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

APR 22 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id No.: 009001. Lindane: Review of neurotoxicity screen study protocols for series 81-8ss (acute) and 82-7ss (90-day) studies.

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I. CONCLUSION

Overview of the protocols as presented indicates that they are apparently consistent with the Guideline recommendations for series 81-8ss (acute neurotoxicity screen) and 82-7ss (90-day neurotoxicity study). Refer to Toxicology Branch Comments Section below for comments on these protocols. It must be noted that it is the registrant's responsibility to provide a final report of the study that meets the criteria for acceptability of toxicity studies.

II. Action Requested

The Centre International d'Etudes du Lindane (CIEL), through their representatives McKenna & Cuneo (refer to letter from Michael R. Neilson dated January 24, 1992), has submitted acute (series 81-8ss) and 90 day subchronic (series 82-7ss) neurotoxicity study protocols for review by Health Effects

Division (HED). These protocols were reviewed and the following comments apply.

III. Toxicology Branch Comments

1. The protocols present an outline of the husbandry and prescreening and general conditions of the conduct of these studies and these appear to be consistent with GLP criteria.

2 Both studies will utilize the Sprague-Dawley strain rat. The testing laboratory (Bushy Run Research Center) asserts that they have previous experience with neurotoxicity studies with this strain of rat. Each study will consist of four groups (a control and three treatment groups) of 15 males and 15 females. The dosing is scheduled to begin when the rats are 8 weeks of age (56 days) for the acute study and when the rats are less than 8 weeks of age for the 90 day study. Thus, they will be within the recommended age range for these studies. During the experimental phase, the animals are scheduled to be housed individually.

No positive controls will be run concurrently. This practice is considered acceptable. Positive control data will be from the laboratories historical control data bank which includes 13 chemicals of different structure. Of the several chemicals listed, DDT (also an organochlorine insecticide) might best represent similar toxicity to lindane.

3. Treatment and Dose Selection. The vehicle to be used for administering the test substance in the acute study is not specified. This vehicle should be one in which the test substance has recently been tested in the strain of rat to be used for the study to determine the time to onset and duration of overt symptoms.

The dose levels for the acute study are not provided but are to be determined based on a preliminary study as in the above paragraph. Dosing "will be staggered over several days to accommodate the schedule for behavioral testing". TB-I considers this practice to be unavoidable especially if all the animals will be tested by the same personnel and with the same equipment.

No vehicle is mentioned for use in the dietary 90 day study. The dose levels are not provided but the criteria for selecting the dose levels are. These criteria are considered appropriate by TB-I.

4. The functional observational battery (FOB) for both studies will be assessed in the room where the animals are housed.

-for the acute study the FOB will be performed at pretest and on the day of treatment (during the first 24 hours

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of treatment, the time will be determined based on the preliminary test), and on days 7 and 14 following treatment.

-for the 90-day study the FOB will be performed at pretest and at weeks 4, 9 and 13.

-animals of the same sex will be evaluated where possible by the same technician. The protocol states that "verification of inter-observer reliability will be added to the permanent study record." The protocol does not state, however, how this will be accomplished.

-Attachment 2 of the protocol defines the Functional Observational Battery and provides a master list and definitions as well as scoring criteria (it is 8 pages long). This appears to be a thorough approach to the FOB aspects of the study.

5. The motor activity (MA) evaluation will be conducted in a "Modified Relocatable Containment System Unit" (Hazleton Systems Inc., Aberdeen, Md.) in special rooms in the same building at the BRRC facilities. These rooms are reportedly modified to control environmental fluctuations in sound, light, temperature and relative humidity. These parameters will be monitored and recorded.

The actual MA is scheduled to be assessed for 15/sex for each dose group. The activity will be assessed using an automated recording apparatus "designed to measure activity in a novel environment (San Diego Instruments Inc., San Diego, California). This system has the reported capacity to monitor 30 animals in each block simultaneously. The registrant should be reminded that Guideline criteria state that each animal "shall be tested individually". Each session is scheduled to last for 90 minutes but the exact parameters to be assessed and the criteria for determining an effect are not provided. Since this is a standard procedure, TB-I assumes that the MA assessment will be complete. It is the registrant's responsibility to provide an acceptable assessment.

TB-I, however, requests that data from sample tests to assure the reliability of the MA device be submitted along with the final report of the study.

6. Neuroanatomic Pathology. The proposed procedures for histopathology and examination of the slides by light microscopy are described. These appear to be consistent with the current Guidlelines.