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DATA EVALUATION RECORD

TRICHLORFON

Acute Oral, Acute Dermal, and Subchronic Oral Toxicity in Rats

CITATION: Edson EF, Noakes DN. 1960. The comparative toxicity of six organophosphorous insecticides in the rat. Toxicol. Appl. Pharmarcol. 2:523-539.

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DATA EVALUATION RECORD

STUDY TYPE: Acute oral, acute dermal, and subchronic oral toxicity in rats.

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ACCESSION NUMBER: 090786.

MRID NUMBER: Not available.

LABORATORY: Chesterford Park Research Station, Saffron Walden, England.

TEST MATERIAL: "Dipterex 50," a 50 percent wettable powder, supplied by Bayer (Leverkusen).

PROTOCOL:

1. "Semiadult" Wistar albino rats that weighed 160-200 g were used (smaller rats were used in subchronic toxicity study). Preliminary tests were conducted on male and female rats to determine "which sex was more susceptible" to test material. The results were not presented but it was reported that males were more susceptible; therefore, males were subsequently used. The rats were maintained under unspecified but "similar conditions of housing and handling."

2. Acute oral toxicity tests were conducted with six rats at each dose level tested. "At least four dosage levels were tested," but were not specified in the report. Test material was diluted 1:2.5 in water, and administered by gavage. The animals were observed for 7 days, and then sacrificed by decapitation and necropsied.

3. Acute effects on cholinesterase activity were investigated using 12 rats dosed orally at 500 mg/kg (about 75 percent of the LD_{50} determined in acute oral toxicity tests). At 2 hours, 24 hours, 4 days, and 7 days after dosing, blood samples for cholinesterase determinations were taken from four rats. At 7 dats, brain cholinesterase activity was also measured. The data were compared to results obtained with an unspecified number of control rats of the same age.

4. Acute dermal toxicity tests were conducted with at least four animals at each of the three dosage levels [doses not specified]. Test material was mixed with water to obtain a smooth paste. The test material was applied to the shaved back (unabraded skin) of the animals, and "smoothed out with a spatula to a thin, even layer over an area approximately proportional to the applied volume." The maximum volume that could be applied by this technique was reported to be 1 ml. The area was then dusted with talc, and the trunk was encircled with a band of plaster. Each animal was caged separately for 20 hours, and then the plaster was removed. The treated area was washed with detergent and warm water, and the animals of one dose level were caged together and observed for 7 days.

5. A subchronic toxicity study was conducted using 10 rats/dose level and 8 control rats. The initial weights of the rats were 99–126 g. The test material was administered via the diet at dose levels of 1, 5, 25, and 125 ppm. The test material was mixed with water prior to its addition to the diet. Stock dilutions were made fresh every 7 days. Determinations of the stock dilutions' toxicities were conducted on freshly made and 7-day old solutions, and no significant differences ($p<0.05$) in toxicity were observed.

   Food consumption and body weights were measured weekly. "Regular observations" were made for pharmacotoxic signs. Erythrocyte and plasma cholinesterase activities were determined after 1, 2, 4, 8, and 13 weeks using pooled samples from four rats of each group. After 15–16 weeks, all animals were sacrificed for necropsies, relative organ weight determinations, and cholinesterase activity measurements (blood and brain).

6. The LD_{50} values were calculated by the method of moving averages (Weil, 1952), and cholinesterase activity was determined by a modified manometric technique (Fenwick et al., 1957) [complete references were missing from copy available for review].

RESULTS:

The acute oral LD_{50} was 649 mg/kg, with 95 percent confidence limits of 553–761 mg/kg. Toxic signs occurred within 15 minutes at all doses tested (doses not specifed), and within 5 minutes at approximate LD_{50} doses. The toxic signs were muscular fibrillation, salivation, lacrimation, urinary incontinence, diarrhea, respiratory distress, body- cooling, prostration, gasping, and death in coma. Convulsions sometimes occurred at doses above the LD_{50}. Death occurred as rapidly as within a few minutes after dosage, depending on the dose employed. Recovery from toxic effects was rapid and all survivors were "clinically normal when sacrificed at 7 days," and "were within normal limits" at necropsy. Animals that died rapidly showed "congestive appearances typical of an asphyxial mode of death, hypersecretion in the gut and bronchial tree."

The acute dermal LD_{50} was >2,800 mg/kg, which was the highest dose tested. No deaths occurred and "only very slight toxic effects" (not described) were observed among the six animals given that dose.

The erythrocyte and serum cholinesterase activities in rats dosed orally at 500 mg/kg were 30-40 percent of the control values 2 hours after dosage. Plasma cholinesterase activity in treated rats was normal 4 days after dosage, and erythrocyte cholinesterase activity in treated rats had increased to 84 percent of the control values 7 days after dosage. Brain cholinesterase activity in treated rats was 87 percent of the control value at sacrifice, 7 days after dosage.

No deaths, other than those due to bleeding accidents, occurred in the subchronic toxicity study, and no toxic effects were observed. Treated rats showed no differences from controls in body weight gains, relative liver and kidney weights (organ weight data were not presented), plasma and erythro- cyte cholinesterase activities (measured throughout the treatment period and at final sacrifice), and brain cholinesterase activity (measured at final sacrifice only). Differences in cholinesterase activities varied as much as ± 30 percent between treatment and control groups, but showed no dose-related or time-related patterns. The mean daily intake of test material was 11.3 mg/kg/day for the high-dose group.

DISCUSSION:

The results were presented in summary fashion, and data for individual animals and dose levels were generally not provided. The results can be used only as supplemental data because of the following deficiencies. Dose levels used in the acute toxicity studies were not specified. A dose-response curve and the times of death of individual animals were not reported for the acute oral toxicity study. The 95 percent confidence interval is 32 percent of the LD_{50}. The results of the preliminary acute oral toxicity tests with females were not provided; only acute toxicity data for males were given. Animals with abraded skin were not used, and females were not tested in the acute dermal toxicity tests. The area of application was not defined for the acute dermal toxicity tests. Pharmacotoxic and gross pathologic observations were not reported for individual animals in the acute toxicity studies. Body weight and food consumption data were not reported for the acute toxicity studies. The observation period was only 7 days for the acute toxicity studies.

In the subchronic toxicity study, only males were used, the age of the animals was not given, hematology, urinalyses, blood chemistry parameters other than cholinesterase activity were not measured, only liver and kidney weights were obtained, and histopathologic observations were not made.

Despite these shortcomings, the results provide useful information on the acute toxic effects of the test material. It is apparent that at dose levels of 500 mg/kg or greater, the test material caused acute toxicity in the rats, manifested by signs characteristic of organophosphate insecticide

toxicity. Brain cholinesterase activity was measured only at 7 days after dosage; possible early effects on cholinesterase activity were not assessed.

CONCLUSIONS:

Under the conditions of this study, the acute oral LD_{50} for Dipterex 50 percent WP in male rats was 649 mg/kg. The acute toxic effects were characteristic of organophosphate toxicity; i.e., rapid severe depression in serum and erythrocyte cholinesterase activity, lacrimation, salivation, tremors, convulsions, and respiratory distress. No toxic effect or inhibition of cholinesterase activity was observed in rats given Dipterex 50 percent WP via the diet at 1-125 ppm for 15-16 weeks. No toxic effect or death occurred among rats administered Dipterex 50 percent WP dermally at doses up to 2,800 mg/kg.

CORE CLASSIFICATION: Supplementary for all studies.

This core classification is based on the deficiencies presented in the Discussion section.