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DATA EVALUATION RECORD

TRICHLORFON

Chromosomal Aberrations in Mice (Dominant Lethal Test)

CITATION: Fischer GW, Schneider P, Scheufler H. 1977. On the mutagenicity of dichloroacetaldehyde and 2,2-dichloro-1,1-dihydroxy-ethanephosphonic acid methyl ester, possible metabolites of the organophosphorous pesticide trichlorphon. Chem. Biol. Interact. 19:205-213.

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DATA EVALUATION RECORD

STUDY TYPE: Chromosomal aberrations in mice (dominant lethal test).

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ACCESSION NUMBER: Not available.

MRID NUMBER: Not available.

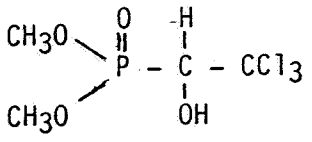
LABORATORY: Academy of Sciences and Martin Luther University, E. Germany.

TEST MATERIAL:

(I) Trichlorphon "very pure preparation, repeatedly recrystallized from benzol and with a melting point at 82-83°C."

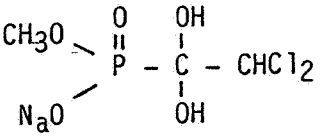
(III) Dichloroacetaldehyde was prepared and purified (using TLC and NMR spectroscopy) for this study.

(V) 2,2-Dichloro-1,1-dihydroxy-ethanephosphonic acid methyl ester was used in the form of its sodium salt; which was prepared and purified (using melting point and NMR spectroscopy) for this study.



(I)

(III)



(V)

PROTOCOL:

Twelve-week old mice were used; these were strains AB Jena-Halle and strain DBA. Solutions of test materials in 0.9 percent NaCl were prepared, and 0.1-ml aliquots were injected, intraperitoneally into male mice [number not stated] to yield "equimolar" doses of (I), (III), and (V) at 405, 176, and 390 mg/kg, respectively.

In the first and second tests,(I) and (III) were administered to AB Jena-Halle mice and DBA mice, respectively. In the third (concurrent with second) and fourth tests, (V) was administered to DBA mice.

Controls received 0.1 ml of 0.9 percent NaCl solution. On the same day of treatment, each male was mated to 3 virgin females of the same strain. The females were examined for vaginal plugs the next morning. Males were mated weekly for 4 or 5 weeks. Pregnant females were dissected on the 18th day after copulation.

"The control series displayed no significant variation within the timespan of the experiments," and consequently the values for each week were averaged together. Averages of "live fetuses/mouse" were analyzed by the t-test. Other parameters were not statistically analyzed. The percent frequency of dominant lethal mutations (DLM) was calculated as:

$$DLM = 100 - \frac{\text{Live fetuses/mouse (treated)}}{\text{Live fetuses/mouse (control)}} \times 100$$

RESULTS:

Table 1 presents the data for all 4 assays by week, with mean values computed by the reviewer.

The results were generally more severe in the AB Jenna-Halle strain. Compared to controls, trichlorphon-treated mice of this strain produced fewer corpora lutea, fewer implantations, fewer live fetuses, and a higher percentage of postimplantation losses. There was a higher percentage of dominant lethal mutations in the AB Jena-Halle strain than in the DBA strain. Desmethyltrichlorphon (V) and dichloroacetaldehyde (III), in general, produced more marked effects in both strains than did trichlorphon.

CONCLUSIONS:

The authors concluded that trichlorphon and two of its degradation products induced impaired embryonic development in AB Jena-Halle and DBA strains of mice. Trichlorphon-treated mice produced fewer corpora lutea, fewer implantations, fewer live fetuses, and a higher percentage of post-implantation loss as compared to controls. The other 2 compounds tested, dichloroacetaldehyde (III) and desmethyltrichlorphon (V), in general produced more marked effects on all the above parameters when compared to trichlorphon. Also, strain AB Jena-Halle had a greater tendency to develop dominant lethal mutations and to respond adversely to treatment than did the DBA strain.

The assays were conducted with 0.9 percent NaCl as the solvent and solvent control. The use of NaCl instead of distilled water is unusual. It is not clear why desmethyltrichlorphon was tested twice in strain DBA and not at all in AB Jena-Halle. There is some confusion over which strains were used for which assay. The methods section stated that strain DBA

would be used for the second and third tests while Table II, which presented the results, stated that AB Jena-Halle males were treated. No criteria were defined for assessing a positive response; only the results for each compound were compared. Statistical analyses were conducted on one parameter only, live fetuses per mouse. Furthermore, the analyses were conducted on weekly data averaged together.

