ATTACHMENT 3: Responses to Disputed Statements

Disputed Statement A: "Lindane is not manufactured in the United States."

Referenced as: 19a, 20a, 21a

Response: This statement is not false.

In the Morton Grove letter dated June 12, 2006, they argue that their products (Lindane Lotion USP 1% and Lindane Shampoo USP 1%) are manufactured in Illinois. But their letter also confirmed that the active ingredient used in those products **(gamma-hexachlorocyclohexane) – commonly known as Lindane** – is *not manufactured* in the United States and is "imported from a supplier."

This fact has been reported by the U.S. Environmental Protection Agency: "Lindane is no longer produced in the United States (however, it is still formulated in this country)" (Lindane Hazard Summary; Lindane Risk Assessment Fact Sheet).

Also, the Commission for Environmental Cooperation (CEC) states: "Lindane is not manufactured in Canada or the United States. It is however imported and used in formulation processes" (Decision Document on Lindane [draft] 2000).

Another CEC document states "Lindane is no longer produced in North America. Lindane was never produced in Canada or Mexico" and "China, India, Romania and possibly Russia currently produce lindane for the world market." (North American Regional Action Plan on Lindane [draft], 2005).

Disputed Statement B: "Worldwide resistance to Lindane has been reported for many years (including in the United States) for both lice and scabies – this means that the organisms have become immune to the chemical."

Referenced as: 19b, 20b, 21b

Response: This statement is not false.

It is well documented that lice and scabies have been resistant or *tolerant* to lindane. Our use of the word "immune" was used to simplify the concept of resistance for the general public. Resistance is a likely concern for patients because "resistance to lindane is widespread and has resulted in decreased efficacy in the United States" (*Mayo Clinic Proceedings* 2004; 79: 661-666).

A 2002 publication of the medical journal *Pediatrics* reported that Lindane "has low ovicidal activity … and resistance has been reported worldwide for many years"(110:638-643). Similarly, a publication of the medical journal *Clinical Infectious Diseases* reported that, "Lindane resistance among head lice has been reported in the United States, the United Kingdom, the Netherlands, and Panama" (2003; 36:1355-1361). The Michigan Department of Community Health states "resistance [for lice] has been reported worldwide for many years" (Michigan Head Lice Manual, July 2004).

A publication of the medical journal *Pediatric Dermatology* reported that, "In view of these risks, lindane should be considered a 'last resort' in these patients, especially since lindane-resistant

scabies has been reported in many countries, including the United States"(2000; 17(2): 154-156). The California Department of Health Services, Division of Communicable Disease Control, published a report warning that, "scabies mites have become increasingly resistant to [1% lindane] and it is no longer recommended" (Management of Scabies Outbreaks in California Healthcare Facilities, May 1999). The Michigan Department of Community Health states: "Lindane is no longer recommended for use [with scabies] due to recent concerns of drug resistance" (Michigan Scabies Manual, May 2005).

MORE INFO: In their June 12, 2006 letter, Morton Grove further criticizes our statement because resistance is a concern for all lice and scabies medications. However, in our documents (Ecology Center Newsletter, Frequently Asked Questions, Fact Sheet for Parents, Top Ten List, Fact Sheet for Healthcare Professionals), we specifically note that resistance is also a problem for the pesticide alternatives to lindane.

Furthermore, Morton Grove argues that lindane prescriptions are *required* each year. There is no evidence that the 300,000 lindane prescriptions were *required*, rather the data merely show that it was prescribed by physicians. Pharmaceutical lindane has been available since 1947, and physicians often prescribe it to children out of habit despite the FDA black box warning. In California, the ban resulted in a change of prescribing practices (Heil, Ann. California's Pharmaceutical Lindane Ban. Sanitation Districts of Los Angeles County). There have been no documented problems in treating lice and scabies in California (in a population of more than 30 million). The current availability of more effective and less toxic alternatives provides physicians with multiple options. The alternatives have proved sufficient for handling lice and scabies cases in California, including in the prison population (ibid).

Disputed Statement C: "The low effectiveness of Lindane is a concern because patients may use the product for longer than indicated, resulting in potentially dangerous absorption and toxic effects."

Referenced as: 19c, 20c, 21c

Response: This statement is not false. The following statement was published in the *Archives of Dermatology:* "The slowest and least effective of all products tested was once again 1% lindane shampoo…. These results, which confirm the findings in the previous 2 studies, are of concern, considering that 1% lindane shampoo has an indicated application time of less than 10 minutes. Increasing the treatment time, which we have seen many parents do in an effort to increase efficacy, could result in increased percutaneous absorption and toxic effects on the central nervous system" (2002; 138:220- 224). This journal article is cited in the document.

MORE INFO: The *Mayo Clinic Proceedings* journal also references the *Archives of Dermatology* article above and comes to the same conclusion that appeared in our materials: "Recommendations for the withdrawl of lindane products are based on concerns that its poor efficacy will result in reapplication and overuse, which increase the risk of adverse events" (2004; 79: 661-666).

Disputed Statement D: "Lindane use is not recommended for treatment of pubic lice."

Referenced as: 19d, 20d, 21d

Response: This statement is not false. A clinical manual entitled, "The Health Care of Homeless Persons: A Manual of Communicable Diseases and Common Problems in Shelters on the Streets," edited by Dr. James O'Connell advises that, "Lindane is no longer recommended for pubic lice." This citation was included in the Ecology Center's document. Similarly, The Medical Letter publication "Drugs for Parasitic Infections" does not list lindane as the drug of choice or as an alternative treatment option for pubic lice (www.medletter.com).

The Michigan Department of Community Health says "The State of Michigan does not recommend using Lindane [for head lice]" (Michigan Head Lice Manual, July 2004). It is often suggested in medical journals that the treatment for pubic lice *should follow the recommended treatment for head lice*. For example, an article in *American Family Physician* reports that pubic lice treatment is the same as for head lice." (2004; 69: 341-8, 349-50). An article in *Extended Product Care News* states "The treatment [for pubic lice] is similar to treating head lice" (2005; 101(5): 58-60).

While Morton Grove is accurate to claim that the CDC currently lists lindane as an alternative to treat pubic lice, we do not claim that CDC recommends otherwise. The CDC pubic lice treatment guideline actually states that lindane is "not recommended for pregnant or lactating women or for children aged <2 years" (STD Treatment Guidelines 2002. www.cdc.gov/STD/treatment/). Furthermore, in the CDC's Fact Sheet for Pubic Lice Infestation, they state "**A lice-killing shampoo made of 1% permethrin or pyrethrin is recommended to treat pubic lice.** These products are available without a prescription at your local drug store. Medication is generally very effective; apply the medication exactly as directed on the bottle. A prescription medication, called Lindane (1%) is available through your health care provider. Lindane is not recommended for pregnant or nursing women, or for children less than 2 years old" (www.cdc.gov/NCIDOD/dpd/parasites/lice/factsht_pubic_lice.htm).

Disputed Statement E: "Use of an FDA-approved lice comb is an effective, non-chemical approach to lice treatment," citing the Lice Meister Comb as an example. Similarly, "thorough combing is emerging as a treatment of choice…"

Referenced as: 19e, 20e, 21e

Response: These statements are not false. The Michigan Department of Community Health and Michigan Department of Education, in a joint publication entitled "Michigan Head Lice Manual," advised that, "The combing method **is** the most time intensive, but for parents who wish to avoid chemical treatments, it is most effective" (emphasis in original). Similarly, the medical journal *American Journal of Pharmaceutical Education* reported that, "Thorough combing as the emerging treatment of choice… pharmacist recommendations should shift in the new millennium to thorough combing with a highly effective comb such as the LiceMeister, which has been registered with the FDA as a medical device…it [comb] also treats the infestation by removing nits. Resistance and toxicity are non-issues with this mechanical lice removal aid" (1999; 63:204-209).

MORE INFO: An article in *Pediatric Drugs* states, "One of the most effective tools for the prevention and control of lice is the louse comb, which should be used regularly for the detection of living lice at an early stage of infestation, and as an accessory to any treatment method to remove

living and dead lice. The louse comb can also be used systematically for the treatment of infestations, for confirmation that treatment with pediculicides has been successful, and for the removal of nits (dead eggs or egg shells)" (1999; 1(3): 211-218).

Disputed Statement F: "The risk for toxic effects is estimated to be 40-400 times lower for permethrin than Lindane lotion."

