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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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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.

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FROM: John Doherty 6/17/86
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)

Budd 6/12/86

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 form 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.