly increased numbers of stillborn pups in pregnant dogs treated orally with lindane.[95] A study involving rat embryo cultures and visceral yolk sacs suggests that lindane embryotoxicity may be related to depletion of embryonic glutathione.[96] Numerous other studies describe the fetotoxicity of lindane.[95,97-104]

Another $GABA_A$ receptor antagonist, benzodiazepine, is reported to have induced a human syndrome involving behavioral dysfunction, hyperexcitability, delayed motor development, mental retardation, abnormal EEGs, and perceptual disorders.[105-108] Others have reported on the binding of benzodiazepine to $GABA_A$ receptors as a result of *in-utero* exposure.[109-111] The fetus is said to be most vulnerable to the effects of benzodiazepines during the second trimester.[112] Other fetal effects reported for benzodiazepines included altered functioning of the hypothalamic-pituitary-thyroid axis,[113] reduced norepinephrine levels, turnover rate and release from the hypothalamus,[114,115] altered choline, GABA and serotonin uptake in exposed adult offspring,[116] altered cellular metabolism in the brain persisting into adulthood,[112] increased kindled seizures in adults exposed *in utero*,[117] altered $GABA_A$ function,[118] altered hippocampal cholinergic receptors in adult offspring,[119,120] and altered the developmental appearance of brain-derived neurotrophic factor.[121] Considering this finding, it is likely that other $GABA_A$ antagonists that operate similarly to benzodiazepines would produce similar effects.

Mechanisms of Action - Kindling, a CNS effect

One of the phenomena which appears to be most widely accepted in response to lindane is that involving chemical kindling. Kindling can be described as the gradual development of seizures in response to brief and minimal electrical stimuli. In studying lindane and endosulfan, one report states, "The physiological responses proved by these bursts promote a persistent alteration in

the nervous system function, one manifestation of which is the development of convulsive behavior and a permanent predisposition to seizures from a variety of other sources."[122] In other words, the establishment of a kindling by lindane can permanently sensitize the central nervous system to seizures from other stimuli. Some of the published information related to this kindling concept appears below and serves to illustrate a different CNS effect of lindane than those producing behavioral alterations as described elsewhere in this document.

Repeated intermittent exposures to lindane in low doses lead to the development of electrographic and behavioral signs of seizures which persists in the rat.[123] A report of neonatal rats exposed either orally or by maternal exposure demonstrated more rapid kindling than controls, and these effects were carried into adulthood,[124] clearly demonstrating the permanency of the kindled state. Other studies in mice[125] and in rats also showed acquired persistent kindling established as a result of lindane treatment. [123,126-128] Another study in rats showed that lindane exposure reduced the number of trials to acquire maximal kindled hippocampal and amygdaloid responses in the rat, showing that lindane can operate through the kindling mechanism in two distinct areas of the brain.[129] Further insight is provided by a study which demonstrated that the kindled state induced by lindane was sustained independent of the lindane concentration in the brains of rats.[74] Yet another study described the kindled state as being permanent once it is established and reported that lindane increases the probability of inducing focal epileptiform activity and increases the rate of generalization of such activity into surrounding brain tissue.[130] A study stated that lindane has a profound effect on the acquisition of the kindled seizures and increases the rate of acquisition in a dose-dependent manner.[131] The same publication stated that the kindling model for epilepsy is sensitive to modulations in adrenergic function which may be involved in the pro-convulsant effects of lindane on acquisition.[131]

Gamma amino butyric acid-A ($GABA_A$) receptor-chloride channel sites may be involved in this complex acquisition process.[52,132-133] Lindane is known to bind to the $GABA_A$ receptor site,[126] but is reported elsewhere to not interact with the GABA-synthesizing enzyme glutamic acid decarboxylase.[75] Some are of the opinion that no conclusion can be drawn about whether or not lindane acts uniquely on the GABA system,[52] and others suggest that GABA may be involved in a protective mechanism to counteract seizures.[134] Cyclic GMP is also considered as a possible $GABA_A$ receptor mediating factor somehow involved in this kindled seizure mechanism.[135] Voltage-dependent calcium channels[136,137] and blockage of $GABA_A$ chloride channels[82,138] have been suggested as mechanisms for the convulsive action of lindane.[136,137] In a recent publication dealing with induction of seizures by lindane, excitatory amino acid antagonists were used in mice to study the protective effects on the lindane induction of convulsions. All the antagonists protected against tonic convulsions induced by lindane, and they

concluded that the excitatory amino acids may be involved in the central action of lindane in inducing convulsions.[133]