Referenced as: 19f, 20f, 21f

Response: This statement is not false. A 1996 study published in the *Archives of Dermatology* concluded that, based on both human and animal studies, "The risk for toxic effects, as assessed by systemic exposure during overuse conditions, is projected to be 40-400 times lower for 5% permethrin cream than for 1% lindane lotion"(132: 901-905). This journal article is cited in the document. Indeed, other articles cite the same information in the same way we cite it. For example, "The toxicity of 5% permethrin cream is estimated to be 40–400 times lower than that of 1% lindane lotion" (*Fundamental & Clinical Pharmacology* 2003; 17: 217–225). In addition, an article in the Indian Journal of Dermatology states "Permethrin is approximately 20 times less permeable through human skin than lindane and the risk for toxic effect is projected to be 40-400 times lower for 5% permethrin cream than for 1% lindane lotion" (2006; 72(1): 33-36).

Disputed Statement G: "Lindane is classified as a 'possible carcinogen' by the EPA."

Referenced as: 19g, 20g, 21g

Response: In our July 17, 2006 letter, we agreed to clarify this statement.

NOTE: As it happens, this statement only appeared in the earliest versions of some documents. Upon learning of the new EPA classification, all of our materials were promptly updated. It is important to note that the International Agency for Research on Cancer (IARC), the premier international cancer organization, currently considers lindane as "**possibly carcinogenic to humans**" (Volume 20: Some Halogenated Hydrocarbons and Preamble to IARC Monographs. http://monographs.iarc.fr/).

The Ecology Center's source for this statement was an active EPA Website (www.epa.gov/ttn/uatw/hlthef/lindane.html). Morton Grove acknowledges in their letter to the Ecology Center that Lindane was previously classified by the EPA as a possible human carcinogen. We recognize, however, that the EPA has elsewhere classified Lindane as having "suggestive evidence of carcinogenicity, but not sufficient to assess cancer risk to humans."

The Ecology Center denies that its previous statement was materially false or that Morton Grove was defamed by any statements published or spoken by the Ecology Center or its representatives. Nonetheless, the Ecology Center is committed to timely and informative publication of material facts on matters of public health. The disputed statement was distributed in a fact sheet to a small number of individuals associated with non-profit organizations that are part of a coalition that works with the Ecology Center, an old edition of The Ecology Center newsletter, and in a fact sheet distributed to one Michigan legislator. Accordingly, the Ecology Center will issue the following statement

in its Fall Newsletter.

Our proposed statement for the Newsletter:

> "In a previous edition of this Newsletter regarding Lindane, we reported that the U.S. Environmental Protection Agency (EPA) classified Lindane as a "possible human carcinogen." At that time, this information was (and still is) published on an active EPA website, but the EPA had, in fact, re-classified Lindane as having "suggestive evidence of carcinogenicity, but not sufficient to assess cancer risk to humans."

Our proposed statement for an updated fact sheet:

> "In a previous fact sheet, we reported that the U.S. Environmental Protection Agency (EPA) classified Lindane as a "possible human carcinogen." At that time, this information was (and still is) published on an active EPA website, but the EPA had, in fact, re-classified Lindane as having "suggestive evidence of carcinogenicity, but not sufficient to assess cancer risk to humans."

MORE INFO: The International Agency for Research on Cancer (IARC) currently considers lindane as "**possibly carcinogenic to humans**" (Volume 20: Some Halogenated Hydrocarbons and Preamble to IARC Monographs. http://monographs.iarc.fr/). The Department of Health and Human Services classifies lindane as "**reasonably anticipated to cause cancer in humans**" (Report on Carcinogens 2002, ehp.niehs.nih.gov/roc/tox10.html).
In addition, lindane (gamma-HCH) isomerizes in the environment to its alpha isomer (alpha- HCH), a compound considered as a **probable human carcinogen by the EPA** (*Bull. Environ. Contam. Toxicol. 1979;* 22(4-5): 699-707; *Chemosphere* 1976; 5(4):245-8; Lindane and other HCH isomers: Risk Assessment Fact Sheet). Lindane and its alpha isomer can isomerize into the beta isomer (beta-HCH) within biological organisms; and about 90% of HCH in human tissue and breast milk is beta-HCH (*Environmental Health Perspectives* 2002; 110(6): A339-A347). Beta-HCH is considered to be a **possible human carcinogen by the EPA** (Lindane and other HCH isomers: Risk Assessment Fact Sheet).

Disputed Statement H-1: "In the FDA's Adverse Event Reporting System, 20% of those reporting health effects (hospitalization, disability or death) due to Lindane used the product according to the directions."

Referenced in: 19h

NOTE: This specific statement only appeared in Jon Fliegel's letter, and was not officially addressed in our response letter dated July 17, 2006. However, the statement is not false and does not require a clarification. Refer to the response for Statement H-2 for more information.

Response: This statement is not false. The FDA Public Health Advisory states "Of the adverse event cases in the FDA database with a serious outcome (hospitalization, disability or death), only 20% used Lindane according to the directions in the label." Although the word "serious" does not appear in our statement, the three "serious" health effects are clearly stated.

Further, the *official medication guides* (labels) for Morton Grove's Lindane Shampoo USP 1% and Lindane Lotion USP 1% contain the same information: "There have been serious cases of adverse events reported for Lindane Shampoo and Lindane Lotion in which a serious outcome (hospitalization, disability, death) has occurred. In approximately 20% of these cases, the shampoo

and lotion were reported to have been used according to the labeled directions."

Disputed Statement H-2: "In the FDA's Adverse Event Reporting System, 20% of those reporting health effects due to Lindane used the product according to the directions."

Referenced in: 20h, 21h

Response: In our July 17, 2006 letter, we agreed to clarify this statement.

As it happens, all of the Ecology Center's *current* published documents specify that 20% of those reporting **serious** health effects (hospitalizations, disability, death) used Lindane according to directions in the label.

In fact, the official medication guides (labels) for Morton Grove's Lindane Shampoo USP 1% and Lindane Lotion USP 1% contain the same information: "There have been serious cases of adverse events reported for Lindane Shampoo and Lindane Lotion in which a serious outcome (hospitalization, disability, death) has occurred. In approximately 20% of these cases, the shampoo and lotion were reported to have been used according to the labeled directions."

The Ecology Center denies that its statement was materially false or that Morton Grove was defamed by any statements published or spoken by the Ecology Center or its representatives. Nonetheless, the Ecology Center is committed to timely and informative publication of material facts on matters of public health. This statement was distributed in an Ecology Center newsletter and in draft fact sheets to a few colleagues and one Michigan legislator. Accordingly, the Ecology Center will publish a clarification statement in an updated fact sheet that will be distributed to the Michigan legislator and to members of our coalition who received the previous fact sheet.

Our proposed correction for the fact sheet reads:

> "In a previous document regarding lindane, we reported that, "In the FDA's Adverse Event Reporting System, 20% of those reporting health effects due to Lindane used the product according to the directions." We should have reported that in the FDA's Adverse Event Reporting System, 20% of those reporting **serious** health effects (hospitalizations, disability, death) due to Lindane used the product according to the directions."

Our proposed correction for the Ecology Center Fall Newsletter:

> "In a previous newsletter factsheet regarding Lindane, we reported that, "In the FDA's Adverse Event Reporting System, 20% of those reporting health effects due to Lindane used the product according to the directions." We should have reported that in the FDA's Adverse Event Reporting System, 20% of those reporting **serious** health effects (hospitalizations, disability, death) due to Lindane used the product according to the directions."

MORE INFO: Morton Grove criticizes our use of this FDA data as defamatory because the total number of adverse effects reported for lindane is low. However, the *official labels* for Lindane Lotion and Lindane Shampoo contain this specific information.

Nonetheless, it is important to consider two factors when interpreting the FDA data. First, the FDA's Adverse Event Reporting System (AERS database) is a voluntary system, and there is a

substantial amount of underreporting. The FDA estimates that between 1 and 10% of all adverse effects are reported, therefore, it is reasonable to assume that many cases of lindane toxicity (up to 99%) have not been reported (EPA Reregistration Decision for Lindane. Case 315).

Second, the amount of lindane used every year (300,000 prescriptions, as indicated by Morton Grove in a previous correspondence with Michigan health organizations) is considerably less than for lice/scabies alternatives or other over-the-counter product such as Tylenol. Tens of millions of customers use acetaminophen products each year (U.S. Food and Drug Administration. Nonprescription Drugs Advisory Committee. 2002. www.fda.gov). Therefore, a raw number of adverse events cannot be used to compare risk of adverse events between lindane and Tylenol. To make a fair comparison, the percentage of adverse events from total use must be calculated—and this is not possible with the AERS.

