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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JAN 16 1987

MEMORANDUM

SUBJECT: EPA Reg. No. 359-686. Lindane: Review of protocol for a 13 week dermal toxicity study with rats.

TOX CHEM No. 527
TOX Project No. 7-0185
Record No. 185399

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Mr. Charles A. O'Connor of the law firm McKenna, Conner and Cuneo in a letter dated November 6, 1986 on behalf of their client Centre International d'Etudes du Lindane (CIEL) is requesting the Environmental Protection Agency to review a protocol for a rat 13 week dermal toxicity study with the insecticide lindane.

This study was previously requested by Toxicology Branch (TB) in order to assess potential toxicity via the dermal route to applicators and other individuals. The kidney and the blood (or bone marrow) may be potential targets for lindane and this study should be designed to assess these in particular as well as the usual parameters of a dermal toxicity study.

Overall Comments

[Note: Emphasis in this protocol review will be on aspects of the study related to particular problems associated with lindane. It is the registrants responsibility to submit studies otherwise consistent with current EPA Guidelines.]

Protocol Title: Lindane: 13 week dermal toxicity study (with interim kill and recovery period) in the rat.

Study Laboratory and authors: Hazleton UK (England), Protocol No. P3239d and HUK Project No. 580/2.

Study directors name is illegible.
Dated October 22, 1986 (as authorized by sponsor)

The basic study plan consists of dosing 4 groups of 49 male and 49 female rats (Wistar strain Crl:(WI)BR) with either 0 (control), low, mid and high dose levels of lindane. The lindane will be applied as a moistened paste to the backs of the rats prepared by periodic clipping. Ten males and 10 females from each group will be sacrificed after six weeks of dosing for the interim sacrifice group. Twenty males and twenty females will be sacrificed after 13 weeks of dosing for the main group. The recovery group consists of 10 males and 10 females from each group which will be sacrificed 42 days (6 weeks) after the last lindane treatment.

Each sacrifice time also includes 3 rats of each sex which will be sacrificed and their carcases assesed for lindane content.

This basic design including selection of the rat strain and interim, terminal and recovery sacrifices is acceptable to TB.

1. Dose level selection. Since the dose levels that will be used were not included, TB reminds the registrants that the high dose level should produce signs of systemic toxicity and not simply local reactions. The lowest dose level should demonstrate a NOEL for any resulting lesions (except irritation at the site of application).

2. Kidney assessment. Overall TB considers that the protocol is vague in describing the special aspects of the study which will assess for potential effects of lindane on the kidney.

   Special aspects of the study that were mentioned in the protocol to assess for kidney effects include urinalysis after "water loading" which includes semi-quantitative assessment of several parameters and preparing three microscopic slides from each kidney.

The specific aspects of the "water loading" procedure were not provided nor were the procedures used to semi-quantitate the urine content described. No mention was made as to whether special stains would be used to detect subtle kidney lesions.

TB recommends that the protocol be rewritten to specifically address the problem of potential kidney toxicity and what will be done in this study to determine the degree to which lindane may cause the same type of kidney pathological responses noted in the subchronic rat feeding study (Research and Consulting Co. Ltd. dated Feb. 3, 1983; see also the TB review by Dr. K. Locke dated June 17, 1983).

TB also recommends that creatinine clearance be evaluated in this study by the same procedures to be used in the rat chronic feeding study to be conducted with lindane (refer to the protocol submitted to EPA by CIEL dated October 1986 and prepared by Life Science Research).

3. Blood and bone marrow assessment. No specific procedures were mentioned in the protocol which will attempt to assess for the potential for lindane to affect the composition of the bone marrow although mention was made that the bone marrow (femur and sternum) will be assessed.

TB recommends that the protocol be rewritten to include provisions which specifically address how bone marrow myelograms will be taken and prepared for microscopy (i.e. which stains will be used and which bone marrow elements will be quantitated).

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Page _____ is not included in this copy.

Pages 4 through 20 are not included in this copy.

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