Mechanism of Action - Seizures, Behavior and $GABA_A$ Receptor Development

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian adult brain. In the adult, GABA inhibits neuronal firing by increasing chloride conductance by blocking $GABA_A$ receptors resulting in a reduction of the inhibitory action of GABA.[82,139,140] Blockade of $GABA_A$ receptors results in seizure activity.[84,133,138,139,141-152] Lindane and chlorinated cyclodienes block these receptors causing seizures and are called receptor antagonists.[151,153,154] Dieldrin and lindane and the excitotoxins PTX and TBPS are $GABA_A$ receptor antagonists and elicit convulsions by blocking the inhibitory action of GABA through interactions with $GABA_A$ receptors/ Cl^- channels.[140] A study of this mechanism examined the effects of excitatory amino acid antagonists which reduced the convulsant properties of lindane and suggested that excitatory amino acid neurotransmission may be involved in the etiology of lindane seizure induction.[133] Several studies demonstrate lindane binding to $GABA_A$ receptors,[141,143,147] while others show that lindane inhibited receptor function.[82,142,146,150,151]

We should understand that gamma-aminobutyric acid (GABA) is one of the most active neurotransmitters in the developing brain,[155,156] and it functions in this capacity by chemically signaling processes involved in developing neurons including those of the monoaminergic type such as serotonergic and dopaminergic receptors.[86,155,157] In the prenatal and early neonatal brain, GABA acts as an excitatory neurotransmitter and trophic factor.[157] Thus, the GABAergic system involving GABA and $GABA_A$ receptors has a controlling role in the proliferation, migration, and differentiation of neurons, a process called synaptogenesis in the developing brain.[140] This is a particularly important concept to grasp since the neuronal network is being controlled by the GABAergic system and regulating $GABA_A$ receptor ligands. This can result in alteration of the expression of $GABA_A$ receptor subunits and binding sites. If GABA regulates prenatal expression of $GABA_A$ receptors, then *in-utero* exposure to $GABA_A$ receptor antagonists such as lindane may influence and interfere with the trophic action of GABA resulting in changes that will persist into and throughout adulthood.[140] In other words, $GABA_A$ receptor antagonists such as lindane can have profound effects on the neurocircuitry of the developing fetus resulting in neurological and behavioral problems which will persist throughout a lifetime.

$GABA_A$ receptors are part of a superfamily of ligand-gated ion channels that possess binding sites for GABA, positive and negative modulators and antagonists such as bicuculline, picrotoxin, TBPS, benzodiazepines, and

organochlorine pesticides such as lindane.[140] $GABA_A$ receptors are complexes of consisting of several glycoprotein subunits, α, β, γ, δ & ρ. In addition, there are various subtypes or isoforms within each subunit that have been isolated and include α1-6, β1-4, γ1-3, δ & ρ1-2,[157] and there are additional variants (γ2S, γ2L).[140] Using competitive RT-PCR (reverse transcription-polymerase chain reaction) techniques for quantifying m-RNA, investigators have been able to show decreased expression of α1, β3, and γ1 $GABA_A$ subunit transcripts com-pared to vehicle injected controls as a result of treatment with dieldrin, and bicuculline,[140] both $GABA_A$ antagonists acting on the same receptors as lindane.[141] These results suggest that prenatal exposure to lindane, dieldrin, or bicuculline could have long lasting effects on developing GABAergic neuronal circuitry, $GABA_A$ receptor function, and behavior in offspring.[140]

While a number of neurotoxins may act on the $GABA_A$ receptors in brain tissue, of particular interest in this discussion is the neurotoxicity of organochlorine pesticides such as the dieldrin and other chlorinated cyclodiene pesticides, lindane and benzodiazepines. All of these act on $GABA_A$ receptor and thereby block the effects of GABA (gamma-aminobutyric acid) on the receptor by binding directly to the chloride channel.[155] One of the techniques for studying the blocking of $GABA_A$ receptors involves the use of a radioactive sulfur tracer [^{35}S]TBPS (t-[^{35}S]butyl-bicyclophosphorothionate) and examining the extent of noncompetitive binding of this tracer to $GABA_A$ receptor/chloride channels before and after treatment with various ligands such as lindane, chlorinated cyclodienes and benzodiazepines.[141,155] Binding of lindane, chlorinated cyclodienes (dieldrin, aldrin, endrin, heptachlor, endosulfan) and benzo-diazepine to these sites has been definitively demonstrated using this technique.[141,142,153,155,157]