Morton Grove also claims that ALL medications are associated with side effects, even with proper use. Alternative first-line scabies and lice medications are no exception—we acknowledge that all have been associated, in rare instances, with serious adverse effects, including death. However, "**lindane has a smaller margin of safety than the other treatments available** [for scabies and lice]" (Mathis. Assessment. FDA Center for Drug Evaluation and Research 2003. www.fda.gov/cder/drug/infopage/lindane/lindanememoassessment.pdf).

To our knowledge, lindane is the only alternative treatment for lice or scabies that has received a "Public Health Advisory" from the FDA.

According to the California Department of Health Services, Division of Communicable Disease Control, "Lindane, used since the 1950's, is both the **least effective and, by far, the most toxic** (*California Morbidity*, March, 1996. http://www.dhs.ca.gov/ps/dcdc/cm/960301CM.htm).

Further, "human skin was 20-fold more permeable to lindane than to permethrin", and "the risk for toxic effects, as assessed by systemic exposure during overuse conditions, is 40 to 400 times lower for 5% permethrin cream than for 1% lindane lotion (*Archives of Dermatology* 1996; 132: 901-905). The major side effects and contraindications noted for permethrin: "itching and stinging on application, may be used in infants and pregnant mothers." The major side effects and contraindications noted for lindane: "seizures, muscle spasms, and aplastic anemia; not for use in infants or pregnant or breast-feeding women" (*New England Journal of Medicine* 2006; 354(16): 1718-27).

Overall, Morton Grove used faulty logic to compare lindane toxicity to Tylenol (adverse effects associated with mis-use). The citation for Tylenol used by Morton Grove actually says: "An estimated 500 deaths per year are attributed to suicidal or unintentional **overdoses** of acetaminophen as well as more than 50,000 emergency room visits. This is the most common form of acute liver failure observed in the United States today. While some are intentional at least 50% of these are unintentional, that is, the patient is consuming more than one preparation of acetaminophen or simply using doses more than suggested by the package insert"(AASLD. Acetaminophen use and liver injury. 2004. www.aasld.org/eweb/DynamicPage.aspx?webcode=FastFacts_Acetaminop).

The important point here is that ALL of these deaths and ER visits are due to **overdoses** of Tylenol—both intentional and unintentional. That is distinctly different from Lindane, where 20% of serious reactions can occur when the person uses Lindane AS DIRECTED (FDA Public Health Advisory). In other words, the margin of safety for Lindane is far less than for Tylenol.

Disputed Statement I: "Due to its toxicity, the FDA recommends not using Lindane to treat individuals weighing less than 110 pounds – this corresponds to most children on whom Lindane is used."

Referenced as: 19i, 201, 21i

Response: In our July 17, 2006 letter, we agreed to clarify this statement.

However, this statement is not materially false. We recently learned (after submitting our response) that the Agency for Toxic Substances and Disease Registry (ATSDR) interprets the FDA warnings about lindane in the same way we did: "**The FDA does not recommend the use of gamma-HCH [lindane] in infants or children or adults weighing less than 50 kg**" (Toxicological Profile for Hexachlorocyclohexanes www.atsdr.cdc.gov/toxprofiles/tp43.html).
[Notes: 50 kg is approximately equal to 110 pounds]

Here are the references we submitted in our July 17, 2006 response letter: The U.S. Centers for Disease Control (CDC) published a report in 2005 (*Morbidity and Mortality Weekly Report;* 54(21): 533-535) that "**use of lindane also should be avoided for persons weighing less than 110 pounds (50 kg).**" Moreover, the Michigan Department of Community Health and Michigan Department of Education, in joint publications entitled "Michigan Head Lice Manual" and "Michigan Scabies Manual" advised that, **"The State of Michigan does not recommend using Lindane."** Also, on the FDA website that includes the Public Health Advisory, a report called "Assessment" says that lindane use "in patients who have not achieved adult stature should be discouraged" and **use of this product [lindane] should be limited to second line therapy in patients who have attained adult stature (approximately 60 kgs)**" (Mathis. Assessment. 2003. www.fda.gov/cder/drug/infopage/lindane/). A report on the WebMD website states that "Lindane is not recommended for babies, older adults, anyone who weighs less than 110 lb, or people who have a weakened immune system", and the cited reference for this statement is the FDA Talk Paper on the public health advisory released for Lindane.

Our proposed correction reads:

> "In a previous fact sheet, we reported that, "Due to its toxicity, the FDA recommends not using Lindane to treat individuals weighing less than 110 pounds – this corresponds to most children on whom Lindane is used." We should have stated that the FDA Public Health Advisory on Lindane says "Lindane is contraindicated for use in neonates and should be used with extreme caution in children and individuals less than 50 kg (110 pounds)."

MORE INFO: In addition to the ATSDR and CDC, some journals interpret the FDA data similarly to our fact sheets. For example, an article in the *American Journal of Managed Care* reports "The FDA has added warnings to the product labeling about the risk of seizure and neurotoxicity associated with lindane and has established restrictions for its use. Lindane should not be used to treat children or small adults (<50kg)" (2004; 10(9) Supp: S277-S282). An article in *Environmental Quality Management* states " The biggest news is the FDA has agreed to recommend that Lindane not be used on children for lice or scabies treatment, and to make other changes in how it is prescribed" (2002; 12(2): 89-95).

Disputed Statement J: "The most effective and least toxic head lice and scabies drug is permethrin."

Referenced as: 19j, 20j, 21j

Response: This statement is not false.

The medical journal *Clinical Infectious Diseases* reported that permethrin is the least toxic pediculocide (2003; 36:1355-1361). The Web MD publication states "the safest and most effective preparation [for lice] is permethrin crème rinse" (Understanding Lice and Scabies—Treatment. 2005. www.webmd.com/content/Article/8/1680_54397.htm).

Furthermore, the U.S. Centers for Disease Control and American Social Health Association consider permethrin as the most effective scabies treatment (INFORM. Lindane-Free Scabies Prevention and Treatment. 2003. www.informinc.org). The International Foundation for Dermatology reports that permethrin is the most effective scabies treatment (Management of Scabies, www.ifd.org/protocols_scabies.htm). In addition, the journal *Community Dermatology,* reports that permethrin is probably the least toxic treatment available [for scabies] (2006; 3:1-16).

Also, the official medication guides (labels) for Morton Grove's Lindane Shampoo USP 1% and Lindane Lotion USP 1% state that permethrin is *safer* than lindane: "The only time Lindane Shampoo [or Lotion] is used first is when someone cannot use safer medicines, which may include permethrin or crotamiton."

MORE INFO (does not appear in our response):

"Permethrin appears to be the most effective drug in both scabies and pediculosis, with evidence of rare microbial resistance and sufficient (no cross-resistance reported so far) efficacy in lindane-resistant infestations" (*Drugs* 2001; 61 (8): 1067-1088).

The Medical Letter "Drugs for Parasitic Infections" publication recommends permethrin as the drug of choice for scabies treatment. Permethrin is also listed as a drug of choice for lice. Lindane is NOT listed as a treatment for either condition (www.medicalletter.org).

A systematic review of lice treatments done in the *British Medical Journal* reported "only permethrin 1% crème rinse showed efficacy in more than two studies with the lower 95% confidence limit of cure rate above 90%", in the "six evaluations of lindane; in none of them did the lower confidence limit for the cure rate exceed 90%, and in two trials even the upper confidence limit was below 90%". Further, the article concluded that [emphasis added] "the **risk of treatment failure was likely to be at least eight times higher with lindane than with permethrin**" (1995; 311: 604-608).

A clinical study published in *Pediatric Infectious Disease Journal* reported that 98% of patients treated with permethrin and 76% treated with lindane were louse-free 2 weeks after treatment (statistically significant) (1987; 6(3): 252-255).

In their June 12, 2006 letter, Morton Grove cites a post-marketing safety trial for permethrin and states that no significant difference was found between the rate of serious adverse events reported for lindane and permethrin (*American Journal of Public Health* 1992; 82: 857-861). In this study, 8 adverse effects from any treatment regimen were considered "medically important". There was no

statistically significant difference for these "medically important" events among various regiments. However, Morton Grove fails to mention that in this study, lindane caused significantly more *total* adverse reactions than permethrin (when considering all treatments for which follow-up information was obtained).

