CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

4/13/87

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Lindane Special Review - Reassessment of Toxicological Significance of Kidney Lesions Observed in Rat Studies

Tox. Chem. No.: 527

FROM: Edwin R. Budd, Section Head
Review Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Concurred 4/9/86

TO: Joanna Dizikes
Special Review Branch
Registration Division (TS-767C)

THRU: Theodore M. Farber, Ph.D., Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Theodore M. Farber 4/13/87

In response to a request from the Science Integration Staff/HED and the Special Review Branch/RD, Toxicology Branch (TB) has reconsidered its assessment of the toxicological significance of kidney lesions observed with lindane in two rat studies.

Prompting this reconsideration was a recent memorandum from Exposure Assessment Branch (EAB) by David Jaquith (no date), in which it was argued that an absorption rate of 100 percent for respiratory exposure should be used for risk assessments relating to forestry workers and to hardwood log and lumber workers. It was also argued in the same memorandum that it would be infeasible and of little usefulness to require the submission of a "particle size and vapor distribution" study, as previously recommended by TB. A dermal exposure study for hardwood log and lumber workers was requested, however. See Attachment 1.

TB was specifically asked to consider the EAB memorandum; to recalculate margins of safety (MOSs) if necessary, based on the memorandum; and to again present an opinion as to whether or not lindane should be considered a candidate for Special Review.

Regarding the EAB memorandum, TB is persuaded to not require the submission of a "particle size and vapor distribution" study. TB will therefore continue to use an absorption rate of 100 percent for respiratory exposures in risk assessments for forestry workers and for hardwood log and lumber workers.

Since MOSs previously calculated by TB assumed an absorption rate of 100 percent for respiratory exposure (and of 10 percent for dermal exposure), the MOSs shown below remain unchanged. See Attachement 2 (TB memorandums by John Doherty, dated June 24 and August 14, 1986).

Forestry Workers

Respiratory exposure (only)	MOS = 5.9
Respiratory and dermal exposure (combined)	MOS = 0.4

Hardwood Log and Lumber Workers

Respiratory exposure (only)	MOS = 8.2
Respiratory and dermal exposure (combined)	MOS cannot be calculated due to lack of dermal exposure information (recently requested by EAB).

TB has no objection to lindane being considered a candidate for Special Review, based on the MOSs presented above, which are clearly sufficiently low to engender serious concern. The toxicological endpoint, as discussed many times previously, is kidney effects observed in a 90-day feeding study in rats (NOEL = 0.03 mg/kg/day) and in a 90-day inhalation study in rats (NOEL = 0.1 mg/M^3, calculated to be equivalent to 0.0106 mg/kg/day). The MOSs presented above were based on the latter, more sensitive study.

TB would also point out, however, that the totality of toxicological evidence available at this time is not strongly convincing (in a quantitative sense) and that these

MOSs are undoubtedly "worst case" estimates of the potential risks to workers. In an attempt to "upgrade" the toxicological data base directly relating to this matter, TB has already requested the submission of additional toxicity studies, including a 90-day inhalation study (in a species other than rats), two 90-day dermal studies (in rats and another species) and two dermal absorption studies (in rats and another species). The request for studies on species other than the rat was made to ascertain whether these kidney lesions may or may not be species-specific. If kidney lesions are observed in additional species, the likelihood that humans are subject to the same lesions is greatly increased.

It might also be recalled that some question continues to exist regarding the pathological seriousness of the kidney lesions of concern. These lesions are not considered to be life-threatening in nature and, in fact, have been shown to be slowly reversible following cessation of dosing. Furthermore, only the anatomical lesion has been demonstrated in experimental animals. Physiological disturbances of kidney function have not been observed. On the other hand, humans with existing kidney damage or prone to such damage may be considerably more vulnerable to kidney damage produced by lindane than other humans.

Numerous other questions not directly related to toxicological studies have also been raised and not yet fully answered. Many of these questions, together with the "pros" and "cons" of possible answers, have been summarized in the Policy Group Briefing Document on Lindane prepared by Carol Monroe, dated September 9, 1986. See Attachment 3.

In summary, TB would support a decision to refer lindane to Special Review at this time notwithstanding the several unresolved issues and unanswered questions regarding the chemical. An additional benefit of such a decision, if it were made, would be to elevate the concerns of the Agency to a higher level of visibility in a formal manner. Under these conditions, registrants of lindane products might be inclined to address outstanding issues and study requirements more punctually and comprehensively than otherwise, and a final regulatory decision might be reached more expeditiously.

