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

JAN 16 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

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

TOX CHEM No. 527
TOX Project No. 7-0182
Record No. 185400

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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 rabbit 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 of 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 rabbit.

Study Laboratory and authors: Hazleton UK (England), Protocol No. P3240d and HUK (HE?) Project No. 580/3.

Study director's name is illegible.

Dated October 22, 1986 (as authorized by sponsor).

The basic study plan consists of dosing 4 groups of 40 male and 40 female rabbits (New Zealand White) for up to 13 weeks with zero (control), and low, mid and high dose levels of lindane. The exact dose levels of lindane were not provided in the protocol. Ten males and ten females from each of the four dose groups will be sacrificed after six weeks of dosing. The main phase consisting of 20 males and 20 females from each dosage group will be sacrificed after 13 weeks of dosing. The recovery animals consisting of 10 male and 10 female rabbits per dose group will be sacrificed 42 days after (6 weeks) the last dermal application of lindane. This basic design, consisting of an interim sacrifice and a recovery period are acceptable to TB.

1. Dose level selection. Since the dose levels that will be used were not included, TB reminds the registrant 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 which attempt assess the kidney as a potential target organ for lindane include mechanically withdrawing the urine from the bladder and making three microscopic slides from each kidney. No special staining techniques were listed for use. Many parameters of the urinalysis are indicated as to be assessed semi-quantitatively but the procedure for semi-quantitative assessment was not described.

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

3. Bone marrow and hematological 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 is 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).

4. TB notes that the protocol states that the lighting cycle will be "14 hours light and 12 hours dark". The light cycle should be 12 hours light and 12 hours dark.

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PROJECT TITLE	LINDANE :13 WEEK DERMAL TOXICITY STUDY (WITH INTERIM KILL AND RECOVERY PERIOD) IN THE RABBIT
PROTOCOL NUMBER	P3240d
HE PROJECT NUMBER	580/3
SPONSOR	Centre International d'Etudes du Lindane, 250 Avenue Louise, BTE 72, B-1050 Bruxelles, BELGIUM.

	signature	date
Issued by Study Director (or Deputy)		17 Oct 1986
Authorised for HUK Management by	G Waite	17 October 1986
	G. WAITE, CONTRACTS ADMINISTRATOR	
*Authorised for Sponsor by		22 Oct. 1986
Acknowledged and implemented by Study Director		

*Instruction to Sponsor. Please type your name and company status underneath your signature, and return one signed copy to HUK as soon as possible.

Lindane toxicology review

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