Another technique used to demonstrate this $GABA_A$ chloride channel inhibition by lindane and chlorinated cyclodienes (endrin, dieldrin, heptachlor, endo-sulfan) employed a radiolabeled chloride [$^{36}Cl^-$]. Using this technique in rats, the authors report inhibition of influx of chloride ion through the $GABA_A$ chloride channel.[142] Clearly, the neurotoxic effects of cyclodienes and lindane are produced by their interaction with the chloride channel coupled to the $GABA_A$ receptor.[151]

Of particular interest in this case is the effect of lindane and other $GABA_A$ receptor antagonists on the developing brain during *in-utero* growth and postnatal periods. GABA has been shown to act as a trophic signal for mono-amine neurons on embryonic Day 14 as reported in rat brainstem cultures.[86] Using RT-PCR techniques and treatments with $GABA_A$ receptor antagonists such as dieldrin and bicuculline, an alteration in the expression of the subunits of $GABA_A$ receptors was reported leading the authors to suggest that this may have an effect on behavior in the developing organism.[140] Other studies have shown

that trophic signaling by GABA is blocked by lindane and dieldrin and that exposure to these chemicals early in life can lead to disruption of monoamine neurotransmitters and produce alterations in $GABA_A$ receptor expression and function.[155,157] Another study of developing neurotransmission by monoaminergic systems was carried out in rat pups. A single dose of lindane on postnatal Day 15 increased the ratio of 5-HIAA/serotonin ratios in several brain regions and the DOPAC/dopamine ratio in the mesencephalon, suggesting enhanced monoaminergic turnover. This imbalance of the central monoaminergic systems and the lindane-induced GABAergic blockade may be the basis for behavioral problems in children exposed *in-utero* or shortly after birth.[86,155,157] Other studies have suggested a relationship between early expo-sure to lindane and neurobehavioral, neurochemical, and electrophysiologic problems.[84]

It has been suggested that *in-utero* and postnatal exposure to organochlorine pesticides including lindane could interfere with the development of the central nervous system.[140] Prenatal exposure to dieldrin or bicuculline, both $GABA_A$ antagonists like lindane, has been shown to alter expression of specific $GABA_A$ subunits in fetal rat brain.[140] Neurobehavioral changes have been noted in postnatal rats and children chronically exposed to organochlorine pesticides during gestation and infancy,[159-162] thereby supporting this viewpoint. Further, dieldrin has been shown to bind to $GABA_A$ receptor subunits in brainstems of rats treated *in-utero* with the pesticide.[140,163] A review on this subject recently stated, "Thus, maternal exposure to organochlorine pesticides could pose a risk to fetal brain development, especially during the first trimester of pregnancy".[157] Both animal studies and case reports show that infants and young children are especially susceptible to lindane-induced neurotoxicity.[60,61,64,66,77,78,164,165,166]

CAUSATION ANALYSIS

In addressing the potential for a causal relationship between [redacted] exposure to lindane during her pregnancy and the very significant central nervous system problems of [redacted], I will consider a number of issues and will ask/answer a number of questions. Pertinent questions include the following.

- Was [redacted] exposed to lindane at a time in her pregnancy when the fetus she was carrying was susceptible to chemical brain damage?

- Was Judith exposed to chemicals that could have harmed the fetus other than lindane? If yes, were these additional materials neurotoxic?

- Did the lindane lotion penetrate [redacted] skin and enter into systemic circulation? If so, was the systemic lindane able to traverse the placenta and reach the fetus?

- If the lindane reached the fetus that Ms. [redacted] was carrying, did it also reach the developing fetal brain?

- If it reached the developing fetal brain, could it disrupt the development process in such a way to have caused [redacted]s developmental delays, encephalopathy, and profound mental retardation?

- Is there sufficient evidence in the scientific literature to show that lindane is a neurotoxicant, that is, does it attack the brain in adults and children?

- Finally, is there a causal relationship between Ms. [redacted]' exposure to lindane lotion during her pregnancy and [redacted]s profound central nervous system developmental problems?

Was [redacted] exposed to lindane at a time in her pregnancy when the fetus she was carrying was susceptible to chemical brain damage?

