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DATA EVALUATION RECORD

TRICHLORFON

Chronic Oral Toxicity - Dogs

CITATION. Doull J, Root M, Vesselnovitch D, Meskauskas J, Fitch F. 1962. Chronic oral toxicity of Dylox to male and female dogs. (An unpublished study submitted by Chemagro Division, Mobay Chemical Corp., Report Number 8644, dated January 3, 1962.)

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6 pages

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STUDY TYPE: Chronic (one year) oral toxicity - dogs.

CITATION: Doull J, Root M, Vesselnovitch D, Meskauskas J, Fitch F. 1962. Chronic oral toxicity of Dylox to male and female dogs. (An unpublished study submitted by Chemagro Division, Mobay Chemical Corp., Report Number 8644, dated January 3, 1962.)

ACCESSION NUMBER: 090786.

MRID NUMBER: Not available.

LABORATORY: Department of Pharmacology and Pathology, University of Chicago, Chicago, Illinois 60637.

TEST MATERIAL: The test material was identified as Dylox (Bayer 13/59, O,O-dimethyl-2,2,2-trichloro-1-hydroxyethyl-phosphonate, technical), which has the common name trichlorfon and was provided by the Chemagro Division, Mobay Chemical Corp., Kansas City, MO.

PROTOCOL:

1. Twenty pure-bred beagle dogs (10 of each sex, 4-6.5 kg in weight) were obtained at 20 weeks of age, acclimated for 4 weeks (including deworming and vaccinations for distemper and hepatitis), and divided into a control and 4 dose groups (2 animals/sex/group). The dogs were housed individually in metabolism cages and provided water and food ad libitum throughout the study.

2. Five dietary levels of Dylox (0, 50, 250, 500, and 1000 ppm) were administered to the control and each dosed group for 1 year. The diets were prepared every 2 weeks by mixing the appropriate amounts of Dylox with ground Rockland Dog Food.

3. The dogs were weighed weekly for the first 4 months of the study and monthly thereafter. Food consumption was determined daily during the "first few weeks."

4. Serum and erythrocyte cholinesterase activities were determined by the method of DuBois and Mangun (Proc. Soc. Exp. Biol. Med. 64:134, 1947) for blood samples obtained from all dogs at least 5 times prior to the start of the study and at 2-week intervals throughout the study. Samples of liver, brain, and blood were obtained at final sacrifice and assayed for cholinesterase activity.

5. After 1 year of dosing, the dogs were sacrificed with pentobarbital and the following tissues were weighed and prepared for histologic examination: brain, liver, kidney, spleen, heart, lungs, thymus, adrenals, urinary bladder, ovary or testis, mesenteric and thoracic lymph nodes, stomach, duodenum, pancreas, ileum, jejunum, colon, skeletal muscle, and sternum.

RESULTS:

Body Weights and Food Consumption: The dogs of the control and all 4 treated groups showed similar weight gains during the study, increasing in body weight approximately 100 percent. No food consumption data were presented; the authors stated that no consistent decreases in food consumption were noted.

Cholinesterase Activity: Serum cholinesterase activity was depressed to 55 percent of its pretest levels within the first 2 weeks of study in the dogs fed 1000 ppm. This activity remained depressed at 45-60 percent of pretest levels for the remainder of the study. Within 2 months, serum cholinesterase activity was depressed to 70 percent of pretest activity in the 500-ppm group and remained depressed at 60-70 percent for the rest of the study. In the control, 50-, and 250-ppm groups, serum cholinesterase levels declined during the first 3 months and remained at approximately 80 percent of pretest levels throughout the study. Erythrocyte cholinesterase activity was depressed in the 1000- and 500-ppm groups to 35 percent at 6 weeks and to 65 percent at 5 months, respectively. Activities in the 50- and 250-ppm groups remained within 20 percent of pretest; data from the control (0 ppm) group were not legible. Cholinesterase activities determined on samples of liver and brain indicated no effect at the 50-, 250-, and 500-ppm dose levels; at 1000 ppm, brain cholinesterase activity was inhibited to a level 60 percent of control.

Pathologic Examinations: At the gross pathologic examinations conducted after sacrifice, the dogs fed 1000 ppm were observed to have "mild to moderate" enlargement of the spleen. No other consistent differences were reported. Determination of relative organ weights verified that the spleens of the high dose animals were 4-5 times heavier than the control group (Table 1), and that all the other groups, except the males at the 500-ppm dose level, showed increases in relative spleen weights of 50-200 percent relative to control (Table 1). The authors attributed the extensive splenic enlargement of the high dose group to 2 animals, one male and one female, which were not "bled-out" and therefore had heavier (blood engorged) spleens. The livers from the dosed groups, except for the 500-ppm males, also were heavier than controls by 17-71 percent (Table 1). Other organs showed differences that were not consistent. Although the differences in liver and spleen weights appeared to be related to the test compound, a definite dose-response relationship was not demonstrated.

