CASWELL FILE

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DEC - 5 1986

MEMORANDUM

SUBJECT: Lindane: Notes related to a company meeting to discuss the revised protocol for the rat chronic feeding/ oncogenicity study.

TOX CHEM No. 527

FROM: John Doherty 10/27/86
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TO: George LaRocca
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THRU: Edwin Budd
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THRU: Theodore Farber
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NOTE: TB requests that a copy of this memo be sent to the CIEL for their confirmation as to specifically what was agreed upon at this meeting.

On Thursday September 18, 1986 a meeting was held in Dr. Farber's office with representatives of the Centre International d'Etudes du Lindane (CIEL) to discuss the protocol for the proposed rat chronic feeding/oncogenicity study. In particular, problems related to assessment for kidney effects and kidney function as well as assessment for potential blood toxicity (aplastic anemia).

Present at the meeting were:

CIEL representatives

Matthew McGrath, McKenna, Conner and Cuneo
Chuck O'Connor, " " "

Dave Olsen, Rhone Poulenc
Dr. Alain Pelfrene, Rhone Poulenc (France)
Nikolaus Wilhelm, Celamerck

EPA Representatives

Dr. Theodore Farber, Chief, Toxicology Branch, HED
Dr. Louis Kasza, Pathologist, Toxicology Branch, HED
Edwin BUdd, Toxicology Branch, HED
John Doherty, Toxicology Branch, HED

Dana Pilett, Registration Division (PM team 15)
Carol L. Monroe, Special Review Branch, Registration Division

The meeting was held at the request of the CIEL (refer to letter from Mr. C.A. O'Connor dated September 10, 1986 attached).

Toxicology Branch (TB) of EPA and the CIEL had a previous meeting to discuss the protocol which was submitted to the Agency for review for the rat chronic feeding/oncogenicity study (refer to TB memos dated July 22, 1986 and August 4, 1986). At the earlier meeting several issues were raised by TB which resulted in advising that the protocol as originally submitted should be modified. The CIEL has since considered TB's comments and has agreed with many of the suggestions made.

In particular the CIEL will include the following in the protocol for this study:

1. The test animals will be the Wistar strain of rats because this strain was used for the 90 day feeding and inhalation studies and developed kidney lesions in response to lindane exposure. Preliminary data from the range finding study using the Sprague-Dawley rat indicated the this strain may not be as sensitive as the Wistar strain. Thus the Wistar strain was chosen in order to avoid possible future problems should the NOEL for the chronic study be higher than the subchronic study conducted with a different strain.

2. The dose levels chosen for the chronic feeding study were 0, 1, 10, 100, and 400 ppm. In the original protocol, the lowest test dose level was scheduled to be 4 ppm. A lower test dose was chosen because the 90 day study showed subtle kidney effects at 4 ppm (which were not considered by TB to be of sufficient magnitude to be considered the LEL for kidney effects). In a chronic feeding study, however, such subtle effects may be compounded over time and the 4 ppm level may show more definite kidney effects and the study if run at 4 ppm might not show a NOEL.

   Based on subchronic feeding data the dose level of 400 ppm is expected to meet or exceed the Maximum Tolerated Dose (MTD).

   TB wishes to advise the CIEL that it does not formally approve of or recommend dose levels for chronic toxicity studies. Selection of the dose levels, although TB tries to make helpful suggestions, is the responsibility of the sponsor.

3. The CIEL agreed to interim sacrifices at 45 days, 6 months, and 1 year. A satellite group will be included and dosed for 12 months and allowed 6 months for recovery at which time the the rats will be sacrificed and examined.

   It was not established at the meeting the number of rats per sex per dose which would be included in each interim sacrifice group or in the satellite group.

4. In addition to the interim sacrifices, blood will be sampled at days 30, 45, 90, 6 months, 1 and 2 years for changes in composition and evidence of hematoxicity.

   Blood assessment will also consist of bone marrow smears from the femur and sternum when these samples are available at the sacrifice times.

5. The status of the kidney will be assessed by both qualitative and semiquantitative urinalyses and blood constitution.

   It was also mentioned that the "water deprivation and/or loading tests" and inulin clearance tests will also be conducted.

   The assessment of kidney function by utilizing kidney cortical strips in vitro (which TB previously suggested) was considered by the CIEL to be impractical for several reasons. For example, since multiple slices of the kidneys will be made for pathological examination,

for many of the rats, there may not be enough viable tissue remaining for such assays. The pathology laboratory where the tissues will be removed will not have the facilities to do the in vitro assay. TB concurs. The assessment of kidney cortical strips will not be part of the study.

6. Three slices of the kidney will be made for histopathological assessment for those test animals at or near the NOEL. At more definite effect levels, only one slice of the kidney will be prepared.

7. Dr. Kasza presented a page from a journal concerning the pathology of the kidney as a repsonse to hexachlorobutadiene. A copy of this handout is attached.

The CIEL will prepare a revised protocol and submit it to the Agency for review.

In addition to the above it was also decided at this meeting that:

1. TB will not require special in vitro tests for aplastic anemia.

2. The CIEL will try to determine the feasibility of performing kidney function tests in mice (with respect to the 90-day inhalation study) and in rabbits (with respect to the 90-day dermal study).