Ms. [redacted] became pregnant on or about April 21, 1986, and gave birth to her child [redacted] on January 21, 1987. On July 16, 1986, toward the end of the first trimester of her pregnancy, Dr. [redacted] gave Ms. [redacted] a prescription for 1% lindane lotion for treatment of her scabies. She was told to apply the lotion to her whole body and let it stay on her skin during the night. Ms. [redacted], after a hot shower, complied with the instructions. It is presently not clear to me whether or not she applied the lotion a second time. She did have some prior exposure on July 10 while applying the 1% lindane lotion to her husband. Assuming for the moment that Ms. [redacted] did experience systemic intoxication by lindane as a result of her dermal application(s) of the lotion, it is clear that the her unborn fetus also was exposed to lindane during a period when a number of critical processes were underway toward the development of a normal brain function, absent the pesticide exposure.[167-170]

Was Judith exposed to chemicals that could have harmed the fetus other than lindane? If yes, were these additional materials neurotoxic?

On June 26, 1986, Dr. [redacted] a dermatologist, gave Ms. [redacted]' and her husband a prescription for Eurax (crotamiton) and Synalar Cream (fluocinolone acetonide). On July 2, 1986, Dr. [redacted] prescribed a combination of Synalar, Eurax, and "Zone A Lotion" (hydrocortisone acetate). All three of these drugs are classified by the FDA as Category C drugs, indicating that there either

may be some teratogenic effects observed in animals or no animal tests have been carried out, and the potential for fetal harm is unknown.[1] While it is true that Ms. [redacted] was exposed to these additional drugs which may have had the potential for causing harm to her unborn child, there is no indication that any of these drugs are capable of neurotoxicity or of influencing the development of the fetal brain.[171]

Did the lindane lotion penetrate [redacted] skin and enter into systemic circulation?

The ability of lindane to penetrate human skin is well known,[1,4-14,19,35,54,56-60,173] and formulation of lindane into lotions or application of lindane lotions after a hot soapy bath enhances that penetration.[5] When used in combination with other oily preparations or lotions, the penetration also would be enhanced.[5] Application of lindane lotions to diseased skin (scabies) increases the efficiency of penetration from 10 to 40 times.[11,13] Studies which measure lindane absorbed through the skin of animals also provide some support for the facility which lindane penetrates skin.[4,5,8-10,12] Even more impressive are the scientific studies which have been published regarding the consequences of dermal application of lindane, i.e.: seizures[19,35,56-64] and aplastic anemia (APLA).[10,22-27] While the citations relating to seizures and APLA are clearly indirect criteria for illustrating dermal penetration of lindane, coupled with the direct evidence, they leave little doubt that lindane readily penetrates healthy human skin and penetrates scabietic skin such as that of Ms. [redacted] at a much more efficient and rapid rate. Ms. [redacted] therefore, was definitely exposed to lindane lotion both dermally and systemically. Ms. [redacted]' blood did contain significant amounts of lindane during that point in her pregnancy.

Was the systemic lindane able to traverse the placenta and reach the fetus?

Chemicals which are lipophilic (soluble in fatty tissue) in most cases will be transferred to the fetus through the placenta. Lindane is lipophilic and does reach the fetus via placental transfer in both animals[89,90] and man.[3,5,16,87,88] This is widely accepted in the scientific community and many warnings have been issued to prevent use of lindane preparations during pregnancy.[5,10,14,61] These warnings are well founded since embryotoxicity and fetotoxicity have been reported in lindane-treated animals including rats, hamsters, rabbits, dogs, and mice.[91-95,97-101,103,104] Fetotoxicity is ample proof that lindane reaches the fetus. Additional support for this will be presented below.

If the lindane reached the fetus that Ms. [redacted] was carrying, did it also reach the developing fetal brain?

Although we have already illustrated this previously by citing the many cases of seizures which resulted from humans being dermally treated with lindane, we can illustrate the neurotoxicity of lindane by citing studies in which seizures occurred after oral ingestion of lindane,[15,18,19,43,65-71] and after inhalation of lindane vapors in man[4,21,34,72] and animals.[45-47,49,73-75,77] Clearly, the brain is a target organ for lindane. "Lindane has a propensity to accumulate in the brain . . ."[5] A more direct approach to the assessment of potential for lindane to reach the brain is to actually measure it in the brain. This can be done easily in animals, but in man only those who have died from lindane poisoning can be examined for obvious reasons. There are cases of human mortalities resulting from oral[15] and dermal exposures to lindane,[4,19] particularly tragic in babies.[19] In some cases histopathological reports illustrate pathological lesions related to lindane exposure.[4,15,43,45,48,50,53] It would appear that the so-called "blood-brain barrier" does not exist when considering lindane.[87] Animal studies, mostly in rats, guinea pigs, and dogs also provide additional evidence that lindane concentrates in the brain tissue,[8,45-52] particularly in white matter where the fat content is greatest.[4,49,50] Lindane clearly targets the brain and concentrates in that organ producing pathological lesions resulting in pathological conditions expressed in the adult as seizures. Exposure of the developing fetus to lindane results in accumulation of lindane in the fetal brain and disruption of the development of the brain and its complex communication system as indicated below.