In the same letter, Morton Grove also refers to a *New England Journal of Medicine* article and states "data from the largest study comparing permethrin and Lindane for the treatment of scabies treatment showed comparably high rates of clinical cure for both of these scabicidal medications." The article actually states [emphasis added]: "Permethrin and lindane are the two most studied topical treatments for scabies. A Cochrane metaanalysis of four randomized trials comparing these agents indicated that **permethrin (given as a single overnight application) was more effective than lindane** (odds ratio for clinical failure, 0.66; 95 percent confidence interval, 0.46 to 0.95). However, there was considerable heterogeneity in effects among studies in the meta-analysis. In the largest trial, there was no difference in clinical cure rates; at an average of 28 days after treatment, complete resolution had occurred in 181 of 199 patients treated with permethrin (91 percent) and in 176 of 205 patients given lindane (86 percent).

Again, the official medication guides (labels) for Morton Grove's Lindane Shampoo USP 1% and Lindane Lotion USP 1% state that permethrin is *safer* than lindane: "The only time Lindane Shampoo [or Lotion] is used first is when someone cannot use safer medicines, which may include permethrin or crotamiton."

Nevertheless, the **potential neurotoxicity of lindane, especially with repeated applications, has limited its use**; the product is no longer available in the United Kingdom or Australia. In an in vitro model assessing systemic exposure during conditions of overuse, the **risk of adverse effects with the use of 5 percent permethrin cream was estimated to be lower by a factor of at least 40 than the risk associated with the use of 1 percent lindane lotion**. In patients, the rate of central nervous system side effects reported by physicians to be at least possibly related to permethrin was low in a 1996 report (1 per 500,000 U of distributed permethrin), with no serious events. Despite its higher cost than lindane, **5 percent permethrin is recommended by the Centers for Disease Control and Prevention (CDC) as firstline topical therapy for scabies**."

Disputed Statement K: "Lindane is acutely toxic to the nervous system and can cause numbness, motor restlessness, anxiety, tremors, cramps, and unconsciousness."

Referenced as: 19k, 20k, 21k

Response: This statement is not false.

Similar findings were published in *Drugs* in a report entitled, "Pharmacotherapy of Ectoparasitic Infections": "Acute lindane intoxication in humans results in central nervous system (CNS) symptoms, such as numbness, motor restlessness, anxiety, tremor, cramps, and unconsciousness which can evolve to coma and death by respiratory paralysis and/or circulatory collapse within the first 24 hours after oral ingestion"(2001; 61(8): 1067-1088). Morton Grove challenges the use of the study because it claims such effects only occur with mis-use, however, other sources indicate that serious adverse effects can occur with proper use:
The U.S. Food & Drug Administration in a document entitled, "FDA Public Health Advisory: Safety of Topical Lindane Products for the Treatment of Scabies and Lice" states [emphasis added]: "The risk of neurologic side effects associated with Lindane is known from clinical trials,

spontaneous post-marketing reporting data and literature reports. These side effects have ranged from dizziness to seizures. In post-marketing reports, neurologic side effects occurred in patients who misused Lindane, **as well as in patients who used Lindane according to labeled instructions**. Among the adverse event reports in the FDA database, 70% reported neurologic events including seizure, dizziness, headache and paresthesia." Further, the FDA Public Health Advisory states "Of the adverse event cases in the FDA database with a serious outcome (hospitalization, disability or death), only **20% used Lindane according to the directions in the label**."

In addition, an article in the journal *Pediatric Dermatology* states, "Lindane is widely distributed throughout the body and slowly metabolized. It has a predilection for storage in fatty tissue as well as the brain, and its levels rise rapidly with repeated frequent applications. Adverse effects due to transcutaneous absorption of lindane include central nervous system irritability, insomnia, vertigo, convulsions, vomiting, diarrhea, restlessness, muscular spasm, loss of equilibrium, and collapse. Rare adverse effects include aplastic anemia, blood dyscrasia, myocardial arrhythmia, and paresthesia of the face and extremities. Neurotoxicity is an important and frequently observed adverse effect of therapy for scabies or pediculosis following repeated applications of lindane" (2004; 21(5): 597–599).

Also, the official medication guides (labels) for Morton Grove's Lindane Shampoo USP 1% and Lindane Lotion USP 1% state [emphasis added] "Lindane Shampoo [or Lotion] may cause serious side effects such as **seizures (convulsions, fits) or death**. Lindane Shampoo [or Lotion] can also make you feel sleepy dizzy, or can cause **body shaking** that you cannot control." Further, "Although seizures were almost always associated with ingestion or misuse of the product (to include repeat retreatment), **seizures and death have been reported when Lindane Shampoo [or Lotion] was used according to directions**."

MORE INFO: An article in the journal *Psychosomatics* states "Of all the isomers [of hexachlorocyclohexane], the gamma-isomer (lindane) has the highest **acute toxicity** in humans." The article describes long-term effects of lindane poisoning which included symptoms mentioned in our statement. Such symptoms included acute central nervous symptoms, major motor ticks, sustained shaking, numbness of tongue and face, leg cramps, and anxiety. (1999; 40(6): 513-517)

Disputed Statement L: "Fourteen other deaths have been attributed to Lindane, but have not been confirmed. All of these 14 deaths involved topical application; in 5 cases, use was in accordance with the directions."

Referenced as: 19l, 20l, 21l

Response: In our July 17, 2006 letter, we agreed to clarify this statement.

Although we used the word attributed in this sentence, we do qualify the statement and say that the deaths "have not been confirmed."

The Ecology Center denies that its statement was materially false or that Morton Grove was defamed by any statements published or spoken by the Ecology Center or its representatives. Nonetheless, the Ecology Center is committed to timely and informative publication of material facts on matters of public health. This statement was distributed in a draft fact sheet to a small number of individuals associated with non-profit organizations that are part of a coalition that

works with the Ecology Center, and to one member of the Michigan legislature. The fact sheet was draft and was never subsequently used. Accordingly, the Ecology Center will publish a clarification statement in an updated fact sheet that will be distributed to the Michigan legislator and to members of our coalition who received the previous fact sheet.

Our proposed correction:

> "In a previous document regarding Lindane, we reported that, "Fourteen other deaths have been attributed to Lindane, but have not been confirmed." We should have reported that fourteen deaths have been **associated** with – but not **attributed** to – the use of Lindane."

Disputed Statement M-1: "Exposure to Lindane can also cause effects on the blood, immune, and nervous systems, and the liver and kidneys."

Referenced as: 19m

NOTE: This specific statement only appeared in the complaint sent to Jon Fliegel, and was not officially addressed in our response letter dated July 17, 2006. However, the statement is not false and does not require a clarification/retraction.

Response: This statement is not false. This information appears in a "Hazard Summary" published by the U.S. Environmental Protection Agency. The Ecology Center did not claim that these effects appeared in human studies. The results reflect findings from animal studies, which are standard and appropriate methods of determining potential human health effects. Furthermore, according to the EPA Hazard Summary, similar effects were noted in chronic inhalation exposures in *humans* including "effects on the liver, blood, and nervous, cardiovascular, and immune systems." (See response for Statement M-2 for more information)

Disputed Statement M-2: "Chronic oral exposure [to Lindane] includes effects on the blood, immune, and nervous systems, and the liver and kidneys."

Referenced as: 20m, 21m

Response: This statement is not false. This information appears in a "Hazard Summary" published by the U.S. Environmental Protection Agency. The Ecology Center did not claim that these effects appeared in human studies. The results reflect findings from animal studies, which are standard and appropriate methods of determining potential human health effects.

In fact, the official medication guides (labels) for Morton Grove's Lindane Shampoo USP 1% and Lindane Lotion USP 1% states [emphasis added] "Predictions of fetal risk **rely heavily on animal data**. However, animal studies may fail to predict effects in humans or may overstate such risks." Also, "**Animal data suggest that lindane may increase the likelihood of neurologic developmental abnormalities**, based on findings at systemic exposures close to that expected in humans when Lindane Lotion is used to treat scabies."

