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DATA EVALUATION RECORD

TRICHLORFON

Carcinogenicity: feeding in rats

CITATION: Doull J, Vessilinovitch D, Fitch F et al. 1965. Chronic oral toxicity of Dylox to male and female rats. (Unpublished report prepared by Department of Pharmacology, University of Chicago, CDL:097552-AN submitted by Chemagro Corp., Kansas City, MO.)

REVIEWED BY:

William L. McLellan, Ph.D.
Project Scientist
Dynamac Corporation
11140 Rockville Pike
Rockville, MD 20852
301-468-2500

Signature: William L. McLellan Ph.D.

Date: July 28, 1983

Cipriano Cueto, Ph.D.
Program Manager
Dynamac Corporation
11140 Rockville Pike
Rockville, MD 20852
301-468-2500

Signature: Cipriano Cueto

Date: 28 July 1983

APPROVED BY:

Irving Mauer, Ph.D.
EPA Scientist

Signature: Irving Mauer

Date: 07.30.83

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STUDY TYPE: Carcinogenicity: feeding in rats.

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ACCESSION NUMBER: Not available.

MRID NUMBER: 00080595.

LABORATORY: University of Chicago, Department of Pharmacology.

TEST MATERIAL: The test compound was identified as Dylox (trichlorfon technical, 99.9 percent purity).

PROTOCOL:

1. The test animals were as follows:

Species/strain -- Sprague-Dawley Rats.

Number and Sex -- 200 female, 100 male.

Age/weight at Initiation -- Weanling rats were used; weight ranged from 54-96 g. Animals were randomized and divided into four groups, each containing 25 males and 50 females.

Husbandry -- Animals were individually housed; animal rooms were air-conditioned (80±3°F), and animals had constant access to food and water.

2. Dylox (lot no. 62-19-33) was administered after mixing with ground Rockland Laboratory Diet at levels of 0 (control), 100, 200, and 400 ppm.

3. The experimental parameters investigated were as follows:

o Food consumption was measured twice a week for the first 30 days.

o Body weight was measured weekly for the first month, and thereafter animals were weighed at biweekly intervals.

- o Clinical observations -- Mortality was followed at weekly intervals. Animals were examined weekly for grossly detectable tissue masses.
- o Necropsy -- Animals that died during the course of the study were autopsied and tissue prepared for histologic examination unless precluded by autolysis. At the end of the feeding period, surviving animals were sacrificed, tissue weighed and prepared for histopathologic study.
- o Tissues weighed at final sacrifice: brain, liver, kidney, spleen, heart, lung, and testes.
- o Tissues examined microscopically: brain, liver, kidney, heart, lungs, spleen, thymus, gonads, adrenal gland, urinary, bladder, mesenteric lymph nodes, stomach, duodenum, pancreas, ileum colon, and sternal bone marrow.
- o Cholinesterase determination: At sacrifice (72 weeks) cholinesterase determinations were carried out on brain, submaxillary gland, serum, and packed erythrocytes from at least 5 animals per sex per group.

RESULTS:

There was no marked change in food consumption or weight gain in dosed animals in comparison to controls. There was no effect on cholinesterase activity. The mortality in both control and treated animals was high between 10 and 18 months, particularly in female rats. It is much higher than expected for this strain of rat. Animals were sacrificed earlier than planned, at 72 weeks, so that there would be 5 animals of each sex at each dose level for cholinesterase determination and pathologic studies. The median survival in control males was 60 weeks. The death rate in females from week 60 to 72 was much greater than in males and not dose related. There were decreases in spleen to body weight ratios and liver to body weight ratios in males on 400 ppm, but not at lower levels in males or at any level in females. There was no statistical analysis of the data. At sacrifice there was a slight inhibition of serum and erythrocyte cholinesterase (c.a. 20 percent and not considered of toxicologic significance) but no decrease in activity in brain or submaxillary gland. Tables 1 and 2 summarize the notable gross and histologic findings. Small numbers of animals were examined and no statistical analysis of the data were performed. There were no marked changes that could be attributed to the dietary administration of trichlorfon; however, the incidence of cystic ovaries was higher in dosed animals than in controls. It cannot be concluded that the

TABLE 1. Incidence of Gross Pathologic Findings

Finding	Sex	Dose Level (ppm)			
		0	100	200	400
Cystic ovaries	F	0/12(0) ^a	2/14(14)	3/9(33)	8/20(40)
Mammary tumors	F	1/12(8)	0/14(0)	1/9(11)	3/20(15)
Lungs-consolidation ^b	F	8/12(67)	6/14(43)	7/9(78)	14/20(70)
+		3	3	5	4
++		4	3	2	6
+++		1	0	0	2
++++		0	0	0	2
Lungs-consolidation	M	1/5(20)	5/6(83)	8/8(100)	2/5(100)
+		0	2	4	1
++		1	1	1	1
+++		0	1	3	0
++++		0	1	0	0
Lungs-consolidation M and F		9/17(53)	11/20(55)	15/17(88)	16/25(64)

^a Percent incidence is given in parentheses.

^b +, ++, +++, and ++++ indicate the severity of the lesions in lungs.

TABLE 2. Histopathology Observations

Finding	Sex	Dose Level (ppm)			
		0	100	200	400
Old ovaries ^a	F	1/5	1/5	1/5	5/5
Cystic ovaries	F	1/5	1/5	1/5	4/5
Mammary tumor ^b	F	1/12	0/14	1/9	3/5
Testes ^c	M	2/5	3/5	3/5	3/5
Lungs ^d	F	5/5	4/5	5/5	5/5
Kidneys ^e	M	3/5	5/5	4/5	5/5
	F	2/5	3/5	2/5	3/5
	M	3/5	5/5	5/5	5/5

^a Primary follicles and ova not found.

^b Fibroadenoma and glandular tumors.

^c Inhibition of spermatogenesis in seminiferous tubules.

^d Chronic and acute bronchitis and pneumonitis.

^e Dilated tubules.

animals were adequately tested for carcinogenicity. The excessive mortality and high incidence of acute bronchitis and pneumonitis may have contributed to the early deaths seen in all groups.

CONCLUSIONS:

Trichlorfon was fed to Sprague-Dawley rats for 18 months at levels of 0, 100, 200, and 400 ppm. Food consumption was measured during the first month and body weights were measured throughout the study. Animals were clinically observed weekly for tissue masses and mortality was followed weekly. Animals that died were necropsied and tissues prepared for histology. At sacrifice, cholinesterase levels were measured in brain, submaxillary glands, erythrocytes, and serum; organs were weighed and tissues examined histologically.

Carcinogenicity of trichlorfon has not been adequately tested in this study because of the high mortality of animals in all groups. In addition, the histopathology on animals that died before the 18-month sacrifice is limited. Sufficient dose levels were chosen to determine a NOEL for systemic toxic effects but because of limited data this value cannot be estimated.

CORE CLASSIFICATION: Invalid.

The following deficiencies in the study were noted by this reviewer:

- o Only 5 animals of each sex in each group that survived to 18 months were examined histologically. This corresponds to 20 percent of males and 10 percent of females started in the study.
- o The thoroughness of the pathologic studies could not be verified because of paucity of data.
- o Gross pathologic examination was performed on only a few animals; furthermore, it could not be determined whether the animals examined were sacrificed or if they were found dead.
- o Food consumption was measured infrequently, therefore intake in mg/kg could not be determined..
- o Mortality data were not clearly presented so that statistical evaluation could be made. The data were presented only graphically.
- o Clinical observations were not presented to assess the cause of premature death of all groups of animals.
- o Cholinesterase activity was determined only at sacrifice.