Attachments

cc: Anne Barton (HED)
Amy Rispin (SIS)
Carol Monroe (SIS)
David Jaquith (EAB)
John Doherty (TB)

FILE - Lindane

rec. by Budd on 1/8/87

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Attachment #1

COPIES TO SIS from A. Barton

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Exposure of Workers to Lindane During Forestry and Hardwood Lumber Use

TO: Anne Barton, Deputy Director
Hazard Evaluation Division (TS-769C)

THRU: Joseph C. Reinert, Chief
Special Review Section
Exposure Assessment Branch (TS-769C)

In August 1985, EAB completed a series of exposure assessments for the insecticide lindane (1). A number of exposure scenarios were evaluated. The exposure estimates for workers applying lindane for forest insect control, which were based on a number of surrogate studies in which backpack equipment was used, yielded potential hourly exposures of 5.3 and 0.094 mg for the dermal and respiratory routes, respectively. These values were not corrected for dermal or respiratory absorption and assumed that 100 percent of the airborne material was respirable. While numerous exposure studies were required for other uses of lindane, EAB did not request further additional studies to refine the estimates of exposure for forest or hardwood use.

EAB has recently been requested to re-examine it's assumption of complete respirability of airborne lindane and to consider requiring a particle size and vapor distribution study for the lindane spray. EAB believes that it is reasonable to use an assumption of complete respirability of airborne lindane for the conduct of a risk assessment for this compound and that such a study is both technically difficult and unnecessary.

Lindane is a moderately volatile compound with a vapor pressure of approximately 10^{-5} mm Hg at 20°C (3). The measurement of aerosol size and vapor distribution for such a volatile compound presents a number of difficulties. Of the several methods available for determination of particle size distributions, those used most often for obtaining personal samples involve the trapping

of the aerosol on filters followed by microscopic examination, impaction on stages followed by quantification, or analysis using electronic instruments, often utilizing light scattering or the electrical properties of aerosols. Personal impactors, using low sampling rates, are often used under actual work conditions.

The trapping of volatile materials on filters or plates, which is a prerequisite for many of the above mentioned methods, is subject to significant losses due to volatilization of the material being examined. The flow of air through filters has been shown to vaporize volatile pesticides trapped on the filters. Lewis (4) found that only 76 percent of lindane was present on glass fiber filters after 1 hour under static (no air flow) conditions. The material had completely disappeared within 24 hours at a flow rate of 280 liters per minute. Losses during sampling at flow rates of 2-5 liters per minute, rates often used for industrial hygiene sampling, have not been determined but may be highly significant. Particles deposited on the stages of an impactor remain subject to the sample airstream and are subject to the same problems with volatilization as conventional filter samples.

Measurement of aerosols under field conditions by electronic or optical instrumentation also has a number of problems. The instrumentation required for such analysis is rather delicate and the results often difficult to validate. The use of these devices under field conditions would be extremely difficult and the accuracy of the results hard to prove.

Technical difficulties in the conduct of a study are not, by themselves, sufficient reason to fail to perform the work. EAB believes that many of the principles discussed as sampling problems also apply to the actual exposure situation. Generation of liquid aerosols of volatile materials creates a dynamic exposure scenario in which the respiratory exposure will be to a combination of both vapor, from the rapidly vaporizing aerosols, and the aerosol form of the material. Both vapors and small aerosols (less than 1 um) can be drawn deep into the lung and may reach the alveoli where they can be rapidly absorbed into the bloodstream (5).

Larger aerosols would tend to be trapped in the upper respiratory tract by sedimentation or impaction (6). The material may then vaporize from these warm sites, generating material that could reach the alveoli. While there may be some oral exposure resulting from the dissolution of the aerosol in the mucous layers followed by coughing up and swallowing, EAB believes that the most prudent approach is to consider all of the airborne material to be respirable and to use the appropriate potency when conducting risk assessments for these workers.

EAB has also reviewed it's exposure assessment for workers using lindane for treatment of hardwood logs and lumber. The

exposure assessment was based on a single study conducted by Zoecon Corporation (Accession Number 264951) and assumed that dermal exposure was negligible compared to respiratory. The treatment of rough sawn lumber by "green chaining" involves the direction of the freshly cut wood into a dip tank containing lindane and/or other chemicals. The treated wood is then removed from the tank and transported by conveyor. As the wood is transported, it is graded and stacked manually. Workers wear heavy rubber boots, aprons, and gloves while performing these tasks. In addition, cargo hooks are often used to handle the wet lumber. This exposure scenario probably generates little aerosol and the airborne lindane is likely to be in the vapor form. EAB assumes that all of this material is respirable.

The study was conducted in 1981 and, while not up to current EAB standards, probably provides a reasonable estimate of the respiratory exposure of lumber yard workers. However, the total exposure of these workers quite probably has some dermal component that was not measured. In order to properly determine the total exposure of workers using lindane to treat hardwood logs and lumber a study will be necessary. Any studies should employ personal monitoring techniques for both dermal and respiratory exposure measurement and protocols should be submitted to the Agency for approval prior to the conduct of the studies.

David Jaquith

David Jaquith
Special Review Section
Exposure Assessment Branch
Hazard Evaluation Division (TS-769C)

REFERENCES

1) Memorandum from D. Jaquith (EAB) to A. Barton (HED) dated 22 August 1985.

2) Haverty, M.I., Page, M., Shea, P.J., Hoy, J.B. and Hall, R.W. (1983) Drift and Worker Exposure Resulting From Two Methods of Appyling Insecticides to Pine Bark, Bull. Environm. Contam. Toxicol., Vol. 30, pp 223-228.