According to the ATSDR Toxicological Profile for Lindane [emphasis added] "Extrapolating animal toxicity data to predict human risk from HCH exposure appears to be reasonable since

similar effects are seen in both species.…**rodents appear to be adequate models for a variety of human effects of HCH exposure**…"

- **Blood:** "Significant suppression in bone marrow cellularity, erythrocyte precursors, and granulocyte-macrophage progenitor cells, and residual progenitor cell damage were reported in male B6C3F1 mice given 20 or 40 mg gamma-HCH/kg/day by gavage in corn oil for 3 days."
- **Immune system:** "Some evidence of possible immunotoxic effects of gamma-HCH [in humans] is available from acute- and intermediate- duration studies in animals..." "antibody response has been reported depressed in rates, rabbits, and mice exposed to gamma-HCH. Biphasic effects on immunosuppression were reported in mice fed gamma-HCH. This is suggestive evidence that HCH may affect the human immune system."
- **Liver:** Hepatocellular damage as indicated by elevation in serum aminotransferases and decrease in hepatic soluble enzymes was found in rats given 72 mg/kg/day gamma-HCH for 2 weeks. Significant increases in hepatic microsomal cytochrome P-450 levels and increases in hepatic microsomal superoxide anion production and cytoplasmic superoxide dismutase activity and lipid peroxidation were found in Wistar rats fed diets containing 1.8 mg/kg/day gamma-HCH for 15 or 30 days.
- **Nervous:** "In humans, the most commonly reported effects associated with oral exposure to gamma-HCH are neurological. Most of the information is from case reports of acute gamma-HCH poisoning."
- **Kidney:** "Progressive renal failure was seen in a woman who died 11 days after intentionally ingesting 8 ounces of a 20% gamma-HCH solution."

The ATSDR Toxicological Profile "similar clinical toxic effects resulting from HCH exposure have been observed in laboratory animals dosed experimentally ***and*** humans experiencing occupational, therapeutic, and accidental domestic exposures to HCH. These include neurological, hepatic, hematological, and dermatological effects."

Furthermore, effects similar to those noted in our statement have been shown in chronic human exposure to lindane. According to the EPA Hazard Summary, similar effects were noted in chronic inhalation exposures in *humans* including "effects on the liver, blood, and nervous, cardiovascular, and immune systems."
An article in *Psychosomatics* states Lindane has "teratogenic, **immunotoxic**, and **neurotoxic** properties." "Lindane and other organochlorine insecticides have been shown on repetitive exposure to produce **hepatic**, **neuronal**, **renal**, and testicular damage, as well as **bone marrow disorders**, **peripheral paresthesias and neuropathies**, muscular weakness, impaired coordination, **aplastic anemia, and agranulocytopenia**" (1999; 40(6): 513-517).

Disputed Statement N: "Studies have shown a positive association between lindane use and increased risk of childhood leukemia and brain cancer."

Referenced as: 19n, 20n

Response: This statement is not false. In a study published in *Archives of Environmental Contamination and Toxicology*, the authors conclude that, "In comparisons to friend controls, significant positive associations [with brain cancer] were observed for use of pesticides to control nuisance pests in the home, no-pest-strips in the home, pesticides to control termites, **Kwell® shampoo [lindane]**, flea collars on pets, diazinon in the garden or orchard, and herbicides to control weeds in the yard."(1993;24(1):87-92). A summary of this study is presented in many

published articles including the ATSDR Toxicological Profile for Hexachlorocyclohexanes: "A case-control study surveying childhood brain cancer cases among Missouri residents found that the odds ratios for the use of Kwell, a shampoo containing lindane for lice control, were slightly elevated during the first 7 months of age to diagnosis (Davis et al. 1992). Thus, **Kwell use was significantly associated with childhood brain cancer compared to controls.** However, this study was limited by small sample sizes, potential recall bias in questionnaires, multiple comparisons, and the lack of detailed exposure information."

In a study published in *Occupational Environmental Medicine*, the authors concluded that "the use of shampoos to treat pediculosis was associated with childhood leukemia (OR = 1.9, 95% CI 1.1 to 3.2)," and lindane was included in this calculation. The ATSDR Toxicological Profile for Hexachlorocyclohexanes states "A number of case reports are available from individuals who had exposure to gamma-HCH in the home, during the handling of the pesticide, or from a nearby formulating plant. Effects that have been described in these case reports include hematological effects including granulocytopenia, aplastic anemia, **paramyeloblastic leukemia**, and pancytopenia."

MORE INFO: An article in the *Israel Medical Association Journal* stated that "eleven instances of aplastic anemia and two of **leukemia** caused by contact with lindane were reported" (2006; 8:196-199). The California Office of Environmental Health Hazard Assessment stated that "granulocytopenia, aplastic anemia, **paramyeloblastic leukemia**, and pancytopenia have been reported in case reports of individuals exposed to lindane and other pesticides in the home or in occupational settings" (Public Health Goal for Lindane in Drinking Water, February 1999). An article in the *American Journal of Industrial Medicine* stated "We previously reported an **association between agricultural use of lindane and risk of non-Hodgkin's lymphoma and leukemia**" (1998; 33:82-87). The Healthy Children Project reported that "**low-level exposures [to lindane] are associated with acute leukemia in children**" (www.healthychildrenproject.org/exposures/pesticides.html).

Disputed Statement O-1: "Among reports in the Toxic Exposure Surveillance System (TESS) database, unintentional ingestion of Lindane was more likely to produce illness than unintentional ingestion of the other three alternative head lice medications combined."

Referenced as: 19o, 20o

NOTE: This specific statement only appeared in Jon Fliegel and Bill Weil's letters, and was not officially addressed in our response letter dated July 17, 2006. Our official response letter addressed Disputed Statement O-2 (see below), which includes the above quote and an additional statement. Nonetheless, the above statement is not false.

Response: This statement is not false. These findings were published by the U.S. Centers for Disease Control in 2005. The report states, "Among TESS reports, unintentional lindane ingestions were more likely to produce illness (857 illnesses of 1,463 ingestions [58%]) than unintentional ingestions of each of three other medications, and more likely to produce illness than all three of those medications combined (523 illnesses of 1,691 ingestions [31%]; odds ratio = 3.16, 95% confidence interval = 2.72 –3.67)" (*Morbidity and Mortality Weekly Report* 2005; 54(21): 533-535). This publication is cited in the document.

Disputed Statement O-2: "Among reports in the Toxic Exposure Surveillance System (TESS)

database, unintentional ingestion of Lindane was more likely to produce illness than unintentional ingestion of the other three alternative head lice medications combined…. An example of unintentional ingestion: A boy age 3 ingested 1 teaspoon of
1% Lindane shampoo and the mother induced vomiting. The boy collapsed and had a tonic-clonic seizure lasting 4-5 minutes and was rushed to the hospital. He was released 3 hours later in stable condition."

Referenced as: 21z

Response: These statements are not false. These findings were published by the U.S. Centers for Disease Control in 2005. The report states, "In November 2004, the
Washington State Department of Health reported that a boy aged 3 years ingested approximately 1 teaspoon of 1% lindane shampoo from a previously used 2-ounce bottle. Subsequently, the mother induced vomiting in the boy twice; 1 hour later the boy collapsed and experienced a tonic-clonic seizure lasting 4-5 minutes. After 3 hours, the child was discharged from the emergency department in stable condition." The report also states, "Among TESS reports, unintentional lindane ingestions were more likely to produce illness (857 illnesses of 1,463 ingestions [58%]) than unintentional ingestions of each of three other medications, and more likely to produce illness than all three of those medications combined (523 illnesses of 1,691 ingestions [31%]; odds ratio = 3.16, 95% confidence interval = 2.72 –3.67)" (*Morbidity and Mortality Weekly Report* 2005; 54(21): 533-535). This publication is cited in the document.

MORE INFO: According to Morton Grove Lindane Shampoo was repackaged to 2 oz. bottles to further enhance safety and minimize potential for misuse. However, despite the smaller packaging, significant toxicity can occur with ingestion of as little as 5 ml (0.17 oz→1/6 bottle) of lindane (*Journal of Emergency Medicine* 2000 18(1): 51-53).

Disputed Statement P: Lindane is considered "the least effective treatment."

Referenced as: 19p, 20p, 21p

Note: This statement was previously combined with "Recent cure rates for lindane have been reported as low as 17%", in the letter from Winston & Strawn dated June 12, 2006. This other statement is now addressed separately as statement Q.

Response: This statement is not false.

A publication of the U.S. Centers for Disease Control reported that, "Lindane also had the **slowest pediculicidal and least effective ovicidal activity** compared with three other approved pediculicides" (*Morbidity and Mortality Weekly Report* 2005; 54(21): 533-535).

An article published in *Archives in Dermatology* in 2001 concluded that "one percent lindane shampoo was the slowest-acting pediculocide and least effective ovicide" (137: 287-292). Another article in *Archives of Dermatology* reported that "the slowest and least effective of all products tested was once again 1% lindane shampoo" (2002; 138: 200-224). Although these studies are "in-vitro" analyses, they are widely cited in the peer-reviewed literature and acceptable in scientific debate.