If it [lindane] reached the developing fetal brain, could it disrupt the development process in such a way to have caused [redacted] developmental delays, encephalopathy, and profound mental retardation?

I have already shown that lindane undoubtedly reached Ms. [redacted] developing fetus. That evidence is quite convincing. I have also demonstrated some of the effects of lindane when it does reach the brain, and I have addressed the involvement of GABA and the $GABA_A$ receptors and subtypes with regard to their interactions with lindane. Some additional discussion on the latter may be appropriate at this time. An excellent review on this subject has been published recently by Lauder *et al*.,[157] and two additional studies which describe the action of lindane and other $GABA_A$ receptor antagonists on the developing fetal brainstem have been published by Dr. Lauder's group.[140,155] In essence, these and the many additional publications cited above show that lindane acts on the $GABA_A$ chloride channels,[141,143,147] thereby disrupting normal GABAergic function.[82,142,146,150,157] These are critical observations since the influence of GABA extends from the fetal brain stem to other parts of the brain sending chemical signals that influence the development of monoaminergic systems such

as serotonin and tyrosine hydroxylase systems, among others.[157] Imbalances in monoaminergic neurotransmitter development, called synaptogenesis, thus occur in various regions of the immature developing brain producing permanent changes in the neurotransmitter network resulting in profound effects on the developing central nervous system.[156] We know that organochlorine pesticides such as lindane bind to $GABA_A$ receptors, inhibit binding of classical antagonists, and block GABA induced chloride fluxes into the mammalian cell,[142,149] and that lindane in particular binds directly to the $GABA_A$ chloride channel.[146,154] Based on the information presented above, it becomes clear that lindane disrupts the formation of normal communication networks in the developing fetal and neonatal brain resulting in neurological and behavioral changes in both man[44,58,63] and animals.[20,77,79-86] Thus, the scientific evidence for suggesting a possible causal connection between fetal lindane exposure and profound decrements in neurological development is sound. It is not surprising that the Centers for Disease Control and even scientific reports supported by the manufacturer of lindane preparations warn against use of these lindane containing products by pregnant women.[5,10,14,61]

Is there sufficient evidence in the scientific literature to show that lindane is a neurotoxicant, that is, does it attack the brain in adults and children?

The evidence presented above is overwhelming in support of a conclusion that lindane is a neurotoxicant. Just the literature relating lindane to the induction of seizures is impressive by itself,[4,21,34,35,45-47,49,50,52,54,55-58,60,73-77] but additional support is found in a body of literature which supports the contention that lindane also promotes continuing seizures (kindling).[74,123-137]

CONCLUSIONS

Finally, is there a causal relationship between Ms. [redacted]' exposure to lindane lotion during her pregnancy and [redacted]'s profound central nervous system developmental problems?

[redacted] was prescribed a 1% lindane lotion that, according to instructions, was applied to her whole body after a hot soapy bath and was left on her body overnight. This happened during her first trimester of pregnancy for her daughter, [redacted] Above, I have presented an overwhelming amount of information from the scientific literature which allows me to state with certainty that, as a result of Ms. [redacted] exposure to the prescribed lotion, lindane was absorbed through her skin, attained her systemic circulation, passed through the placenta, entered into systemic circulation in the fetus, and concentrated in the fetal brain. I have presented much additional scientific evidence demonstrating

the effects of lindane on the developing brain through binding to $GABA_A$ receptors and subtypes resulting in disruption of the neuronal circuitry and leading to profound central nervous system effects. Brittany is now experiencing some of those effects.

I opine that it is highly probable that [redacted] current central nervous system problems, including her behavioral problems and profound mental retardation, are a result of disruption of normal brain development brought about by exposure to lindane while in her mother's womb.

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CONSULTOX, LIMITED

Date

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