3) Matsumara, F. (1975) Toxicology of Insecticides, Plenum Press, New York.

4) Lewis, R.G. (1976) Sampling and Analysis of Airborne Pesticides. In:Air Pollution From Pesticides and Agricultural Processes, R.E. Lee Ed., CRC Press, Inc., Cleveland OH.

5) Menzel, D.B. and McClelland, R.O. (1980) Toxic Responses of the Respiratory System. In:Toxicology: The Basic Science of Poisons, J. Doull, C.D. Klaassen, and M.O. Amdur Eds., MacMillan Publishing Co., Inc., New York.

6) West, J.B. (1982) Pulmonary Pathophysiology - The Essentials, Williams and Wilkins, Baltimore, Md.

7) EPA Lindane Position Document 4.

8) EPA (1985) Guidance for the Reregistration of Pesticide Products Containing Lindane as the Active Ingredient. EPA RS-85-027.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Attachment #2

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

24

MEMORANDUM

SUBJECT: EPA ID No. 009001: Lindane: Toxicology Branch Position On Potential Toxicity Via Inhalation to the Kidneys and Blood (Bone Marrow) as Noted in the Subchronic (90 day) Inhalation Study Translated from German.

TOX CHEM No. 527
TOX PROJECT No. 1758
Record No. 174083

FROM: John Doherty
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Carol Langley, PM Team 73
Special Review Branch
Registration Division (TS-767C)

THRU: Edwin Budd, Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Theodore Farber, Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Background:

Toxicology Branch (TB) recently completed a review of a subchronic inhalation study with lindane in which rats were exposed for 90 days. (See review by J.D. Doherty, April 25, 1986 entitled "Lindane - Special Review: Review of a Rat Subchronic Inhalation Toxicity Study with Lindane.") The review of this study indicated a NOEL of 0.1 mg/m^3 for effects on the kidney (weight changes and histopathologic lesions). Review of this study also indicated that the composition of the bone marrow also showed indications of adverse effects of lindane at 5.0 mg/m^3, the only dosed group assessed for bone marrow composition.

Because only the high dose test group was assessed, no NOEL was assigned for effects of lindane on the bone marrow in this study.

The Special Review Branch (SRB) of Registration Division is requesting that TB provide a memorandum discussing the TB position on the significance of the results of this subchronic inhalation toxicity study. In response to SRB's request, TB is providing the following discussion which includes theoretical margins of safety (MOSs) and comments on the nature of the lesions noted as well as on the method used to generate the atmospheres containing lindane under the test conditions.

TB Comments:

1. Nature of the Kidney Effects Induced by Lindane.

The effects of lindane on the kidneys of male rats in this study consisted of increased kidney weight which can be described as slight to moderate (an increase of 9.8% for mean absolute weight and 8.2% for mean relative weight for the group receiving 0.5 mg/m^3 and 11.7% for mean absolute weight and 19.2% for mean relative weight for the group receiving 5.0 mg/m^3 when compared to the control group weights). The histopathological findings consisted of "cloudy swelling of the tubule epithelia", "dilated renal tubules with protein containing contents", and "proliferated tubules". Both the weight increases and the histopathological changes were not evident after a 6-week recovery period. Only slight increases in kidney weights in the high dose test group (9.2% mean absolute and 7.9% mean relative weights) without accompanying pathological changes were noted in the female rats in this study.

Because of the reversibility of the effects on the kidney, the effects on this organ are considered to be transient. Based on both clinical assessment of the blood (electrolytes, etc.) and urinalyses, the effects of lindane on the kidney did not result in an overt functional impairment of this organ.

The data thus indicate that lindane induces in this study a transient effect on the kidney without a consequential functional impairment in male rats exposed to 0.5 and 5.0 mg/m^3. Female rats are at best marginally affected.

2. Lindane Effects on the Bone Marrow.

The TB review of the subchronic inhalation study with lindane revealed that both male and female rats dosed with 5.0 mg/m^3 had apparently compound-related changes in the composition of the bone marrow. Since only the bone marrow from the rats in the high-dose test and the control groups were assessed, no NOEL for this potential effect of lindane could be established. It could not be determined whether the variations in the bone marrow composition noted in the high dose group when compared with the control group were within the normal range of variations which might be expected for these parameters.

Thus, the potential for lindane to induce changes in the bone marrow composition was not sufficiently investigated by this study. The registrants were asked to present a defense that the changes noted were not in fact due to lindane. TB also requested that the composition of the bone marrow (myelograms) be determined in all future subchronic and chronic studies with lindane in order to clarify the potential for lindane to affect the composition of the bone marrow.

In conclusion, additional research related to the potential for lindane to cause changes in the composition of the blood are needed before the information on this potential effect of lindane is used in risk assesments. It should be noted, however, that the magnitude of the potential effects of lindane on the bone marrow at 5 mg/m^3 was of a low to moderate order and no changes in the whole blood were noted to indicate that the bone marrow effects noted at this level were physiologically consequential.

