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DATA EVALUATION RECORD

TRICHLORFON

Three-Month Subchronic Administration of Trichlorfon
to the Dog in the Diet

CITATION: Williams MW, Fuyat HN, and Fitzhugh OG. 1959. The subacute toxicity of four organic phosphates to dogs. Toxicol. Appl. Pharmacol. 1:1-7.

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DATA EVALUATION RECORD

STUDY TYPE: Three-month subchronic administration of Trichlorfon to the dog in the diet.

CITATION: Williams MW, Fuyat HN, and Fitzhugh OG. 1959. The subacute toxicity of four organic phosphates to dogs. Toxicol. Appl. Pharmacol. 1:1-7.

ACCESSION NUMBER: 090786.

MRID NUMBER: Not available.

LABORATORY: Division of Pharmacology, Bureau of Biological and Physical Sciences, Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C.

TEST MATERIAL: The test material was identified as Dipterex and was reported to be of technical grade. The purity was assumed to be 100 percent for dosing purposes. No other information pertaining to test material identification, source, or purity was provided. Three additional organophosphates (methyl parathion, Diazinon, and chlorthion) were tested separately but concurrently with Dipterex.

PROTOCOL:

1. Mixed breed dogs each weighing about 6 kg were utilized in the study. One male and one female dog were assigned to each dose level. The age and source of the dogs were not provided. Four additional dogs (sex unspecified) were used as controls.
2. Dipterex was mixed with commercial dog food at concentrations of 50, 200, and 500 ppm. The Dipterex diets were offered to the dogs ad libitum for a 12-week period. The other organophosphates (methyl parathion, Diazinon, and chlorthion) were similarly prepared and administered. Food consumption was not determined. The control dogs received commercial dog chow.
3. Following a one-week acclimation period the animals were allowed a four-week control period during which five plasma and red blood cell (RBC) cholinesterase determinations were made. The blood samples used for the determinations were obtained by jugular puncture. The 12 week Dipterex treatment phase of the study followed the control period. During the treatment phase, plasma and RBC cholinesterase determinations were made at the end of the first week and every second week

thereafter. An eight-week post-treatment control phase followed treatment during which RBC and plasma cholinesterase determinations were made at unspecified intervals. The animals were not sacrificed, thus, brain or other tissue cholinesterase levels were not determined, and no tissues were taken for pathologic examination.

4. Cholinesterase activity was measured by determining RBC and plasma enzyme induced pH changes with reference to time in an acetylcholine substrate preparation. These determinations were made during the treatment and post-treatment period. Changes in excess of two standard deviations from the control period values were considered statistically significant.

RESULTS:

The results of the RBC and plasma cholinesterase determinations were reported as the percent change from the pretreatment control values and presented graphically. No actual cholinesterase activity values were reported.

The authors stated that significant depressions in plasma and RBC cholinesterase activities were detected within two weeks of treatment with Dipterex at 500 ppm. The cholinesterase depressions were "borderline" at 200 ppm and no depressions occurred at 50 ppm. Plasma cholinesterase activity decreased more rapidly than RBC cholinesterase activity with a maximum depression of 40 percent in plasma cholinesterase activity occurring at six weeks of treatment among the high dose dogs. Maximum depression of RBC cholinesterase activity at 500 ppm was about 55 percent and occurred during weeks 8-12 of the treatment phase. Both the plasma and RBC cholinesterase activities returned to pretreatment levels by the fourth week of the post-treatment control phase.

"Borderline" RBC cholinesterase depression was reported for chlorthion at 15 ppm in the diet. Methyl parathion depressed RBC and plasma cholinesterase activity at dietary levels of 20 and 50 ppm and Diazinon depressed plasma cholinesterase activity at dietary levels of 0.75 and 75 ppm.

DISCUSSION:

The study provides only limited data on subchronic toxicity of Dipterex in dogs. It is clear that Dipterex ingestion produced a depression in plasma and RBC cholinesterase activity; however, no other meaningful information can be derived from the published data. The following additional deficiencies are noted:

- o Only one dog/sex was used at each treatment level.
- o Actual cholinesterase values were not reported.
- o Dietary intake was not monitored.

- o Clinical observations and possible signs of cholinesterase inhibition were not reported.
- o The dogs were of mixed breed and their age and source were not specified.

CONCLUSIONS:

The administration of Dipterex in the diet to mixed breed dogs at a concentration of 500 ppm resulted in 40 and 55 percent inhibition of the plasma and RBC cholinesterase activities, respectively, when compared to the pretreatment levels. "Borderline" cholinesterase depression resulted from dietary levels of 200 ppm and no depression resulted from a dietary level of 50 ppm. Based on the data reported, the NOEL for cholinesterase inhibition was greater than 50 ppm but less than 200 ppm.

CORE CLASSIFICATION: Supplementary data.

This classification is based primarily on a limited number of animals used and the lack of any report on clinical observations for possible toxic signs.