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

DEC 24 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg No. 359-686. Lindane: Review of protocol for the rat chronic feeding and oncogenicity study (Life Science Research, prepared October, 1986)

TOX CHEM No. 527
TOX PROJECT No. 7-0183
Record No. 185398

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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 chronic feeding and oncogenicity study on lindane.

Toxicology Branch (TB) has previously reviewed earlier protocols for this study. Refer to memos from J. Doherty dated July 22, 1986, August 4, 1986 and December 5, 1986). This latest version of the protocol contains alterations made in response to TB's previous recommendations.

Overall Comments

[Note: Only aspects of the study related to particular problems associated with lindane will be commented on. It is the registrants responsibility to submit studies consistent with current EPA Guidelines.]

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| Protocol title: | Lindane: Combined oncogenicity and toxicity study by dietary administration to Wistar rats for 104 weeks. |
| Study laboratory and authors: | Life Science Research, Eye, Suffolk, IP 23 7PX England, Study No. CIL/001/LIN, October 1986.<br><br>Dr. Simon Amyes - Study Director<br>Dr. D.J. Ford - Quality assurance manager<br>Dr. A. Pelfrene - Monitor for CIEL |

The basic study plan consists of dosing Wistar strain rats with 0, 1, 10, 100 and 400 ppm of lindane for 104 weeks. The following aspects of this protocol which were included to assess problems particular to the potential chronic toxicity of lindane as well as certain other aspects of this study are indicated below.

1. Interim sacrifices are scheduled for 6, 26, 52, 78, and 104 weeks.

2. The group that will be sacrificed at 78 weeks will receive their lindane fortified diets for 52 weeks and basal diet for an additional 26 weeks to allow a recovery period from any chronic effects developing during the one year of exposure.

3. There will be 15 rats per sex per dose per group for each of the interim sacrifice groups. There will be 55 rats per sex per dose for the rats scheduled for the oncogenicity phase (104 weeks of dosing).

4. Six transverse sections from each kidney will be taken. Three will be stained with hematoxylin and eosin. The other three will be stained with Masson's trichrome.

5. Two bone marrow smears will be prepared from each rat. One will be stained with Pappenheimer's stain and the other will be stained with Wrights's stain.

   A quantitative myelogram will be obtained from the slides stained with Wright's stain and any changes noted will be confirmed by the slides stained with Pappenheimer's stain.

   According to Dr. L. Kasza, TB pathologist, this choice of stains is acceptable.

6. Routine histological examination will be made on a comprehensive set of tissues/organs for all rats in the control and high dose group. Selected tissues/organs from rats in the lower dose groups will be examined if the high dose group shows a response and a NOEL needs to be established.

   The protocol also provides that the liver, bone marrow (sternum and femur) and gross lesions for all animals in the lower dose groups will be examined. Six sections from both the left and right kidneys from all animals will be examined.

   TB requests that the <u>testis</u> and <u>spleen</u> be examined for all dose groups.

7. Water consumption will not be monitored. TB advises that since the kidney is a potential target organ for toxicity effects of lindane that water consumption should be monitored. Water consumption need not be monitored throughout the experiment but it should be monitored at least the week preceding scheduled sacrifices.

8. Urinalysis, hematology and blood chemistry determinations will be monitored prior to initiation of the test diet, at 6, 13, 26, 52 and 78 weeks and at termination.

   <u>The protocol should include one more sampling time at 30 days for assessment of blood elements, urinalyses and clinical chemistries</u> to assess for early transitory effects of lindane. This 30 day sampling time was recommended at the September 18, 1986 meeting.

   Urinalysis will be taken under special conditions following deprivation of diet overnight. The protocol does not specifically state if the rats will be deprived of water overnight. Each rat will be given 20 ml/kg of tap water

by gavage and placed into an individual metabolism cage.

The only other aspect of special kidney function will be creatinine clearance based on the plasma levels of creatinine, urine creatinine concentration and urine volume.

No mention of special procedures to both qualitatively and semi-quantitatively assess the urine contents or to measure the specific gravity was mentioned in the protocol. The registrant is reminded that urinalysis must be both semi-quantitative and qualitative because the kidney is a potential target organ for lindane.

TB previously requested that the registrant conduct "water deprivation and/or loading tests" according to the procedure described by Kluwe (Tox. Appl. Pharmacol. 57:414-424 (1981)). The protocol as presented does not clearly describe how they will do this type of test other than give 20 ml/kg of water.

The registrant is reminded that TB previously suggested (following the recommendation of Dr. L. Kasza, TB pathologist) that at each sacrifice time, the urine should be mechanically removed from the bladder of each rat when possible and assessed for its contents both qualitatively and quantitatively (refer to the notes of the company meeting prepared by J. Doherty dated July 22, 1986; see also the Kluwe reference above).

In conclusion, the registrant is requested to rewrite their plans and procedures for assessing the effects of lindane on the kidney especially including detailed descriptions of the "water deprivation and/or loading tests" as well as the methods to be used to semi-quantitatively assess the urine.

9. TB requests that the heart, lung and pituitary be included in the list for which organ weights will be determined.

10. The study contains a proof of absorption aspect which includes five males and five females from each group that will be sacrificed and the liver, kidney and brain analyzed for lindane content. No explanation for inclusion of this aspect of the study was presented but the registrant is welcome to include it in the study.

LSR Schedule No. CIL/001/LIN

LSR Enquiry No. ZZZ/1407A

# LINDANE : COMBINED ONCOGENICITY AND TOXICITY STUDY BY DIETARY ADMINISTRATION TO WISTAR RATS FOR 104 WEEKS

Protocol prepared for

Centre Internationale des Etudes du Lindane

by

Life Science Research Limited
Eye, Suffolk, IP23 7PX
England

October 1986

This document presents the FINAL PROTOCOL, which comprises 20 pages.

The history of this protocol, to the point of approval by the Sponsor is recorded on the following two pages. Thereafter, protocol amendments are issued for signature by both parties.

Lindane toxicology review

Page _____ is not included in this copy.

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