Similarly, a 2004 publication of the medical journal *Pediatrics* advised that reported recent cure

rates for Lindane were 17%, the lowest of four "neurotoxic pediculicides used to treat head lice" (114:e275-e279).

A publication of the California Department of Health Services reported that, "Lindane, used since the 1950s, is both **the least effective** and, by far, the most toxic" treatment for head lice (*California Morbidity*; March 1996).

A systematic review of journal articles on the effectiveness of head lice treatments concluded that lindane is "**not sufficiently effective" to justify its use**, and its risk of treatment failure was "at least eight times higher" than permethrin. Furthermore, in the seven studies selected for the analysis, lindane showed the lowest cure rate (43%) after 14 days. (*British Medical Journal* 1995; 311: 604-608).

The Merck Manual: Home Edition states "Lindane…also cures lice infestation but is **not as effective as the other preparations** and is not recommended for children because of neurologic side effects" (www.merck.com/mmhe/print/sec18/ch210/ch210c.html).

In an INFORM fact sheet (an environmental non-profit organization), they report the efficacy rates of selected head lice studies reviewed in 1995 (Lindane-Free Head Lice Prevention and Treatment, www.informinc.org):

Pediculocide	Efficacy Rate
Permethrin 1% crème rinse	96%-100%
Pyrethrin 0.3% lotion	94%
Malathion 0.5% lotion	98%
Lindane 1% shampoo	43%-93%

Disputed Statement Q: "Recent cure rates for lindane have been reported as low as 17%."

Referenced as: 19q, 20q, 21q

Note: In the Winston & Strawn letter dated June 12, 2006, this statement was combined with "Lindane is considered the least effective treatment," but is now listed as a separate statement in the lawsuit. The other statement is now addressed separately as statement P.

Response: These statements are not false. A study in *Archives of Dermatology*, concluded that "the slowest and least effective of all products tested was once again 1% lindane shampoo, killing only 2% of lice at 20 minutes and 8% at 1 hour; after 3 hours of continuous exposure only **17%** of the lice tested were dead" (2002; 138:220-224).

Winston & Strawn challenged our use of this study because it was an "in-vitro" analysis and doesn't provide a true "cure rate". However, this study is scientifically acceptable and widely cited in the literature. For example, a 2004 publication of the medical journal *Pediatrics* cited this study as a "**cure rate**" for lice and reported recent cure rates for Lindane were 17%, the lowest value in the table comparing four "neurotoxic pediculicides used to treat head lice" (114:e275-e279). Also, an article in *Mayo Clinic Proceedings* journal references this study and states "In a recent comparison of lindane, malathion, pyrethrin, and permethrin used to treat both treatment-sensitive and treatment-resistant lice collected from a patient population in Florida, 1% lindane was the slowest and least effective product, **apparently killing no lice after 10 minutes, the**

recommended application time for lindane shampoo. After 3 hours of exposure, only **17%** of lice were dead" (2004; 79: 661-666).

Disputed Statement R: "Will a phase out lead to consumers purchasing Lindane from Canada? No. Although obtaining Lindane does not require a prescription in Canada, it is only available behind-the-counter and requires a pharmacist's recommendations (and possibly a referral from a physician)."

Referenced as: 19r, 20r, 21r

Response: This statement is not false. Part of these statements appears in a document published by the U.S. Environmental Protection Agency entitled, "Assessment of Lindane and Other Hexachlorocyclohexane Isomers." The document advises that, "Lindane is approved in Canada for lice and scabies treatment as a non prescription "behind the counter drug"… Lindane products have been classified as Schedule 2 products by the National Association of Pharmacy Regulatory Authorities (NAPRA), which means that 'professional intervention from the pharmacists at the point of sale and possibly referral to a practitioner' is required."

MORE INFO: Morton Grove fails to include our entire statement. We qualify the above statement with: Also, with the wide availability of safer and more effective alternatives in the US, *it seems unlikely that a consumer would travel to Canada to purchase lindane*. Nonetheless, neither we nor Morton Grove can exactly predict if a phase out of lindane would result in purchasing the product from Canada. However, it is reasonable to assume that citizens would likely buy a widely-available lindane alternative at local pharmacies.

NOTE: Lauren attempted to purchase lindane from a Canadian pharmacy website (Rx Canada), and was not able to because they *required a prescription*.

In addition, in our own reading of the United States Code, it would be unlawful to purchase lindane from Canada:

Federal law prohibits the importation of pharmaceuticals that are dispensed without a valid prescription. (21 U.S.C. § 353(b)(1)).

Federal law prohibits the importation of an FDA-approved pharmaceuticals that is manufactured within the United States. (21 U.S.C. § 381(d)(1)). (NOTE: Not sure if this is relevant because lindane is NOT manufactured in the United States. Lindane is imported and *formulated* into Lindane Lotion and Lindane Shampoo by Morton Grove).

Both laws imply that it would be unlawful to purchase lindane from Canada (through internet or pharmacy without prescription). Michigan ban would likely result in physicians not prescribing lindane, but using alternatives.

Disputed Statement S: "One dose of Lindane can contaminate 6 million gallons of water."

Referenced as: 19s, 20s, 21s

Response: This statement is not false.

The Los Angeles County Sanitation Districts calculated that a single treatment of lindane for head lice, when rinsed down the drain, contributed enough lindane to the water entering treatment facilities to bring 6 million gallons of water over the CTR standard (Commission for Environmental Cooperation. The North American Regional Action Plan on Lindane and Other Hexachlorocyclohexane Isomers, 2005).

Note that in an article in *Environmental Quality Management*, the California calculation is cited the same way we cite it [emphasis added]: "Lindane can contaminate water resources, especially when its use is widespread. **A single head lice or scabies treatment can contaminate 6 millions gallons of water**—and cost an average of $4,000.00 to remove from wastewater (Winter 2002; 89-95).

MORE INFO: The following explanation of the California water quality issue is directly quoted from a Commission on Environmental Cooperation document (The North American Regional Action Plan on Lindane and Other Hexachlorocyclohexane Isomers, 2005):
"The state of California has taken regulatory action on lindane. In May 2000, the California Toxics Rule (CTR) established a new water quality criterion of 19 ppt (parts per trillion) lindane in existing or potential drinking water supplies for protection of public health based on potential cancer risk to humans. Studies conducted of water exiting the Los Angeles County Sanitation Districts' treatment facilities found both peak and mean levels in many cases to be higher than the new (state) effluent standards. These standards were equal to the US national water quality criterion for water bodies that are existing or potential drinking water sources. As available treatment technology was unable to adequately remove lindane from the water, a preventive strategy to allow compliance was required.

The Los Angeles County Sanitation Districts calculated that a single treatment for head lice, when rinsed down the drain, contributed enough lindane to the water entering treatment facilities to bring 6 million gallons of water over the CTR standard. Based on a review of California pesticide applicator records and physician surveys conducted by these same districts, there were no significant agricultural sources identified in the region, **indicating that nearly the entire load was the result of pharmaceutical use**. Initially, an education campaign with pharmaceutical lindane providers was started to discourage use. While this appeared to decrease the inflow levels of contamination, it was inadequate to comply with the new standards. A bill was then sponsored in the California assembly, which passed without opposition, to ban the sale of all pharmaceutical lindane in the state of California beginning in Jan 2002."

Furthermore, the hypothetical experiment cited by Morton Grove involving the theoretical dumping of lindane into Albany, NY water system is not based on the same water quality standard as California calculation. The EPA's MCL is 0.2 ppb (200 ppt). To the best of our knowledge, the "study" *only* appears on the www.lindane.com website that was funded by Morton Grove (and not in any peer-reviewed journals or government documents). Overall, the real data from California provide a real example of the impact of pharmaceutical lindane on water quality—and how a ban resulted in detectable decreases of lindane in water to below the California standard (see graphs from Los Angeles County Sanitation District).

Disputed Statement T: "ATSDR ranks Lindane 32 of 275 in the list of CERCLA priority

pollutants due to its toxicity, potential of exposure, and frequency of occurrence at National Priority Sites."

Referenced as: 19t, 20t, 21t

Response: This statement is not false. Hexachlorocyclohexane, Gamma (Lindane) is ranked #32 on the "2005 CERCLA Priority List of Hazardous Substances" which is prepared by the U.S. Department of Health & Human Services Agency for Toxic Substances & Disease Registry and the U.S. Environmental Protection Agency. The Ecology Center's statement accurately describes the List as "a prioritization of substances based on a combination of their frequency, toxicity, and potential for human exposure at NPL sites."

