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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Lindane: Toxicology Branch response to the letter from Mr. Matthew J. McGrath concerning 1) extension of the due date for the mouse inhalation study, 2) evaluation of bone marrow myelograms in the mouse inhalation study, 3) progress of the subchronic dermal studies in rats and rabbits and extension of the due date for the chronic feeding/oncogenicity study in rats.

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FROM: John Doherty
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THRU: Edwin Budd
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Mr. Matthew J. McGrath, counsel for the Centre International d'Etudes du Lindane (CIEL) has submitted a letter (attached) dated December 3, 1987 concerning certain problems particularly related to the subchronic inhalation study with mice and the subchronic dermal study with rabbits as well as other issues related to toxicity studies required in the Registration Standard for lindane. The following is an issue by issue listing of the items discussed by Mr. McGrath.

1. Request for a six month time extension for the due date for the subchronic inhalation study with mice (82-4).

Mr. McGrath's report states that the testing laboratory experienced several problems which delayed the start up of this study. These problems included revisions in the protocol which were made by Toxicology Branch (TB) of EPA. For example, there were questions concerning the criteria for the exposure levels (signs of toxicity vs levels of lindane in the blood) and the particle size of lindane in the test atmosphere. It was eventually decided that toxicity is the more important end point than blood levels of lindane (refer to J. Doherty memo dated April 21, 1987).

The problem of generating an atmosphere of lindane of a uniform particle size (< 5 um) required the testing laboratory to devise a way to grind the lindane samples into small pieces as well as to experiment with several methods for generating the atmosphere. The Wright Dust generator was eventually selected as the preferred method for generating the atmosphere. It was still later noted that the aerosol photometer used to provide a qualitative estimate of the chamber concentration was not sensitive enough to measure atmospheric levels below 10 mg/m^3. A more sensitive photometer and state of the art Wright dust feeders were purchased to further increase the accuracy of the generating exposure concentrations.

TB agrees that both the CIEL and the Bushy Run Research Center (BRRC) testing facility are justified in making the request for a six month extension for the due date for this study. TB has no objection to the extension of the due date.

TB cautions, however, that the testing laboratory should not rely on the aerosol photometer alone to determine the atmosphere levels of lindane. The atmosphere should be sampled and the lindane concentration should be determined chemically.

Although not mentioned in Mr. McGrath's letter, TB has been informed via a telephone call on November 10, 1987 from Dr. Glenn Simon, Toxicologist, Rhone-Poulenc Co., and a representative of the CIEL, that many mice in the high dose group died as a result of inhalation exposure to lindane. Dr. Simon requested permission to change (reduce) the number of mice which would be examined for blood lindane levels so that more mice would be available for the more important clinical and histopathological aspects of the study. TB asked Dr. Simon to prepare a letter describing what happened (number of mice dying etc.) and to describe the remedial steps taken. This letter regarding the mouse inhalation study has not been received by TB as of December 11, 1987.

2. Evaluation of bone marrow myelograms in the subchronic inhalation study with mice (82-4).

Mr. McGrath explained that BRRC felt that they did not have the level of expertise that would satisfy EPA in evaluating the bone marrow myelograms. Eventually a subcontractor (Dr. Walter Loeb, METPATH in Rockville, Md.) was located who could evaluate the myelograms and also meet Good Laboratory Practice Regulations.

Mr. McGrath explained that the cost of evaluating myelograms from all 240 mice would be $18,240. This would add a considerable increase to the original cost of the inhalation study which had already greatly exceeded its original estimate. Mr. McGrath proposed that only the myelograms from the mice in the control and high dose groups (10 per sex per group per sacrifice) be evaluated by Dr. Loeb and that the slides from the mid and low dose groups be evaluated only if indications of adverse effects are noted.

TB will accept this proposal if the physical procedure for obtaining, fixing, staining and storing the myelograms from the mid and low dose groups are such as to not compromise or otherwise affect the integrity of the evaluation. TB will require ~~than~~ that all of the bone marrow samples (from both the sternum and the femur) be prepared (i.e. removed from the bone, fixed and stained) at the same time from all groups of mice.

3. Subchronic dermal studies (82-3).

Mr. McGrath reports that the rat subchronic dermal study is proceeding on schedule and the due date (July 30, 1988) is expected to be met.

The rabbit subchronic dermal toxicity study was forced to be terminated because of the unexpected occurrence of dermatitis and subcutaneous infections. CIEL is currently in the process of reviewing the situation and plans to submit a status report and revised schedule in the near future.

4. Chronic feeding and oncogenicity study in rats (83-1 and 83-2).

There were several delays in getting this study started at the Life Science Research Laboratory in England. These delays related to revisions in the protocol which were requested by TB and to the need to restart the study after it was first initiated because the rats were found to have Tyzzer's disease. Mr. McGrath expects that the study will be submitted to the Agency in August of 1990 or nine months after the original due date.

TB has no objections to the extension of this due date.