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# DATA EVALUATION RECORD

## TRICHLORFON (Dipterex)

## Subchronic Feeding Study in Rats

CITATION: DuBois KP, Doull J, Rehfuss PA. 1956. The effects of diets containing Dipterex on rats. (Unpublished Chemagro Report No. 1376, submitted November 27, 1956).

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ACCESSION NUMBER: 090786.

MRID NUMBER: Not available.

LABORATORY: Department of Pharmacology, University of Chicago, Chicago, Illinois.

TEST MATERIAL: Dipterex (0,0-dimethyl-1-hydroxy-2,2,2-trichloroethylphosphonate) was described as a 50 percent soluble powder and was supplied by the Chemagro Corporation. No further information pertaining to the purity of the test material was provided.

PROTOCOL:

1. The test animals were Sprague-Dawley rats weighing 52-68 grams. The animals were randomly assigned to one of four groups. Each group contained 13 animals of each sex. Ten of the animals per sex group were used to measure growth and food consumption. The remainder of the rats were used to measure brain, RBC, serum, and submaxillary gland cholinesterase activities.

2. Dipterex was added to Rockland Rat Diet to provide dietary concentrations of 0, 20, 100, and 300 ppm. The diets were prepared as needed in 5 kg batches. Analyses of the diets were not reported.

3. The rats received the test diets for 16 weeks. Daily observations for general behavior, appearance, and toxic signs of cholinesterase inhibition were conducted. Food consumption and body weights were recorded daily during the first 10 days of the study, and on every second day during the remainder of the 16 weeks.

   Three male and female rats from each group were sacrificed at the end of the 16 week feeding period and examined for histopathologic lesions. For these animals, the brain, lungs, heart, left kidney, stomach, submaxillary gland, adrenal glands, spleen, and left testis of males were weighed in addition to being examined.

The cholinesterase activity of the serum, red blood cells (RBC), brain, and submaxillary gland were determined from three males and females of each group at the end of the 16-week feeding period. Several (exact number unspecified) animals from each group were sacrificed after 2 months on study, and the above tissues were assayed for cholinesterase activity. Cholinesterase activity was measured by the methods of DuBois and Mangun. (DuBois KP and Mangun G. 1947. Proc. Soc. Exper. Biol. Med. 64:137.)

4. No statistical analyses of the data were performed.

RESULTS:

It was reported that none of the animals "exhibited any symptoms which could be attributed to the presence of the insecticide in the diet." The data for body weight and food consumption were reported graphically. The graphs indicated that the body weights and food consumption among the Dipterex groups were similar to the control group. No deaths occurred during the 16-week feeding period.

The cholinesterase activities of the animals sacrificed at the end of the study are presented in Table 1. Among the males, cholinesterase activity was depressed by greater than 10 percent of the control activity in the serum and RBC at 300 ppm. Cholinesterase activity in the females was depressed by greater than 10 percent of the control activity in the brain, serum, and RBC at 300 ppm. The serum cholinesterase activity was also depressed by greater than 10 percent among the 100 ppm males and females. No cholinesterase activity data were presented for the animals sacrificed after 2 months on study, but the results were reported to be similar to those obtained at the terminal sacrifice.

No differences were observed when the organ weight to body weight ratios of the brain, lung, heart, spleen, left kidney, and left testis of the Dipterex-treated groups were compared to the control group. The ratios were presented for the males and females combined. No gross or microscopic Dipterex-related lesions were noted.

DISCUSSION:

The study provides useful information demonstrating the cholinesterase-inhibiting effects of Dipterex at dietary levels that produce no overt toxic signs of cholinesterase inhibition.

The organ-to-body weight ratios were combined for both sexes precluding an evaluation of possible Dipterex effects on each sex.

The most serious deficiency noted in the report was inaccuracies (or typographical errors) in the reported cholinesterase activities. Two instances existed (20 ppm male RBC and 100 ppm female brain cholinesterase

TABLE 1. Cholinesterase Activity in Selected Tissues of the Rat[a]

| Tissue | Sex | Dietary Concentration of Dipterex (ppm) 0 | 20 | 100 | 300 |
|---|---|---|---|---|---|
| Brain | M | 91.5 (87.3-93.7) | -[b] | 93.8 (86.8-102.8) | 94.3 (90.0-97.3) |
| | F | 92.3 (90.8-94.5) | 94.3 (91.3-98.7) | 89.5[c] (89.7-95.3) | 76.1 (68.1-83.6) |
| Submaxillary Gland | M | 23.4 (21.1-23.9) | 24.8 (22.8-25.9) | 23.0 (21.7-25.0) | 22.1 (19.9-25.3) |
| | F | 25.3 (25.5-27.1) | 26.1 (23.9-29.5) | 24.1 (21.2-28.1) | 24.2 (23.0-25.1) |
| Serum | M | 6.2 (5.6-6.8) | 6.0 (5.3-6.6) | 5.1 (4.7-5.3) | 4.7 (3.9-5.1) |
| | F | 25.3 (21.8-27.9) | 24.3 (23.1-25.9) | 21.7 (17.2-24.2) | 19.5 (17.7-22.5) |
| RBC | M | 9.7 (8.9-10.1) | 9.6[c] (9.9-11.3) | 9.9 (9.6-10.4) | 8.4[c] (8.3-9.0) |
| | F | 12.1 (11.9-12.3) | 12.6 (11.4-13.4) | 12.1 (11.3-13.0) | 10.2 (9.3-10.7) |

[a]Expressed as µl of $CO_2$ produced in 10 minutes per 50 mg of wet tissue. Data presented as average value and (range of the values).

[b]Data illegible in original report.

[c]Data presented as it appeared in the original report. Source of the error is not apparent to this reviewer.

activities) where the average value reported was less than the lowest value obtained. Another instance (300 ppm male RBC) occurred where the average cholinesterase activity value is not mathematically obtainable from the range of individual values reported. Thus, the accuracy of the remaining values may be in question.

CONCLUSIONS:

The dietary administration of Dipterex for 16 weeks to Sprague-Dawley rats at concentrations of 0, 20, 100, and 300 ppm produced no adverse clinical signs of toxicity and did not depress body weight gains or food consumptions. No effect on the organ-to-body weight ratio of select tissues was detected at terminal sacrifice.

The 16-week administration of 100 or 300 ppm Dipterex in the diet depressed serum cholinesterase activity in the male and female rats. The administration of 300 ppm Dipterex in the diet depressed RBC cholinesterase activity among both sexes and brain cholinesterase activity among female rats. Based on the depression in cholinesterase activity, the LEL for Dipterex administered in the diet to Sprague-Dawley rats was 100 ppm and the NOEL was 20 ppm.

CORE CLASSIFICATION: Supplementary data.

The major deficiencies noted in the study were the use of a small number (13/sex) of animals per test group, the use of only three animals per sex per test group for cholinesterase activity determination, and the absence of analyses of Dipterex concentrations in the experimental diets.