3. Method of Generation of the Test Atmosphere (La Mer Generator) and the Relevance of This Study to Actual Use Conditions.

In the subchronic inhalation toxicity study the atmosphere containing lindane was generated using a La Mer generator, an apparatus which produces fine particles of sodium chloride coated with the test material (in this case lindane). The particles produced are nearly all of respirable size (arithmetic mean 1.11 um) and capable of penetrating deep into the lung. The

question has arisen as to the relevance of this method of generation of the test material in relation to assessing hazard under actual use conditions.

TB acknowledges that the use of the La Mer generator may give results that overestimate the inhalation hazard under actual use conditions because the particles generated experimentally are nearly all of respirable size. This method, however, is considered by TB to be useful in assessing the worst case of potential inhalation toxicity. Since the particle size of the atmospheres containing lindane are not known (personal communication: David Jaquith, Chemist, Exposure Assessment Branch) using this method assesses the hazard if all of the particles generated in actual use are of respirable size. To the extent that particles formed during actual use are larger than the particles generated, the test method tends to overestimate the hazard.

4. Determination of Theoretical Margins of Safety (MOS) for Inhalation Exposure to Lindane.

Rats in the subchronic inhalation toxicity study with lindane were exposed for 6 hours per day for 90 days. Since there were no interim sacrifices, the time of onset of the effects of lindane could not be determined. Thus, the data generated from this study are most directly applicable to determining theoretical MOSs for indoor uses of lindane that result in repeated and/or continuous exposure for 90 days or longer. The data are of limited usefulness for exposures of shorter durations and outside exposure where there is ventilation.

In actual use situations, there are only two uses involving chronic exposure (greater than 1 year) to lindane (refer to K. Barbehenn memo dated Sept. 18, 1985 entitled "Further Revision of Lindane Risks", attached, for the relevant exposure data). These are flea collars and shelfpaper where the inhalation exposure is low (1.6×10^{-6} and 1.2×10^{-5} mg/kg/day respectively). The theoretical MOSs for these uses are 6625 for the flea collar use and 883 for the shelfpaper use which were calculated as follows:

MOS = [NOEL in mg/kg/day]/[Exposure in mg/kg/day]

For the flea collar use, this equation is:

$$MOS = [10.6 \times 10^{-3} \text{ mg/kg/day}]^{*}/[1.6 \times 10^{-6} \text{ mg/kg/day}]$$

$$= 6625$$

For the shelf paper use, this equation is:

$$MOS = [10.6 \times 10^{-3} \text{ mg/kg/day}]/[1.2 \times 10^{-5} \text{ mg/kg/day}]$$

$$= 883$$

The use of lindane for hardwood log treatment potentially results in 200 days of exposure and the use of lindane for moth treatment potentially results in 225 days of exposure for "employees." Based on the subchronic inhalation study and potential respiratory exposure the MOS for these uses is 8.2 and 35.3 for the hardwood treatment and moth treatment uses respectively. These MOSs were calculated as follows:

For the hardwood log treatment use, the MOS equation becomes:

$$MOS = [10.6 \times 10^{-3} \text{ mg/kg/day}]/[1.3 \times 10^{-3} \text{ mg/kg/day}]$$

$$= 8.2$$

For the moth treatment use, the MOS equations becomes:

$$MOS = [10.6 \times 10^{-3} \text{ mg/kg/day}]/[3 \times 10^{-4} \text{ mg/kg/day}]$$

$$= 35.3$$

One other use of lindane relates to "forestry" application in which the applicators may be exposed for 30 days to 1.8×10^{-3} mg/kg/day for a resulting MOS of 5.9. which was calculated as follows:

$$MOS = [10.6 \times 10^{-3} \text{ mg/kg/day}]/[1.8 \times 10^{-3} \text{ mg/kg/day}]$$

$$= 5.9$$

*The NOEL of 0.1 mg/m^3 for the subchronic inhalation study converts to 10.6×10^{-3} mg/kg/day of lindane inhaled and presumably absorbed. See APPENDIX I.

TB notes the MOS's of 8.2 and 5.9 both relate to forestry uses which involve outside exposures where there should be adequate ventilation. Furthermore, in the case of the "forestry" use where the exposure has been estimated to be 30 days, use of this inhalation study data may not be appropriate for determining a MOS because there is no direct evidence that kidney effects develop after such a short duration of exposure.

The MOSs for these uses represent a worst case and includes the assumption that all of the lindane inhaled is absorbed into the body. The MOSs for the actual uses of lindane in these situations are considered by TB to be most likely much higher.

Many other uses of lindane have either single-day-per-year exposure times and/or a very low respiratory exposure and individual MOS's were not determined.

APPENDIX I

Determining the dosage of lindane to rats exposed to aerosol concentrations of 0.1 mg/m^3 lindane.

