RD-1072
TXR-1859

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

007859

APR 10 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ID 009001-9: Lindane: Evaluate immunohistochemical report for localization of Alpha$_{2u}$-globulin in kidneys in rats.

Tox.Chem.#527
Proj.# 0-0450
Record #257334

TO: M. Rice (PM 81)
Special Review Branch
Special Review and Reregistration (H7508C)

FROM: Marion Copley, D.V.M., Section Head
Section 2, Toxicology Branch I
Health Effects Division (H7509)

4/10/90

THRU: Karl Baetcke, Ph.D., Chief
Toxicology Branch I
Health Effects Division (H7509)

CONCLUSIONS:

The reported results support the author's conclusion that

> "... alpha$_{2u}$-globulin accumulated in the proximal tubules of male rats treated with lindane in a dose dependent manner. The lowest dose tested, 1 ppm (Group 2M), appeared to represent a no-effect level for the 30 day interim sacrifice."

It would be premature to alter the regulation of lindane since the significance of this type of kidney lesion is currently under evaluation by the Agency Risk Assessment Forum.

ACTION REQUESTED:

Centre International d'Etudes du Lindane ("CIEL") has submitted for evaluation a report titled "Immunohistochemical localization of alpha$_{2u}$-globulin (a2u$_g$) in kidneys of rats treated with lindane" by James Swenberg, DVM, PhD. and Daniel Dietrich, PhD (report attached). Mr. O'Connor, III (council for CIEL) in his letter dated 12/22/89, has stated that,

> "Since alpha$_{2u}$-globulin is unique to male rats and has not been shown to be produced by humans, the regulation of lindane based upon kidney pathological changes in male rats appears inappropriate."

BACKGROUND:

A 2-year chronic feeding study (#CIL002) was conducted by Life Science Research Ltd. for "CIEL" using Wistar rats. Lindane was present in the diets at 0, 1, 10, 100 and 400 ppm of males and females. Ten rats per group were sacrificed at 30 days. All males and control and high dose female kidneys were examined for the presence of the male rat specific protein, alpha$_{2u}$-globulin, (m.w. - 18,700 da) using immunohistochemical localization techniques.

CIEL has, in the past, claimed that the renal nephropathy observed in the male rats exposed to lindane (Study # 88/CIL002/816) was due to alpha$_{2u}$-globulin and therefore is similar to nephropathy observed with certain hydrocarbons. In response, the Agency requested additional information to support this claim.

RESULTS AND DISCUSSION:

Slides from the control and high dose female groups were negative for the presence of a2ug. All males were positive for the presence of a2ug with a dose related increase in extent and intensity of staining and the amount of the kidney affected (see Table 8 in the attached report). The low dose (1 ppm) (1.5±0.5) animals were similar to controls (1.7±0.9) with a doubling of the grading following exposure to 10 ppm lindane (3.2±1.0) in the diet. It was also reported that males receiving 100 ppm had a minimal number of granular casts at the junctions of proximal tubules and the thin limbs of Henle. Males in the 400 ppm group had an increase in the number of granular casts. These casts stained positive for a2ug. It was suggested by the authors that the casts were composed of cells dying of a2ug overload.

Examination of the kidney using Masson Trichrome (males - controls, low and high; females - controls and high) indicated the presence of small droplets in the control and low dose males and control and high dose females. The other males had large distinct droplets in the proximal tubules. H & E staining indicated areas

> "containing hyaline droplets of varying shapes ... multifocal cortical tubular necrosis of varying intensity, cortical tubular regeneration and granular casts at the junctions of the proximal tubules and the thin limbs of Henle."

Other details concerning the protocol and results of this oncogenicity study were not presented in this report. It could not be determined whether there would be additional sampling times for a2ug.

To date only the 1 year interim report and this special report have been submitted and evaluated by the Agency. The full oncogenicity study will be completely evaluated when received and

the implication(s), if any, of the lindane associated accumulation of a2ug will be reevaluated at that time. However, the Agency is currently evaluating whether it is appropriate to regulate chemicals based on the above type of lesions in rats. The Agency will also determine what criteria would need to be fulfilled in order to conclude that the lesions are related to alpha$_{2u}$-globulin accumulation.

cc: J. Dohertv

MCP\D:\LINDANE.A2U.4/10/90

Lindane toxicology review

Page _____ is not included in this copy.

Pages 4 through 14 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
