

US EPA ARCHIVE DOCUMENT

DATA EVALUATION RECORD
TRICHLORFON

(M, 07.30.83)

Carcinogenicity--Oral ~~Feeding~~ in Mice

CITATION: Teichmann HB, Hauschild F. 1979. Testing of O,O-dimethyl-~~(1,hydroxy-2,2,2-trichloroethyl)-~~phosphonate (Trichlorfon) for carcinogenic activity in mice by oral, intraperitoneal and dermal application. Arch. Geschwulstforsch. 48(4):301-307 (translation).

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page (Jm, 07.20.83)
STUDY TYPES: Carcinogenicity—Oral ~~Feeding~~, Intraperitoneal Injection, or Dermal Application in Mice.

CITATION: Teichmann HB, Hauschild F. 1979. Testing of 0,0-dimethyl-(1,hydroxy-2,2,2-trichloroethyl)-phosphonate (Trichlorfon) for carcinogenic activity in mice by oral, intraperitoneal and dermal application. Arch. Geschwulstforsch. 48(4):301-307 (translation).

ACCESSION NUMBER: Not available.

MRID NUMBER: 0069026.

LABORATORY: Central Institute for Cancer Research, Berlin-Buch.

TEST MATERIAL: Trichlorfon, synthesized and repeatedly recrystallized, served as the test compound. Purity was not stated.

PROTOCOL:

1. Mice of the AB/Jena strain were used for the test. Test animals were 8 weeks old at the start of the study. Groups of 30 males and 30 females were used for orally, dermally and intraperitoneally, dosed groups, including controls, and were housed 10/sex/dose route/cage.
2. The compound was administered as follows:
 - a. Oral (gastric intubation); 30 mg/kg as a 1 percent solution (isotonic NaCl) of neutralized sample, 2 times a week for 73 weeks.
 - b. Intraperitoneal: Doses of 28.2 mg/kg body weight in isotonic saline of a neutralized sample, 2 times per week, for 73 weeks.
 - c. Dermal: Doses of 0.25 ml of a 1 percent solution in acetone were applied to shaved skin on back of mice, 2 times a week for 75 weeks.
3. With respect to parameters investigated, only tumor findings were reported.

RESULTS:

There was no significant increase over controls in the incidence of tumors or incidence of any specific tumor for either males or females treated by the oral, the intraperitoneal or the dermal routes. The data on malignant and benign tumors for control and test animals are summarized in Tables 1-3. The mean life span of the groups treated with trichlorfon was lower than the corresponding control groups. The mean body weights were lower for both treated males and females than for animals in the corresponding control groups. Mortality data are summarized in Table 4. No individual animal data were reported. Since animals did not survive over a significant portion of their life span, this study is not an adequate assessment of carcinogenicity. Only one dose level was used; this level may have been too high since 66 and 95 percent of males treated by the oral or intraperitoneal routes died compared to 37 and 66 percent of control males, respectively.

CONCLUSIONS:

An 80-week study was conducted to test the carcinogenicity of trichlorfon in AB/Jena mice when the compound was administered by oral gavage, intraperitoneal injection or by application to the shaved skin. Thirty animals of each sex were used in test and control groups. The dose levels were based on 5 percent of the LD₅₀ value. For oral, intraperitoneal and dermal routes, doses of 30 mg/kg, 28.2 mg/kg, and 2.5 mg/mouse, respectively, were administered 2 times a week for 75 weeks and surviving mice observed until 80 weeks.

No excess in total number of tumors or of any specific type of tumors was found when treated males or females were compared with controls. At 52 weeks of dosing there a marked increase in mortality in groups dosed by the oral or intraperitoneal route when compared to controls; at 75 weeks mortality was excessive in all groups.

CORE CLASSIFICATION:

This study is classified as Core Invalid because animals did not survive a sufficient fraction of their expected lifetime, insufficient number of animals were used, and only one dose level was tested. Under the conditions of this study, it is impossible to assess the carcinogenic potential of the test compound or determine a chronic LOEL.

The following deficiencies were noted by this reviewer:

1. Insufficient animals were used in the study.

2. Mortality was exceptionally high at 75 weeks in all treated groups.
3. Only tumor findings were reported; there was no evidence that a complete histopathologic examination of the animals was performed.
4. Doses were based on LD₅₀ values, not on a subchronic dosing study, only one dose level was used for each route of administration, and animals were dosed only two times per week.
5. Although it was stated that mean body weights were lower in both treated males and females, no data were provided and no indication was made that the weights were statistically different. Food consumption data were not provided.
6. The doses given orally or by the intraperitoneal route exceeded the maximum tolerated dose (MTD) and resulted in poor survival of all dosed animals.
7. No observations of toxic signs were provided and no hematology or clinical chemistry determinations were provided.

TABLE 1. Tumors in Mice Administered Trichlorfon by Oral Gavage

Tumors	Control		Dosed 9/58	
	Male	Female	Male	Female
<u>Malignant</u>				
Fibrosarcoma	1	1	2	1
Reticulum cell sarcoma	1	0	2	1
Lung carcinoma	1	0	0	0
Mammary carcinoma	0	1	0	0
Leukemia	0	2	0	3
<u>Benign</u>				
Lung adenoma	1	0	1	1

TABLE 2. Tumors in Mice Administered Trichlorfon Intraperitoneally

Tumors	Control		Dosed	
	Male	Female	Male	Female
<u>Malignant</u>				
Fibrosarcoma	3	0	4	1
✈ Lung adenocarcinoma	1	0	1	0
Leukemia	0	1	0	2
Mammary carcinoma	0	3	0	1
Reticular cell sarcoma	0	2	0	0
<u>Benign</u>				
Lung adenoma	1	0	1	1

TABLE 3. Tumors in Mice Administered Trichlorfon Dermal

Tumors	Control		Dosed	
	Male	Female	Male	Female
<u>Malignant</u>				
Fibrosarcoma	2	2	3	2
Lung carcinoma	1	0	2	1
Reticular cell sarcoma	0	1	0	1
Leukemia	0	2	1	3
Mammary carcinoma	0	1	0	0
<u>Benign</u>				
Lung adenoma	2	1	1	1
Skin papilloma ^a	0	0	1	0

^a At site of application.

TABLE 4. Mortality at 52 Weeks and 75 Weeks

Route/Sex	Control			Treated		
	No. ^a	52 ^b wk.	75 wk.	No.	52 wk.	75 wk.
<u>Oral</u>						
Male	30	6	11	30	8	20
Female	29	7	26	28	14	27
<u>Intraperitoneal</u>						
Male	30	2	20	30	9	28
Female	30	5	22	30	8	28
<u>Dermal</u>						
Male	30	7	27	30	2	11
Female	30	7	26	30	5	24

^a Number of animals at start of study.

^b Cumulative deaths.