A. Rat respiratory data [Reference-Handbook of Biological Data, W.S. Spector (Ed.), W.B. Saunders, Publisher, Philadelphia, Penn., 1964, p.220]

	Mouse	Rat
Respiratory rate (breaths per minute)	163	85.5
Tidal Volume (ml.)	0.15	0.86
Minute volume (liters/minute)	0.024	0.0735

B. Rat atmospheric data from study. 0.1 mg/m^3 or 0.1 ug/l.

C. Calculation:

(minute volume) x (concentration at NOEL) = exposure at NOEL

(.0735 liters/min) x (0.1 ug/l) = 7.35×10^{-3} ug/rat/min.

7.35×10^{-3} is the amount of lindane inhaled per min. Assume all inhaled lindane is absorbed into the body by the lung.

Convert exposure per min to exposure per six hours:

(7.35×10^{-3} ug/rat/min) x 60 min/hr x 6 hr = 2.646 ug/rat/day.

Convert to units of body weight per day.

[Exposure per day]/[estimated weight of rat]*= Exposure in mg/kg

*Assume the rats weigh 250 gm or 0.25 kg.

[2.646 ug/rat/day]/[.250 kg] = 10.584 ug/kg/day

Convert to mg (1 ug = 10^{-3} mg):

10.6×10^{-3} mg/kg/day is the amount of lindane the rats at the NOEL were exposed to and absorbed into their body assuming that all of the lindane inhaled is absorbed.

Attachment #2
(continued)

Kyle

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 18 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Further Revision of Lindane Risks

TO: Jan Auerbach, Acting Branch Chief
Insecticide - Rodenticide Branch, RD (TS-767)

Since we have but recently been informed that the current labels for moth sprays require only respirators as protective equipment for application and unoccupied buildings/storage bin sprays require no protective clothing, we have corrected our analysis which assumed that protective clothing only was required for both uses. The attached table replaces that of September 13.

Kyle Barbehenn, Biologist
Science Integration Staff (TS-769)

cc: Anne Barton
Amy Rispin
Joe Reinert
Dana Pilitt

Table 1
Exposures and Risk Factors Associated with Lindane Uses
Using New Exposure and TOX Data

	Annual # days Exposed	Daily Exposure (mg/kg) with protective clothing required by current labels Dermal	Respiratory	MOS 1/ (0.3 mg/kg)	PD-4 MOS (5 mg/kg)	Cancer Risk Current	PD-4
ornamentals (commercial)	4	0.13	8.6×10^{-4}	400*	280	8×10^{-5}	1×10^{-4}
avocados	2	.27	2.3×10^{-3}	200*	99	8×10^{-5}	2×10^{-4}
pecans							
applicator	1	.57	Negligible	90*	99	8×10^{-5}	7×10^{-5}
mixer/loader	1	.46	Negligible	110*		7×10^{-5}	
combined	1	1.0	Negligible	50*		1×10^{-4}	
livestock	1	.11	1.5×10^{-4}	450 *	448	2×10^{-5}	2×10^{-5}
ornamentals (homeowners)	1	5.4×10^{-2}	5×10^{-4}	5000 *	3846	8×10^{-6}	2×10^{-6}
forestry							
applicator	30	0.10	1.8×10^{-3}	25	1767	4×10^{-4}	1×10^{-4}
mixer/loader	30	0.15 - 0.9 2/	Negligible	3-20 2/		4×10^{-3} - 7×10^{-4} 2/	
combined	30	0.25	1.8×10^{-3}	11		1×10^{-3}	
mas trees-foliar	1	6.8×10^{-2}	1.2×10^{-3}	700 *	500	1×10^{-5}	1×10^{-5}
rawlspace:							
applicators	5	1.5×10^{-3}	7.7×10^{-4}	2×10^{4} *	5435	7×10^{-6}	7×10^{-6}
residents	30		6.9×10^{-4}	430	7246	6×10^{-6}	6×10^{-6}
eed treatment:							
applicators	2	9.3×10^{-3}	8.6×10^{-5}	5000 *	5000	3×10^{-6}	3×10^{-6}
seed sowing	2		1.7×10^{-3}	3000 *	2941	5×10^{-6}	5×10^{-6}
ıg dust:							
applicators	2	4×10^{-3}	3×10^{-5}	1200 *	11628	1×10^{-6}	1×10^{-6}
residents	6		8.6×10^{-5}	6×10^{4} *	52140	4×10^{-7}	4×10^{-7}