CORE CLASSIFICATION: Unacceptable.

The following deficiencies were noted:

- o Only one dose of each compound was tested.
- o No positive controls were included.
- o The tests were conducted for 4-5 weeks, whereas 8 weeks are needed to complete the spermatogenic cycle in mice. The reason for the abbreviated tests was not stated.
- o Statistical analyses were not performed on most of the data; only for live fetuses.
- o Effects on specific stages of the spermatogenic cycle cannot be assessed because weekly control data were averaged together. Furthermore, it was not appropriate to average the live fetus data to perform statistical analyses.

TABLE 1. Summary of Results Produced in Four Dominant Lethal Assays, and Calculated Means[a]

Test Series and Strain	Compound (Concentration)	Week	N[b]	Corpora Lutea/ Mouse		Implantations/ Mouse		Live Fetuses/ Mouse		PV[c]		DLM[d]	
1 AB Jena-Halle	Trichlorfon (405 mg/kg)	1	16	13.75		9.06		6.44		28.96		25.55	
		2	11	10.91		6.82		4.09		40.00		52.75	
		3	11	10.09		4.18		3.64		13.04		57.92	
		4	5	12.80		6.80		4.80		29.41		44.51	
		5	8	12.63	(12.03)	9.13	(7.20)	6.63	(5.12)*[e]	27.40	(27.76)	23.35	(40.81)
	Dichloroacet-aldehyde (176 mg/kg)	1	19	13.16		8.74		6.68		23.49		22.77	
		2	13	10.08		5.77		3.54		38.67		59.08	
		3	18	12.22		8.61		6.22		27.74		28.09	
		4	7	11.86		10.00		8.57		14.29		0.92	
		5	8	11.38	(11.74)	10.50	(8.72)	7.38	(6.47)*[e]	29.76	(26.79)	14.68	(25.11)
	Control		52		12.85		10.21		8.65		15.25		
2 DBA	Trichlorfon (405 mg/kg)	1	24	9.46		8.88		8.04		9.39		-4.01	
		2	27	9.07		7.89		6.89		12.68		10.87	
		3	25	8.32		7.72		6.28		18.65		18.76	
		4	21	9.05	(8.97)	8.33	(8.21)	7.57	(7.20)*[f]	9.34	(12.51)	2.07	(6.92)
	Dichloroacet-aldehyde (176 mg/kg)	1	24	8.85		8.04		7.29		9.33		5.69	
		2	24	9.13		8.38		6.75		19.40		12.68	
		3	15	8.67		8.00		7.40		7.50		4.27	
		4	23	8.17	(8.70)	7.57	(8.00)	6.61	(7.01)*[g]	12.64	(12.21)	14.49	(9.28)
	Control		89		9.11		8.40		7.73		8.02		
3 DBA (run concurrently with 2)	Desmethyl-trichlorfon (390 mg/kg)	1	26	9.42		8.62		7.19		16.52		6.99	
		2	30	8.53		7.69		6.66		13.41		13.84	
		3	19	8.47		7.79		7.05		9.46		8.80	
		4	25	9.00	(8.85)	8.32	(8.11)	7.04	(6.98)*[g]	15.38	(13.69)	8.93	(9.64)
4 DBA	Desmethyl-trichlorfon (390 mg/kg)	1	12	8.25		7.25		6.42		11.49		7.89	
		2	14	8.64		8.50		6.57		22.69		5.74	
		3	16	7.88		7.56		6.19		18.18		11.19	
		4	20	7.05		6.90		6.05		12.32		13.20	
		5	18	7.33	(7.83)	7.06	(7.45)	5.72	(6.19)*[h]	18.90	(16.71)	17.93	(11.19)
	Control		77		8.14		7.71		6.97		9.60		

[a] The means are in parentheses and were prepared by the reviewer.

[b] N = Number of impregnated and pregnant females per week.

[c] PV = Postimplantation loss of embryos, in percent.

[d] DLM = Dominant lethal mutations, in percent.

[e] Statistically different from control ($p<0.0005$).

[f] Statistically different from control ($p<0.025$).

[g] Statistically different from control ($p<0.005$).

[h] Statistically different from control ($p<0.001$).

* Statistical analyses (t-tests) performed by authors on weekly data averaged together.