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

JAN 16 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. No. 359-686. Lindane: Review of a protocol for a 5 day pilot inhalation study with mice.

TOX CHEM No. 527
TOX Project No. 7-0184
Record No. 185396

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Mr. Charles A. O'Connor of the law firm McKenna, Conner and Cuneo on behalf of their client Centre International d'Etudes du Lindane (CIEL) is requesting the Environmental Protection Agency to review a protocol for a 5 day pilot inhalation study with mice.

Toxicology Branch has previously reviewed protocols for a subchronic inhalation toxicity study in mice (refer to J. Doherty memo dated August 6, 1986 for EPA Reg. No. 359-686).

Study title: Lindane Technical 5-Day Inhalation Pilot Study on Mice.

Laboratory and Authors: Bushy Run Research Center (Project No. 86-85-80200)

Dennis R. Klonne, Study Director
Darol E. Dodd, Manager Inhalation Department
Linda J. Calisti, Quality Assurance
Fred R. Frank, Director

Glenn S. Simon, Sponsor Representative

The purpose of this study (as quoted from the protocol) is as follows:

"The purposes of this study are to determine: 1) appropriate procedures for analyzing lindane technical in the blood of exposed mice; such factors as the amount of blood required and the appropriate time for obtaining samples in relation to the end of the exposure will be evaluated, 2) appropriate procedures for analyzing various excretory products in the urine (non-standard analyses which are being conducted for the 14 week inhalation study), and 3) appropriate procedures for preparing bone marrow smears for myelograms and evaluating Pappenheimer bodies."

1. Since this protocol is exploratory as indicated above, Toxicology Branch (TB) cannot really comment on its appropriateness for meeting testing requirements for lindane. Once the registrant and testing laboratory agree upon the procedures to be used for sampling blood for lindane determination, analyses of the urine and on the procedure for preparing bone marrow smears for myelograms as indicated above, the procedures selected may be sent to EPA for review prior to initiating the 14 week inhalation study.

2. TB recognizes the importance of doing this pilot study especially in relation to quantitating the blood levels of lindane following exposure. The method for generation of the aerosol must result in particles that are of a respirable size and are absorbed by the mice. Assessment of the blood levels for lindane will assure that lindane actually was absorbed.

The protocol provided for two target levels of atmospheric exposure to lindane. The registrant is reminded that the exposure levels based on the quantity of lindane in the blood should be in the same range as in the rat inhalation study (Frauenhofer Institut für Toxikologie, 1983). Since a special type of generator was used in that rat study which will not be used in this proposed study, the actual atmospheric concentrations of lindane may be of lesser significance than the blood levels of lindane in the proposed study. Thus the development of an assay to quantitate lindane in the blood is very important.

3. The urinalyses aspect of this pilot study does not include any special procedures such as food and water deprivation prior to testing and administration of water by gavage prior to collection of the urine. For example, will a "water deprivation and/or loading test" be attempted for this pilot study with this species? Also no mention was made if the mice will be housed in individual animal metabolism cages for collection of urine.

4. As far as point 2 in the above quotation is concerned, there is no provision in the protocol for assessing "various excretory products in the urine (non-standard analyses....etc)". It is

unclear what the proposed study will be doing to assess for "appropriate procedures" or what exactly are the "excretory products" which will be assessed for. Is urinalyses limited to volume, sodium, potassium, chloride, creatinine, and quantitative protein determinations or will metabolites of lindane also be assessed?

5. The bone marrow will be stained with Prussian Blue for the evaluation of "Pappenheimer bodies". The protocol for the rat chronic feeding study stated that the bone marrow will be stained with Pappenheimer's stain and with Wright's stain. According to Dr. Louis Kasza, TB pathologist, Wright's stain is very widely used and may be more acceptable. The registrant is requested to provide justification for the stain selected.

The stain which best assesses for the presence of those blood elements which may have been affected by lindane in the 90 day rat inhalation study (Frauenhofer Institut fur Toxikologie, 1983) should be used. See review of this study by J. Doherty dated April 25, 1986 where it is indicated that reticulocytes, stem (stab) cells, myeloblasts, promyelocytes, myelocytes, basophilic erythroblasts, polychromated erythroblasts, macrolymphocytes, and small and medium size lymphocytes all showed indications of possibly being affected by lindane.

Why are bone marrow samples being evaluated for "Pappenheimer bodies"? The bone marrow myelogram should be assessed for other changes as noted in the rat inhalation study.

6. The final report of the study should contain the results of the urinalyses and the bone marrow evaluations.

The proposed conditions including dose levels and the rationale for their selection for the 14 week inhalation study together with the assay procedures to be used for urinalyses and bone marrow assessment should also be included in the final report.

Lindane toxicology review

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