Table 1 continued

	Annual # days Exposed	Daily Exposure (mg/kg) with protective clothing required by current labels Dermal	Respiratory	MOS 1/ (0.3 mg/kg)	PD-4 MOS (5 mg/kg)	Cancer Risk Current	PD-4
cucurbits							
applicator	3	2.4×10^{-2}	8.6×10^{-6}	2000 *	28736	1×10^{-5}	2×10^{-7}
mixer/loader	3	6.6×10^{-2}	NA- negligible	150 *		1×10^{-4}	
combined	3	7.1×10^{-2}		140 *		2×10^{-4}	
Xmas trees(stump-slash)	1	0.14	2.2×10^{-3}	360 *	256	2×10^{-5}	3×10^{-5}
pineapples	1		9.7×10^{-8}	5×10^{7} *	1×10^{6}	2×10^{-10}	2×10^{-10}
flea collars	365		1.6×10^{-6}	35000	145349	4×10^{-6}	7.2×10^{-6}
shelf paper	365		1.2×10^{-5}	25000	725000	1×10^{-5}	2.1×10^{-6}
homesprays:							
applicators	1	9×10^{-4}	6.3×10^{-4}	7000 *	1520	2×10^{-6}	4.4×10^{-6}
residents	3		8.6×10^{-5}	6×10^{4}*	55556	4×10^{-7}	4.2×10^{-7}
hardwood logs	200		1.3×10^{-3}	230	962	4×10^{-4}	3.6×10^{-4}
dog dips (vet) 3/, post treatment exp., owner	12	1.2×10^{-3}		2500 *	71667	2×10^{-6}	4.2×10^{-6}
	3		8.6×10^{-5}	6×10^{4} *	58140	N/A 4/	4.2×10^{-7}
dog shampoos:							
applicators	1	3×10^{-2}		1700 *	1562	5×10^{-6}	4.5×10^{-6}
residents	3		8.6×10^{-5}	6×10^{4} *	58140	N/A 4/	4.2×10^{-7}

Table 1 continued

	Annual # days Exposed	Daily Exposure (mg/kg) with protective clothing required by current labels		MOS 1/	PD-4 MOS	Cancer Risk	
		Dermal	Respiratory	(0.3 mg/kg)	(5 mg/kg)	Current	PD-4
moth spray:							
current applicators (w/protective clothing)	26	1.8×10^{-3}	2.6×10^{-5}	1500	37425	3×10^{-5}	5×10^{-5}
	26	(3.6×10^{-4})	(2.6×10^{-5})	(5000)		(1×10^{-5})	
employees	225		3×10^{-4}	1000	55556	1×10^{-4}	3×10^{-5}
unoccupied structures and storage bin sprays:							
current label (w/protective clothing)	12	0.17	7×10^{-4}	20	121957	3×10^{-4}	6.4×10^{-7}
	12	(3.4×10^{-2})	(7×10^{-4})	(75)		(7×10^{-5})	
(plus respirator)	12	(3.4×10^{-2})	(7×10^{-5})	(90)		(6×10^{-5})	
green house fumigation			N/A 4/				

1/ Where an asterisk is indicated, the exposure is acute and the MOS (margin of safety) is associated with the maternal/fetotoxic NOEL of 5 mg/kg, as in PD-4. MOS = (NOEL)/Exposure.

2/ MOS of 20 and a cancer risk of 7×10^{-4} if servicing one applicator; MOS of 3 and a cancer risk of 4×10^{-3} if servicing six applicators.

3/ The number of days exposed per year and the cancer risk for dog dip applications have been adjusted from that in PD-4 to conform with the new labeling restrictions.

4/ N/A = Exposure data not available. Exposure data is being required under this standard.

REVIEWER

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Attachment #2 (continued)

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

AUG 14 1986

MEMORANDUM

SUBJECT: Theoretical Margins of Safety for lindane exposure: Recalculation to include both dermal and inhalation exposure for specified uses.

TOX CHEM No. 527

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In a previous memo from Toxicology Branch (TB), Margins of Safety (MOSs) for certain uses of lindane were calculated based on inhalation exposure (refer to J. Doherty memo dated June 24, 1986 for EPA ID. No. 009001 addressed to C. Langley). In an interdivisional meeting held on July 9, 1986, it was decided that additional calculations of the MOSs for these same uses would be desirable. The revised calculations should include dermal as well as inhalation exposure. As per instructions from Amy Rispin, the dermal exposure information provided by Kyle Barbehenn (memo dated September 18, 1985 attached) should be used.

Inspection of the data tables provided by Dr. Barbehenn reveal that there is no dermal exposure listed for ~~one~~ four of the five uses of lindane for which MOSs were calculated in the original June 24, 1986 memo. For example there is no human dermal exposure for the flea collar, shelf paper or hardwood treatment uses of lindane. The fourth use for which a MOS was calculated was for moth treatment by "employees" based on 225 days/year exposure. No human dermal exposure is listed in the Barbehenn memo for this use. Dermal exposure is listed, however, for moth treatment applicators with 26 days per year exposure. The exposure in this case is not likely to be continuous for 26 days. In the June 24, 1986 memo, it was decided, however, that the use of the 90 day inhalation study was inapplicable for exposures of less than 90 days because there was no evidence that lindane exposure for shorter periods such as 26 days per year (not continuous exposure) results in kidney effects.

As per discussion with Dr. Barbehenn on July 22, 1986, it was decided that the fifth use of lindane (that of the forestry application) would be used as a model for estimating a MOS for lindane use where the combined inhalation and dermal exposures are incorporated. It should be noted that this is a model system only and represents a combined worst case exposure.