Disputed Statement U: "Lindane is a chlorinated pesticide (in the same group as DDT) used to treat lice and scabies. It is also used in agriculture as seed treatment for barley, corn, oats, rye, and wheat."

Referenced as: 19u, 20u, 21u

Response: This statement is not false. Overall, we do not say or imply that actual lindane medications are used in agriculture; they just have the same active ingredient—lindane. Lindane is the common name for the compound gamma-hexachlorocyclohexane (HCH).

The EPA discusses the uses for lindane in a similar manner. An EPA document entitled, "Lindane RED Facts" reports that, "Lindane is an organochlorine insecticide used as a pre-plant seed treatment for barley, corn, oats, rye, sorghum, and wheat…Lindane is also currently approved by the U.S. Food and Drug Administration (FDA) for use in pharmaceutical products intended to control head lice and scabies (mites) in humans."

Another EPA document states "In North America, lindane is used in agriculture, veterinary science, and public health…Lindane and the other HCH isomers are members of the organochlorine family of chemicals… Lindane, the gamma isomer, has been widely used as an insecticide for decades" (Lindane and other HCH isomers: Risk Assessment Fact Sheet).

The following articles support our classification of lindane as an organochloride pesticide in the same group as DDT. An article in *Mayo Clinic Proceedings* states "Lindane is an organochloride marketed in a 1% concentration shampoo. This agent has been under increased scrutiny because of its toxic adverse effects. Lindane has neurotoxic properties similar to those of DDT, killing lice by overstimulation of the parasite's central nervous system" (2004; 79: 661-666). An article in the journal *Drugs* states "The toxic effects of lindane in mammals…resemble those of other pesticides of this group [e.g. dichloro-diphenyltrichloroethane (DDT)] in causing mainly neurotoxic symptoms" (2001; 61(8): 1067-1088).

MORE INFO: Overall, we do not say or imply that actual lindane medications are used in agriculture (they just have the same active ingredient—lindane). However, pharmaceutical grade lindane ("p-grade") is a purified version of the *same* insecticide (gamma-HCH) used in agriculture. Pharmaceutical use of lindane poses particular health concerns given its direct application to human skin, especially in children. (The North American Regional Action Plan (NARAP) on Lindane and other Hexachlorocyclohexane (HCH) Isomers, 2005).

In the June 12, 2006 letter, Morton Grove argues that the alpha and beta isomers of HCH have been used in agriculture, and are responsible for some of the health effects we address. Alpha and beta-HCH have *no insecticidal properties*. These isomers were present as *inert ingredients* in technical grade lindane, which was banned in the U.S. in 1978. Also, alpha and beta-HCH are waste products of lindane production and breakdown (isomerization) products from its use. While they are more persistent in the environment (particularly beta-HCH) they are not "notably more toxic" than the gamma-HCH isomer, as Morton Grove alleges. The citation used by Morton Grove to support this claim actually says: "As with lindane, all other isomers of HCH cause acute and chronic neurotoxic effects and can produce liver and kidney effects" (The North American Regional Action Plan on Lindane and other Hexachlorocyclo-hexane (HCH) Isomers, 2005). Further, an article in *Psychosomatics* states "**Of all the [HCH] isomers, the gamma-isomer (lindane) has the highest acute toxicity in humans**" (1999; 40(6): 513-517).

Disputed Statement V: "A phase out of pharmaceutical lindane will likely prevent long-term neurological impairment in some patients, which would cost family members and society a large amount of resources."

Referenced as: 19v, 20w, 21aa

This statement was NOT included in the Winston & Strawn letter dated June 12, 2006, and therefore, we were not given a chance to respond to this statement in our official letter dated July 17, 2006. Nonetheless, the statement is not false.

The statement is a general opinion without strong, definitive language. It simply implies that a phase out of lindane would likely result in reduced poisonings and therefore reduced costs associated with emergency room visits, physician consultations, and treatments. Although the most severe cases of poisonings come from the mis-use of lindane medications, mis-use is a clinical reality. As noted in *Archives of Dermatology* (2002; 138:220- 224) and *Mayo Clinic Proceedings* (2004; 79: 661-666), the poor efficacy of lindane is a concern because it may result in reapplication or overuse of lindane. Patients may also mistake lindane for an oral medication, resulting in toxic health effects from ingestion (*Morbidity and Mortality Weekly Report* 2005; 54(21): 533-535).

Although rare, serious adverse effects (hospitalization, disability, death) from pharmaceutical lindane use have been reported to the FDA. Such serious events can reasonably be anticipated to have substantial costs for patients and families.

For example, a study published in *Psychosomatics* outlines the long-term effects of lindane poisoning from three applications of scabies treatment (1999; 40(6): 513-517).

- "This report documents a long-term case of severe hexachlorocyclohexane (lindane) poisoning in which, despite prompt medical treatment, the patient continued to experience neurological and psychiatric symptoms for **20 months after her poisoning**."
- "**The symptoms produced by these agents may last for weeks to months and patients often experience periodic relapses despite adequate therapy because of the initial lipid storage and subsequent redistribution of these chemicals.** Following partial recovery from an exposure, patients evidence an increased susceptibility to subsequent reexposure for about 3 months."
- "Sanfeliu et al. demonstrated that repetitive, low-level, nonconvulsant doses of lindane produced **long-term changes** in cerebral 2–14C-deoxyglucose uptake throughout the

subcortical structures of the brain, but particularly in the dorsal cochlear nucleus and the dentate gyrus. The researchers suggested that these increases in uptake in the subcortical regions of the brain…are responsible for the **functional alterations (mood, affect, sensations) seen during the course of long-term lindane poisoning**."

Disputed Statement W: "Lindane is no longer registered by the EPA for veterinary use in the United States due to its potential to cause cancer and birth defects."

Referenced as: 19w, 20x, 21bb

This statement was NOT included in the Winston & Strawn letter dated June 12, 2006, and therefore, we were not given a chance to respond to this statement in our official letter dated July 17, 2006. Nonetheless, the statement is not false.

According to the EPA, "**lindane is no longer registered for veterinary uses in Canada or the United States**." Currently, the only registered use for lindane in agriculture is a "seed treatment on six agricultural crops: barley, corn, oats, rye, sorghum, and wheat" (Lindane and Other HCH Isomers—EPA Risk Assessment Fact Sheet).

According to the Program on Breast Cancer Environmental Risk Factors, "use of lindane was restricted by the EPA due to **concerns over its potential to cause cancer and birth defects in animals**" (*Pesticides and Breast Cancer Risk: An Evaluation of Lindane*, 2006. http://www.envirocancer.cornell.edu/ factsheet/Pesticide/fs15.lindane.pdf).

The ATSDR Toxicological Profile for Lindane [emphasis added]: "February 1977, EPA issued a notice of Rebuttal Presumption Against Registration (RPAR), now called a Special Review, and continued registration of pesticide products containing gamma-HCH. EPA took this action in response to indications of gamma-HCH's **potential carcinogenic effect**, possible **developmental and reproductive effects**, possible blood dyscrasias, and delayed toxic effects, as well as its acute toxic effects seen in aquatic wildlife. In October of 1983, EPA issued a "Notice of Intent to Cancel Pesticide Products Containing gamma-HCH." The contentions concerning developmental and reproductive effects were successfully challenged by industry…The notice restricted certain applications of gamma-HCH on **livestock**, structures, and **domestic pets** to certified applicators or persons under their direct supervision. In November 1993, EPA issued a "Notice of Receipt of a Request for Amendments to Delete Uses" for several formulations of gamma-HCH powder, 99.5% technical-grade HCH, and dust concentrate, which would **delete from the pesticide label most uses of gamma-HCH for agricultural crops and use on animals and humans**. According to the EPA's most recent Registration Eligibility Decision (RED), **the only current food/feed use of gamma-HCH that is being supported for re-registration is seed treatment** on barley, corn, oats, rye, sorghum, and wheat."

According to an article in *U.S. Pharmacist* "In the 1970s the EPA began to examine the potential carcinogenicity, teratogenicity, and other toxicities surrounding lindane, resulting in the narrowing of lindane's agricultural uses. In accordance with the federal law mandating reevaluation of all pesticides first registered before November 1, 1984, to ensure safety standards, the EPA began to reevaluate lindane for reregistration purposes" (2003; 28(09)).

There is evidence in the literature that lindane causes cancer and birth defects in animals [emphasis added]:

According to the International Agency for Research on Cancer, "there is *sufficient evidence* that alpha-HCH, **lindane** and technical HCH are **carcinogenic in mice**" (IARC Monograph Volume 20, 1979).

