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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: March 25, 1982

SUBJECT: Review of Validated IBT Rat Reproduction Study of Curacron (CGA-15324), IBT No. 623-07924
Tox. Chem. 266A

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Recommendation:

1) This study is classified as Supplementary Data due to a lack of raw data to support reported histological results. The NOEL for cholinesterase depression is 1.0 ppm. The NOEL for reproductive effects is > 20 ppm.

Review of Data:

Three-Generation Reproduction Study, Rat. Performed at Industrial Biotest Laboratories (IBT No. 623-07924) and submitted by Ciba-Geigy Corporation.

(This study was validated by this reviewer on April 8, 1980 and revalidated on March 19, 1982. The study was classified as "Supplementary Data" based on the following deficiencies and discrepancies;

1. The number of tissues examined microscopically could not be determined.

2. A bias was introduced into selection of animals for histopathology due to animals being selected in a nonrandom manner.

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3. Observations were not recorded on a daily basis for the F_0 and F_1 generations.

4. Animals dying during the course of the study were not examined histologically to the extent required by the protocol.

5-8. Other deficiencies and discrepancies were concerned with the lack of raw data for environmental conditions, source, strain or age of animals, diet prep. records for weeks 1, 37 and 54 and fewer diet analysis results than samples taken.

The validation noted that an upgrading of the study to Valid may be possible if a tissue inventory indicates that all required tissues are present and histopathology observations can be confirmed through reexamination of tissues.)

Rats of unknown age or strain were assigned to test groups to receive either 0, 0.2, 1.0 or 20 ppm (Note: actual dietary levels were at least 9% less for each dose group). Eight males and 16 females were assigned per dose level. Mating trials were initiated when animals reached "100 days of age", although the age of animals could not be documented. At 10 day intervals, males were rotated until copulation was confirmed or until each female had been paired with a maximum of 3 males. The first litters were weaned at 21 days, sacrificed and discarded. The second (b) litters were reduced to 10 pups per litter on lactation day 10, although the method of selecting these animals was not specified. These procedures were repeated for all groups of each generation. Animals of the F_0 and F_1 generations were observed sporadically for mortality and behavioral reactions, animals of the F_2 generations were observed daily. Progeny were examined at birth for abnormalities and the number of viable and stillborn pups were recorded. Parents were sacrificed after the weaning of the second litter. All parental animals, all surviving males and 8 females from each parental generation of all groups, and 10 male and 10 female weanlings from the control and T-III groups were necropsied.

At least 5 males and 5 females were examined microscopically from the control and T-III groups of each generation. At least 10 males and 10 females from the control and T-III groups of the F_{3b} generation were examined microscopically. It could not be determined which tissues were actually examined.

The design of the experiment was as follows;

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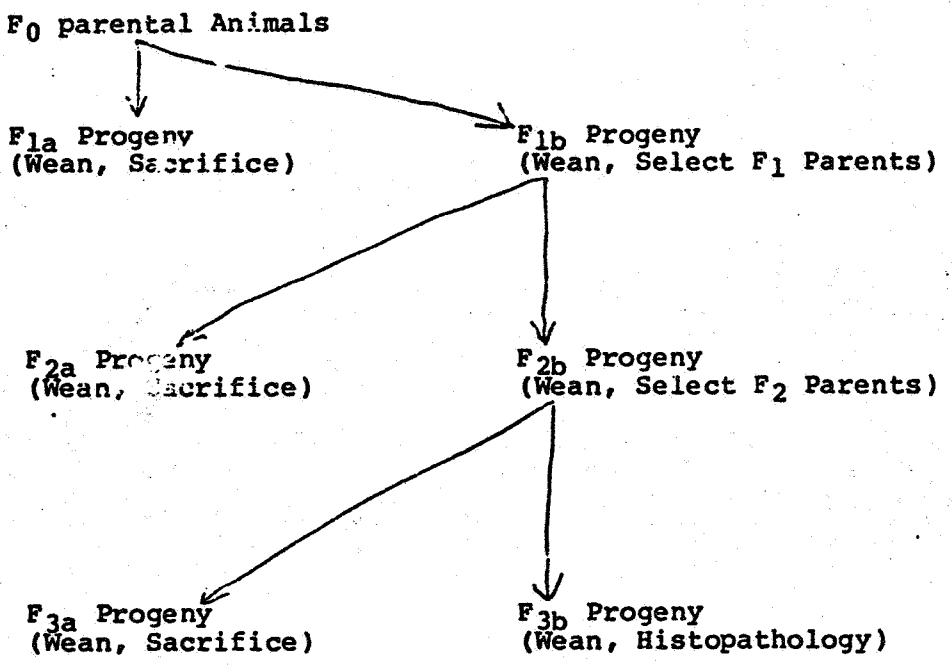

Results: Forty one parental animals died during the course of the study and Dr. Jerry Hardisty of Experimental Pathology Labs has diagnosed chronic murine pneumonia or acute bronchopneumonia as the cause of death of at least 35 of these animals. The pattern of deaths did not appear to be compound-related (12, 8, 11 and 10 deaths in the control, 0.2, 1.0 and 20.0 ppm groups, respectively).

No observations were recorded that appeared to be associated with exposure to test compound.

Plasma cholinesterase activity was depressed in high dose females of each generation (35.8, 52.5 and 41% of control values for the F_0, F_1 and F_2 generations respectively). Erythrocyte cholinesterase activity was reduced in high dose males and females of each generation (males: 77, 56.4 and 59.7% of control values; females: 71, 59 and 56% of control values, for the F_0, F_1 and F_2 generations, respectively). Brain cholinesterase activity did not appear to be effected by compound exposure. The mating fraction (number of copulations/number of estrous cycles) was slightly decreased in both the a and b litters of the T-III group F_0 and F_1 generations ($p > 0.05$). Other reproduction indices did not appear to be effected by treatment. Pup weight, number of pups delivered and pup survival through day 21 of lactation did not appear to be effected by treatment.

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Body weights of treated pups at 21 days were similar to, or greater than, that of control pups. The incidence of external abnormalities was similar in each dose group. Organ weights and organ weight ratios did not appear to be effected in a treatment related manner.

Although no treatment related gross or histological changes were noted, the histological examination of all required tissues was not supported by the raw data.

Core Classification: Supplementary Data. (If the histology deficiency noted above can be satisfied, an upgrading of this study to Valid, Core Minimum may be possible). The NOEL for cholinesterase depression is 1.0 ppm in this study based on a depression of plasma cholinesterase in females and erythrocyte cholinesterase depression in both sexes at 20 ppm. The NOEL for reproductive effects is > 20 ppm.

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