Total exposure: respiratory = 1.8×10^{-3} mg/kg/day
dermal = 25.0×10^{-3} mg/kg/day*
26.8×10^{-3} mg/kg/day

MOS = [NOEL from the inhalation study]/[Total Exposure]

" = [10.6×10^{-3} mg/kg/day]/[26.8×10^{-3} mg/kg/day]

" = 0.396

A MOS of less than 1 results. This MOS was arrived at essentially by relating dermal exposure to a NOEL derived from an inhalation study. TB expresses the reservation that determining a theoretical MOS by combining dermal exposure with an inhalation NOEL would likely overestimate the MOS by giving a lower numerical value and implying a greater hazard than exists. A better estimate of the MOS resulting from dermal exposure would be made by incorporating the NOEL from a dermal toxicity

*The dermal exposure of 25×10^{-3} mg/kg/day was derived from Dr. Barbehenn's table which indicated an exposure of 0.25 mg/kg/day. This was multiplied by 0.1 to adjust for 10% absorption to give the amount of lindane theoretically absorbed from this use.

study. TB again notes that the forestry application use is for 30 days/year (not continuous) whereas the inhalation study was a 90 day (continuous exposure) study which is not considered by TB to be applicable for the purposes of determining a MOS for this use. Using the NOEL from the study with the continuous exposure period would again result in overestimating the MOS.

Lastly, using the model equation as above, a theoretical MOS for the "moth spray applicators" can be calculated to be 51.5 as follows:

$$\begin{aligned} \text{Respiratory Exposure} &= 2.6 \times 10^{-5} \text{ mg/kg/day} \\ \text{Dermal Exposure} &= 18.0 \times 10^{-5} \text{ mg/kg/day} \\ \text{Total} &= 20.6 \times 10^{-5} \text{ mg/kg/day} \end{aligned}$$

$$\text{MOS} = [10.6 \times 10^{-3} \text{ mg/kg/day}]/[20.6 \times 10^{-5} \text{mg/kg/day}]$$

$$= 51.5$$

This MOS is also considered to be an overestimation because the exposure is not continuous and a dermal toxicity study was not used in combination with dermal exposure. Note also that this MOS number is higher than the MOS of 35.3 which was calculated for inhalation exposure to "employees", a different subset of workers for the moth treatment use of lindane.

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Attachment #3

BRIEFING ON LINDANE

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I. REASON FOR GOING TO POLICY GROUP

The support team will brief the Policy Group on the question of initiating a Special Review on Lindane.

II. ISSUES TO BE ADDRESSED BY POLICY GROUP

Should lindane be placed in Special Review based on two studies in rats (oral and inhalation) showing histopathological effects in kidneys which are slowly reversible? In some cases the MOSs for exposed workers are below 10.

III. BASIS FOR CONCERN

GRASSLEY-ALLEN NOTICE AND REGISTRATION STANDARD FOR LINDANE

During the development of the Registration Standard for Lindane the Agency reviewed a 90-day subchronic feeding study in rats which showed histopathological changes in the kidney. The Agency determined that the changes were irreversible. The NOEL was calculated to be 0.3 mg/kg/day. The Margin of Safety for forestry use was 11.0 (with protective clothing); for hardwood logs and lumber, 230 (based on dip use with protective clothing). These Margins of Safety were considered to be unacceptable by the Agency. Some hardwood log and lumber workers may be chronically exposed for 200 days per year and because extrapolation of chronic risk based on a subchronic study should allow a 1000-fold safety factor, the MOS of 230 may not be adequate to protect against kidney damage.

A Grassley-Allen letter was sent to Lindane registrants on September 19, 1985 describing the Agency's concerns about the kidney effects and the unacceptable Margins of Safety. The Lindane Registration Standard was signed on September 30, 1985, announcing that the Agency was initiating a Special Review on the basis of kidney effects. No PD-1 accompanied the document and none has since been issued. On October 22, 1985, the Centre International d'Etudes du Lindane (CIEL) responded and stated that a 45 day recovery period showed that the kidney effects were reversible. After reevaluating

the data the Toxicology Branch (TOX) agreed with CIEL that the effects are reversible, although slowly reversible.

OPP MEETING WITH DR. MOORE

On November 22, 1985, OPP presented the facts to Dr. Moore. He decided that we should not place Lindane in Special Review because there was only one study showing the kidney effects and they were reversible.

INHALATION STUDY

A subchronic 90-day rat inhalation study with lindane was available at the time the Standard was issued but had not yet been translated from the original German. By the time the study was translated and reviewed, the meeting with Dr. Moore in November had already taken place. TOX concluded that this study also showed that lindane produced kidney lesions. There were tubular swellings in the kidney which reversed over time. The NOEL was 0.1 mg/M^3. Using this NOEL, the Margin of Safety (based on inhalation exposure only) for the forestry use was calculated to be 5.9; for hardwood log and lumber use, 8.2; and for commercial moth treatment in dry-cleaning establishments, 35.3. The latter (commercial moth treatment) can be discounted because there are no labels carrying that use anymore. Two labels do provide for commercial applicator use of lindane moth spray in homes to treat sweaters and blankets, but the exposure would be considerably less than the exposure of 8 hrs per day for a year for commercial dry cleaning establishments.

