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

JUN 16 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Lindane: Meeting with the CIEL group to discuss the current status of toxicity testing and the revised protocol for the rabbit 90-day subchronic dermal toxicity study.

TOX CHEM No.: 527

FROM: John Doherty 6/13/88
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: George LaRocca
Product Manager #15
Registration Division (TS-767)

THROUGH: Edwin Budd
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 6/14/88
6/16/88

On June 9, 1988 at 1:00 PM a meeting was held at the request of Mr. Charles A. O'Connor, III of the law firm McKenna, Conner and Cuneo on behalf of the Centre International d'Etudes du Lindane (CIEL). Present at the meeting were:

CIEL and associates:

Peg McMullen, Rhone Poulenc Co.
Glenn Simon, Rhone Poulenc Co.
David Brown, Hazleton, UK
Nikolaus Wilhelm, CIEL
Mark McGrath, McKenna, Conner and Cuneo

EPA:

Dana Pilett, Reg. Div.
Ted Farber, Tox. Br. HED
Ed Budd, Tox. Br. HED
John Doherty, Tox. Br. HED

The meeting was requested primarily to discuss the protocol for a rabbit dermal toxicity study but other issues related to the toxicity testing of lindane were also discussed.

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The meeting was initiated by Dr. Simon briefly stating that the rat subchronic dermal toxicity study is expected to be submitted to the Agency on schedule (due in July of 1988). Dr. Simon also briefly discussed some of the problems related to testing lindane in a subchronic inhalation study in mice. The original high dose level (10 ug/m^3) of lindane used for this study resulted in death to some of the mice and the high dose was thus reduced to 5 ug/m^3. The mice apparently tolerated this dose level. The final report for this study is expected to be sent to the Agency in October of 1988. The rat chronic feeding study is also currently underway and there have been no further complications and the study is expected to be completed on schedule.

Dr. Brown, the toxicologist associated with the Hazleton Laboratory, then proceeded to describe how the lindane would be applied to the rabbits and kept in place using an aluminum foil backed gauze patch and system of bandages. The lindane will be suspended in carboxymethyl cellulose (5% in water) and kept in contact with the rabbits skin for 6 hours. After this time the bandages and foil will be removed and the area washed with an infant soap and rinsed to prevent infection. Dr. Farber suggested that the aluminum foil patch might be perforated to promote ventilation and Dr. Brown agreed to consider this suggestion. The issue of using carboxymethyl cellulose was raised with regard to whether or not this material would compromise the study by damaging the skin. All agreed (including EPA staff) that experience with carboxymethyl cellulose does not indicate that its use would compromise the study.

The question arose as to how many kidney slides would be read to assess for the effect of treatment on this organ. The protocol called for preparing three slides per kidney but implied that only one slide per animal would be read to start with. It was agreed that all six slides per rabbit would be assessed for the control and high dose treated rabbits for the first reading. If there are indications of effects in the high dose group, the six slides from the mid dose group would be assessed and so on until a clear NOEL is established (or the extent of kidney damage in the low dose group is established). It was also agreed that the protocol is sufficient in its current form with regard to the procedure to be used for staining the kidney slides. For example, the current protocol calls for staining with haematoxylin and eosin and at the pathologist's discretion with other appropriate special staining techniques if required. It was suggested by J. Doherty that the protocol should contain a discussion as to how the pathologist intended to assess for the types of kidney lesions previously noted in the rat subchronic feeding study. For example, any alternative staining techniques and the rational for using them might have been included in the protocol.

The issue of the time at which sampling the blood for

lindane content (which is critical to demonstrating that the lindane was absorbed) was also discussed. The time indicated in the protocol (after at least 18 hours of fasting and after an undetermined time since the last application of lindane) would not give an accurate estimate of the maximum blood level of lindane attained during the exposure period because the elimination of lindane from the rat is fairly rapid (half-life in hours). Toxicology Branch (TB) suggested that some of the rabbits (for example 5) be bled just before the lindane application is removed (about five hours) and this blood sample be used for lindane analysis. The CIEL group agreed to modify the protocol based on this suggestion.

TB also agreed that it was advisable to stagger the starting times for the different phases of this study such that the number of rabbits requiring daily applications of lindane or vehicle control would be reduced. TB considers that such staggering would help to reduce the strain on the rabbits since at some times during the course of the study as many as 320 rabbits would have been treated. Staggering the staring times will reduce this number to 160 rabbits.

The CIEL was reminded that TB previously requested (J.Doherty review dated April 17, 1987) that product information for the "BM-test-7" sticks to be used for the analysis of the urine be provided to the Agency so that the limits of detection and differences indicated by these "sticks" can be obtained by the Agency. Dr. Brown agreed to send this information.

The CIEL group agreed to submit a revised protocol incorporating the suggestions and discussions made at this meeting. TB stated that it had no objection to the study being started immediately.

Meeting Afterward

After the meeting J. Doherty had a discussion with Dr. Leonard Slaughter, TB consulting pathologist, regarding the overall problem of conducting a subchronic dermal toxicity study of 90 days duration with rabbits. Dr. Slaughter stated that the organism Pasteurella multocida is a common infection in rabbits that should be manageable. He suggested that the original source of rabbits may have had an unusual high titer of this organism. Dr. Slaughter also implied that good laboratory practices such as proper ventilation and better efforts made to not spread the infection about the laboratory or the research facility should prevent serious infection with this microorgamism. Interestingly, Dr. Slaughter suggested that the rabbits could be made specific pathogen free by delivering the rabbits by cesarian section and immediately transferring the pups to a clean environment. Such a procedure would be expensive and time consuming.

HAZLETON UK
Otley Road, Harrogate
North Yorkshire HG3 1PY England

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PROJECT TITLE — LINDANE :13 WEEK DERMAL TOXICITY STUDY (WITH INTERIM-KILL AND RECOVERY PERIOD) IN THE RABBIT

PROTOCOL NUMBER — P4147d

HUK PROJECT NUMBER — 580/6

SPONSOR — Centre International d'Etudes du Lindane,
250 Avenue Louise,
BTE 72,
B-1050 Bruxelles,
BELGIUM.

DEFINITIVE

	signature	date
Issued by Study Director (or Deputy)		22 April 1988
Authorised for HUK Management by	G. Waite	21 April 1988
	G. WAITE, CONTRACTS ADMINISTRATOR	
*Authorised for Sponsor by		22 April 1988
	Dr. N. Wilhelm	
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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