Machemer GS 0104 108

6

Releasable

Trichlorfon (TCF) Caswell No. 385
(EPA Registration 3125-9)

DATA EVALUATION RECORD

STUDY TYPE: (Oral) Rabbit Teratology.

ACCESSION NUMBER: 244915

MRID NUMBER: (Not assigned)

SPONSOR: Mobay Chemical Corporation, Report #69299, submitted March 24, 1981.

CITATION: "L 13/59 (Trichlorfon). Evaluation for Embryotoxic and Teratogenic Effects on Orally Dosed Rabbits," by Dr. L. Machemer.

CONTRACTING LAB: Bayer AG Institut Für Toxikologie, Report No. 8430.

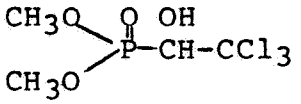
DATE: June 8, 1979

TEST MATERIAL: Technical, 98.4% TCF.

REVIEWED BY: Irving Mauer, Ph.D., Geneticist (TB/HED) Irv Mauer 04-15-83

DATE OF REVIEW: April 6, 1983

PROTOCOL: Chemically, trichlorfon is O,O-dimethyl-2,2,2-(trichlorohydroxyethyl)-phosphonate, with the following structural formula:



Fifteen inseminated female Himalayan rabbits per group were given daily oral doses (by gavage) of TCF (in 5 ml/kg 0.5% Cremopher Emulsion) from day-6 through day-18 of gestation (total of 13 doses) at 5, 15 and 45 mg/kg. Control animals received 5 ml/kg of the carrier. Does were examined and weighed daily. On gestation day-29, fetuses were resected (by cesarean), and the following recorded:

a. The number of implantations.

b. The number of viable and dead fetuses and embryos.

c. The sex of each fetus.

58

d. Litter weight and average fetus weight per litter.

e. The number of stunted fetuses (weighing less than "25 grams". [stated, but presumably 2.5 was meant.]

f. The average placental weight per litter.

g. Thorough inspection of all fetuses for external anomalies and alterations.

All fetuses were autopsied, and the following regions examined:

(i) All abdominal and thoracic organs;

(ii) The brain, for malformations after removal of the head on a plane from angle of mouth to point of ear attachment, fixation in 70% alcohol: formol:glacial acetic acid (80:20:5 parts by volume), and preparation of cross-sections with a razor blade;

(iii) After clearing in dilute potassium hydroxide solution, the skeleton stained with Alizarin Red S, and entire bone system assessed.

The following numbers of fetuses examined by these standardized methods were as follows:

Test group	Number of fetuses
Control	81
5 mg/kg	92
15 mg/kg	78
45 mg/kg	72

Statistical significance was assessed by the following methods:

1. Non-parametric ranking, by the "U" test of Wilcoxin, Mann and Whitney for weight gains, number of implantations, number of fetuses, number of resorptions, fetal weight and placental weight;

2. The chi-square test (with Yates correction) for the numbers of fetuses with skeletal alterations, anomalies, and stunting;

3. Either the chi-square test (with Yates correction), or Fisher's Exact Test, for incidences of fertilized and pregnant does, depending upon expected frequency.

Significance of differences between treated and control groups was set at the 5% level ($p < 0.05$).

RESULTS: Except for reduced food intake by 2 does of the 5 mg/kg group and 3 of the 15 mg/kg group, accompanied by loss of hair in 2 does of the 5 mg/kg group (which occur occasionally in these rabbits and thus cannot be attributed to administration of the test compound), treatment with TCF at dose levels up to and including 15 mg/kg/day per os did not appear to have any detrimental effects on the physical appearance or behavior of the does.

At 45 mg/kg/day, however, 2 of the 15 does aborted, one each on gestation days-20 and -24. These two rabbits showed signs associated with abortion, e.g., reduced food intake, intestinal disorders (manifested in one animal by failure to defecate, and in the other by diarrhea), and a "sickly" appearance.

One female treated at 15 mg/kg/day died of acute pneumonitis during the test, but all the other test animals survived until cesarian section. Therefore, doses up to and including 45 mg/kg/day were not considered lethal.

The following table summarizes the average weight gains reported (expressed in grams) made by the does of the different test groups during the treatment period from gestation day-6 to -18 as well as throughout gestation. Only does with viable fetuses at cesarian section were recorded.

	Average weight gain (in g) during:	
Test group	Treatment period	Entire gestation period
Control	130.7	155.4
5 mg/kg	74.0	179.7
15 mg/kg	70.4	185.0
45 mg/kg	67.7	125.8

Thus, it appears that although the does of each treated group made less weight gain on the average than the controls during the treatment period, the difference was not statistically significant. The average weight gains made by the does of the TCF-treated groups throughout gestation varied greatly, but the authors observed no indication of any systematic treatment-related influence on this parameter. (The individual results of doe body weights are presented in Tables 1-4 attached to the report.)

Of the does which copulated twice, the following incidences of fertility and pregnancy at Cesarian section were recorded:

Dose (mg/kg)	No. of inseminated females	Fertilized females: Total	Fertilized females: % of inseminated	Pregnant females: Total	Pregnant females: % of fertilized
0	15	14	93.3	14	100.0
5	15	15	100.0	15	100.0
15	15	13	86.6	13	100.0
45	15	15	100.0	13	86.6

Hence, group fertility incidences (percentage of fertilized does in relation to those inseminated), which would not have been influenced since treatment commenced on gestation day-6, did not vary appreciably in any of the test groups, and were within the normal range (as also compared to historical records) for the rabbit strain used in this study.

It was also evident from the pregnancy rate (the above tabulation) that treatment with TCF at doses up to and including 15 mg/kg did not have any embryolethal effect. However, since the pregnancy rate in the 45 mg/kg group was decreased due to two abortions (compared to none in the control group), a treatment-related effect could not be excluded by the authors.

Data from the examination of cesarean-resected fetuses, presented for individual test animals in Tables 1 through 4 of the report (with group averages summarized as Table 5), revealed no statistical significant differences between treated groups (any dose) and the control in average numbers of implantations, live fetuses (although reduced due to the two abortions), or resorptions (insignificantly increased due to the same 2 abortions); and, no appreciable changes in sex ratio, fetal or placental weights, or the occurrence of stunted fetuses. Skeletal retardation was not observed in any group.

The following malformations, considered by the authors to be spontaneous, were seen in the control group and in the 5 mg/kg group (only) as follows:

Dose (mg/kg, p.o.)	Doe No.	Number of malformed fetuses	Malformation
0	1182	1	Kinky tail
	1183	1	Arthrogryposis of left forepaw
	1189	1	Arthrogryposis of both forepaws
5	1201	1	Rib fusion (4th and 5th, right)
15	-	-	None
45	-	-	None

The authors concluded that the administration of TCF at doses up to 45 mg/kg/day caused decreased weight gain in treated does, but was not lethal; had no evident untoward effects on appearance and behavior, but 2 of the 15 does aborted, manifesting adverse signs (thus contributed to embryonic toxicity, but only as a consequence of maternal effects).

No maternal or fetal effects were recorded in the 5 and 15 mg/kg groups.

Hence, the authors considered the maternal (and fetal) NOEL of TCF in these rabbits to be 15 mg/kg p.o.

Finally, TCF apparently has no propensity to produce teratogenic effects at doses up to 45 mg/kg.

REVIEWER'S EVALUATION: The study is considered Core-Minimum Data.