TABLE 1. Liver and Spleen Weights and Their Ratios to Body Weight in Dogs Fed Dylox

Organ	Group (ppm)	Sex	Weight (g)	Ratio (g/100 g)	Difference[a] (Percent)
Liver					
	Control	M	175.0	2.41	—
		F	155.0	2.44	—
	50	M	319.5	2.83	+17
		F	324.5	3.37	+38
	250	M	337.5	3.05	+26
		F	227.5	3.13	+28
	500	M	393.5	2.17	-10
		F	302.0	4.17	+71
	1000	M	428.0	3.71	+53
		F	382.5	3.32	+36
Spleen					
	Control	M	13.0	0.18	—
		F	11.0	0.17	—
	50	M	30.5	0.27	+50
		F	33.5	0.34	+200
	250	M	30.5	0.28	+56
		F	23.5	0.32	+88
	500	M	31.5	0.18	0
		F	19.5	0.28	+65
	1000	M	101.5	0.88	+489
		F	67.0	0.92	+541

[a]Difference in the ratios from control.

The major findings of the histopathologic examination of the tissues were reported in the spleen, adrenal, liver, and gonads, although none of the results were presented for individual animals. Three of the 4 dogs fed 1000-ppm showed "marked congestion" of the spleen and all 4 dogs displayed lymphoid atrophy of this organ. At the 500-ppm level, 3 dogs showed splenic congestion and 2 lymphoid atrophy. In addition, several of the dogs fed the Dylox-containing diets had hyperplastic cortical nodules of the adrenal gland; no such lesions were observed in the control animals. The incidences of these nodules in the 50-, 250-, 500-, and 1,000-ppm groups were 2/4, 1/4, 1/4, and 3/4, respectively.

Histopathologic findings in liver tissue consisted of "foci of chronic inflammatory cells" which were evident in both control and dosed animals. Incidences in the 250-, 500-, and 1000-ppm groups were 2/4, 3/4, and 3/4, respectively; incidences for the control and 50-ppm groups were not legible. Finally, the 2 male dogs fed 1000-ppm exhibited less spermatogenesis than the males of the control or other dosed groups.

DISCUSSION:

Although this study adequately demonstrated the effects of dietary consumption of Dylox (trichlorfon) on cholinesterase activity, five deficiencies in the experimental design and report precluded adequate evaluation of the test material's chronic toxicity: too few animals were tested in each group, dosing was conducted for 1 year only, no clinical pathology studies were conducted, and histopathologic findings for individual animals were not presented. Consequently, dose-related increases in liver and spleen weights could not be substantiated by either changes in blood chemistry indicative of hepatic or splenic injury or by histopathologic evidence of injury. These increases in organ weights and the findings of lymphoid atrophy in spleen and inflammatory cells in liver primarily in the dosed animals strongly suggested dose-related effects. In their report, the authors stated that, because the lymphoid atrophy was associated with "marked congestion" of the spleen, the atrophy was an artifact of necropsy. However, one high-dose female and one 500-ppm male displayed congestion without lymphoid atrophy. More thorough testing, e.g., with larger groups for a longer period of time and including clinical studies, is needed to verify these apparent effects. In addition, the observation of hyperplastic cortical nodules in the adrenal gland of several Dylox-treated dogs may be of importance since no such nodules were found in the control dogs. However, it should be noted that the small number of dogs examined (4 per group) may have precluded detection of these common and spontaneous nodules in the control animals. In any case, these briefly reported findings cannot be dismissed and further study is needed to assess their significance.

CONCLUSIONS:

Beagle dogs fed dietary levels of 500 and 1000 ppm of Dylox (trichlorfon) displayed depressions of serum and erythrocyte cholinesterase activity within 2 months of dosing; brain cholinesterase activity measured at 1-year sacrifice was depressed at the 1000-ppm level. Liver and spleen organ-to-body weight ratios were increased over the controls by 17 to 71 and 50 to 541 percent, respectively; however, these increases did not display a consistent dose-response relationship. Histopathologic changes were also reported in the livers (chronic inflammatory cells) and spleens (lymphoid atrophy) of the animals dosed at 500 and 1000 ppm; and decreased spermatogenesis was seen in the two male dogs of the 1000-ppm group. However, too few animals were tested to verify these changes as definite effects of the test material. In addition, hyperplastic nodules were

observed in the adrenals of dogs in each of the dosed groups while none were observed in the controls. These lesions may have resulted from consumption of the test material; however, the size of the groups precluded a definitive conclusion. Consequently, the results of the study adequately identified 250 and 500 ppm as the NOEL and LEL, respectively, for effects on cholinesterase activity; however, due to the deficiencies in design and reporting as outlined in the Discussion, the study is not adequate for evaluating other aspects of the chronic toxicity of Dylox.

CORE CLASSIFICATION: Supplementary. The basis for this core classification is the following deficiencies: 1) too few animals were tested, 2) no clinical studies were performed, 3) dosing was limited to 1 year, and 4) histopathologic findings were not reported for individual animals.