As with the previous study, the kidney effects are reversible. However, the calculated Margins of Safety indicate that lindane has the potential to cause temporary kidney lesions in humans. Sensitive members of the population would have the greatest potential risk.

ISSUE: SHOULD THE AGENCY INITIATE A SPECIAL REVIEW ON LINDANE BASED ON THE EVIDENCE SUMMARIZED BELOW?

PROS

1. Rats exposed to lindane develop histopathological effects in their kidneys.
2. Two independent studies with 2 routes of exposure (oral and inhalation) show kidney lesions.
3. Based on the inhalation NOEL, The Margins of Safety for forestry and hardwood uses are 5.9 and 8.2, respectively.
4. People with pre-existing kidney damage, the elderly, or people exposed to other chemicals causing kidney damage may be further burdened by exposure to lindane.
5. The MOSs were calculated taking into account protective clothing for forestry and hardwood uses. Additional protective clothing requirements to reduce risks further are probably infeasible.
6. Kidney damage is known to occur in laboratory animals after 90 days of exposure; the minimum time of exposure to produce kidney lesions is not known, but may be less than 90 days. Forestry applicators are

exposed intermittently for 30 days over 3 months. It is possible that they could develop the lesion after only 30 days of exposure.

7. With dermal exposure and potential risk added to the inhalation risk, the MOS may be even lower.

CONS

1. The histopathological effect completely, though slowly, reverses over time.
2. The effect is not life-threatening.
3. There is no evidence of clinical effects.
4. The effect may not be as "serious" as oncogenicity or teratogenicity.
5. The inhalation study was a 90 day subchronic study, whereas forestry workers are exposed intermittently for 30 days over 3 months. Thus, the duration of exposure under use conditions is not comparable to experimental conditions.
6. The aerosols generated in the 90 day inhalation study were designed to be of optimal respirable size. The aerosols generated in actual use may or may not be of respirable size. (On the other hand, they may be swallowed, absorbed by the GI tract, and damage the kidney via this route.)
7. There may not be a serious exposure problem regarding the number of workers exposed: there are estimated to be only 1000 to 2000 forestry applicators and 840 applicators for the hardwood log and lumber use.

DATA REQUIRED

The Agency has required in the Registration Standard a chronic feeding study, a dermal absorption study, 90-day dermal and inhalation toxicity studies in 2 species and a forestry dissipation study. These studies should provide critical information on the onset, duration, and functional significance of the kidney effects caused by lindane. The last of these studies is due to be received by approximately December 1987.

BENEFITS

USDA has stated that lindane is necessary for forestry use in Colorado, Washington and Oregon against the mountain pine beetle. No alternatives are available since the cancellation of EDB. In the Southeastern U.S., an alternative to Lindane, Dursban, is used because it is effective on the Southern Pine Beetle and is not a Restricted Use chemical for forestry, as lindane is.

There are no alternatives for hardwood log and lumber use of lindane.

POSSIBLE REGULATORY MEASURES IF THE AGENCY DOES A SPECIAL REVIEW ON LINDANE

1. Cancel registrations of lindane for forestry and hardwood uses because of the kidney effects.
2. Allow registrations of lindane for forestry use to remain in the Northwest because no alternatives for control of the mountain pine beetle are available. The States could apply for a "Special Local Need."
3. Classify lindane as a Restricted Use chemical for application to hardwood logs and lumber (it is already Restricted Use for forestry). The drawback to this regulatory action would be that while the number of applicators exposed would be decreased, the exposure for an individual Certified Applicator would be increased.
4. Require applicators who use lindane for hardwood log and lumber to wear MSHA/NIOSH - approved respirators. This action would reduce the Margin of Safety by approximately an order of magnitude from 8.2 to 82.0. Drawbacks to this regulatory action might be that (1) applicators may not wear the respirator because it's too hot and (2) it may be unsafe to wear a respirator because vision may be obstructed in workers in this physically dangerous operation.

5. Require forestry applicators to wear an MSHA/NIOSH-approved respirator. This would reduce inhalation exposure from 5.8 to approximately 58.0. However, the bulk of the exposure to forestry applicators is dermal and labels already provide for protective clothing requirements.

6. Label Warning

"Do Not Use this Product If You Have Kidney Disease"

or

"Tests in laboratory animals have shown toxic kidney effects from exposure to lindane."

Statements such as the above would provide for informed consent for an applicator who chooses to use lindane.

IV. RECOMMENDATION

The team was not able to decide whether the kidney effect was a serious enough effect, given the fact that it is reversible, to cause the Agency to initiate a Special Review on lindane. However, because the Agency is on record in the Registration Standard saying we would initiate a Special Review, a FEDERAL REGISTER Notice should be published as soon as possible stating either (1) the Agency is initiating a Special Review on lindane or (2) the Agency is not initiating a Special Review on lindane. The reasons for either position should be detailed in the Notice.