"Researchers have found that the long-lasting chemical [lindane] can cause liver, kidney, neurologic, and immune system damage; **birth defects; cancer**; and death" (*Environmental Health Perspectives* 2001; 109(6):A254).
Lindane "damages human liver, kidney, neural and immune systems and **induces birth defects, cancer**, and death" (*J Soc Biol* 2002; 196(4): 325-38).
In a study of mallard embryos, "**lindane was teratogenic, resulting in multiple defects** but only at doses that were greater than five times the field level of application" (*Archives of Environmental Contamination and Toxicology* 2001; 11(1): 79-86).
In a study that exposed rat embryos to lindane, multiple defects were found including "distended anterior cardinal veins, thinning of the neuroepithelium in forebrain and hindbrain regions, and abnormal branchial arch development" (*Reproductive Toxicology* 1994; 8(4): 351-62).

Disputed Statement X: "A study in the journal *Clinical Infectious Diseases* states that 'the availability of efficacious agents with more favorable safety profiles has virtually eliminated its [Lindane] use for head lice in the United States."

Referenced as: 20v, 21v

Response: This statement is not false. The statement accurately reflects a statement made in an article published in *Clinical Infectious Diseases*. The article states, "However, the availability of efficacious agents with more favorable safety profiles has virtually eliminated its use for lice treatment in the United States." (2003; 36:1355-1361).

MORE INFO: Other sources also report similar findings. An article in *American Family Physician* states "lindane shampoo is used infrequently now because of concerns about neurotoxicity, resistance, and slow killing time" (2004; 69(2): 341-348). The CDC's *Morbidity and Mortality Weekly Report* states that there has been a "67% decrease in lindane prescriptions from 1998-2003" (2005; 54(21): 533-535). An article in *Mayo Clinic Proceedings* states "Although lindane was once considered a primary treatment of head lice, poor efficacy and serious adverse events have resulted in use restrictions" (2004; 79: 661-666).

Disputed Statement Y: "The authors 'strongly recommend its removal from the market' due to very poor pediculocidal and ovicidal effectiveness, potential toxic effects on nervous system, resistance, and environmental contamination."

Referenced as: 21x

Response: You have not alleged that this statement is false. This information was published in the *Archives of Dermatology.* The published article states, "In view of extremely poor pediculocidal and ovicidal activity, potential toxic effects on the central nervous system, resistance, and environmental contamination, we see no reason for, continued use of lindane in the United States, and as stated in Update 2000, we strongly recommend its removal from the market" (2002;

138:220-224). This journal article is cited in the document. Similarly, the Michigan Department of Community Health "Michigan Head Lice Manual" advises, "The State of Michigan does not recommend using lindane," and cites reasons such as central nervous system toxicity in humans if used incorrectly, low ovicidal activity, and resistance.

MORE INFO (does not appear in our response): Many medical organizations in the state of Michigan support a phase out of pharmaceutical lindane including: Michigan State Medical Society, Michigan Chapter of the American Academy of Pediatrics, Michigan Nurses Association, Michigan Council on Maternal and Child Health, Wayne County Medical Society, and the Michigan Council of Nurse Practitioners.
The *Mayo Clinic Proceedings* journal states "The adverse effects associated with lindane are serious enough that recommendations range from using it with caution to withdrawing it from the market entirely. The sale of any product containing lindane for the treatment of lice or scabies in humans has been banned by the state of California because of concerns about neurotoxicity and negative effects on the environment. Recommendations for the withdrawal of lindane products are based on concerns that its poor efficacy will result in reapplication and overuse, which increase the risk of adverse events" (2004; 79: 661-666). According to the California Department of Health Services, "Given that 1% lindane shampoo (Kwell®, etc) is less effective and has more potential toxicity than the easily available alternatives, there is no reason to continue prescribing this material for the control of head lice in California" (Head Lice (Pediculus humanus capitis): A Heady, Nitpicky and Lousy Problem. *California Morbidity*, March 1996).

Disputed Statement Z: "This in vitro study compared the efficacy of various pediculocides and ovicides at determined time intervals over three hours. Lindane was least effective of the six products tested, killing only 61% of lice and 24% of eggs in three hours. When compared to the results of a similar study done in 1984, the recent study showed Lindane to be much less effective in killing lice and nits. This suggests a possible increase in resistance to Lindane among lice."

Referenced as: 21w

Response: This statement is not false. The statement summarizes findings that were published in the *Archives of Dermatology*. The published article states, "The 1% lindane shampoo displayed poor pediculocidal and ovicidal activity. After 3 hours of observation, lindane had killed only 61% of the lice tested, and its ovicidal activity (24%) was the lowest of all the products tested. Lindane also performed poorly in comparison with results from the previous study, showing a sharp decline in ovicidal activity. In 1984, 1% lindane shampoo was available as a brand name product (Kwell). The decline in ovicidal activity may be due to changes in the sourcing of ingredients that have occurred over the years or possibly to the development of resistance"(2001; 137:287- 292). This journal article is cited in the document.

Disputed Statement AA: "The use of pediculocidal shampoos (including Lindane) was associated with increased risk of childhood leukemia, with odds ratios of 1.5 (95% CI 0.9 to 2.5) for use of pesticide in one head lice episode and 1.9 (9 5% CI 1.1 to 3.3) for use of pesticide in two or more episodes."

Referenced as: 21y

Response: In our July 17, 2006 letter, we agreed to clarify this statement.

As it happens, this statement was only published in a draft summary sheet distributed to one member of Michigan legislature and a few members of our coalition.

The Ecology Center denies that its statement was materially false or that Morton Grove was defamed by any statements published or spoken by the Ecology Center or its representatives. Nonetheless, the Ecology Center is committed to timely and informative publication of material facts on matters of public health. This statement was distributed in a draft fact sheet to a small number of individuals associated with non-profit organizations that are part of a coalition that works with the Ecology Center, and to one member of the Michigan legislature. The fact sheet was draft and was never subsequently used. Accordingly, the Ecology Center will publish the following statement in an updated fact sheet that will be distributed to the Michigan legislator and to members of our coalition who received the previous fact sheet.

Our proposed correction:

> "In a previous document, we reported that "The use of pediculocidal shampoos (including lindane) was associated with an increased risk of childhood leukemia, with odds ratios of 1.5 (95% CI 0.9 to 2.5) for use of pesticide in one head lice episode and 1.9 (95% CI 1.1 to 3.3) for use of pesticide in two or more episodes." We should have reported that "Overall, the use of shampoos to treat pediculosis was associated with childhood leukemia (odds ratio = 1.9, 95% CI 1.1 to 3.2)."

Disputed Statement BB: "Lindane is easily absorbed into fat and neural tissues and has caused neurotoxicity and anemia in patients."

Referenced as: 21n

Response: This statement is not false. A 2003 report published in *Clinical Infectious Diseases* advised that, "Lindane is easily absorbed into adipose and neural tissue and has caused neurotoxicity and anemia in patients" (36:1355-1361). This journal article is cited in the document.

MORE INFO: An article in *Pediatric Dermatology* states "Being lipid soluble, it is also readily absorbed via transcutaneous absorption, ranging from 9% to 80%...Adverse effects due to transcutaneous absorption of lindane include central nervous system irritability, insomnia, vertigo, convulsions, vomiting, diarrhea, restlessness, muscular spasm, loss of equilibrium, and collapse. Rare adverse effects include aplastic anemia…" (2004; 21(5): 597-599). A report on the FDA website states "it [lindane] has higher percutaneous absorption than other approved scabicides and pediculocides. This greater systemic exposure may translate to a greater potential for serious adverse events… Lindane has a smaller safety margin than the other treatments available…" (Mathis, L. Assessment. 2003. www.fda.gov/cder/drug/infopage/lindane/).

Disputed Statement CC: "Lindane resistance among head lice has been reported in the United States, the United Kingdom, the Netherlands, and Panama." (2003; 36:1355-1361).

Referenced as: 21o

Response: This statement is not false.

The statement is a direct quote from a journal. A publication of the medical journal *Clinical Infectious Diseases* reported that, "Lindane resistance among head lice has been reported in the United States, the United Kingdom, the Netherlands, and Panama" (2003; 36:1355-1361).

Similarly, a 2002 publication of the medical journal *Pediatrics* reported that Lindane "has low ovicidal activity … and resistance has been reported worldwide for many years"(110:638-643). The Michigan Department of Community Health states "resistance [for lice] has been reported worldwide for many years" (Michigan Head Lice Manual, July 2004).