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OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT Methidathion, Updated Qualitative Risk  
Assessment - Mouse Study

Caswell No. 378B

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Summary

The feeding study of methidathion exhibited an oncogenic effect in terms of significant increases in liver tumor (carcinomas and/or adenomas) in male mice with increasing doses of the chemical. In addition mortality increased significantly in male mice, mainly due to increases in the highest (100 ppm) dose group.

Female mice were not significantly affected by dose increments of this chemical, neither in survival nor in excess production of tumors.

006497

1087

-2-

Background

At the request of Dr. Copley, an updated Qualitative Analysis was prepared on data from a 2-year chronic/dietary study of methidathion in mice by International Research and Development Corporation (Mattawan, MI) for Ciba-Geigy Corporation. The study included 50 animals of each sex, placed in dietary groups of 0, 3, 10, 50, and 100 ppm of methidathion.

Qualitative Analysis

A statistical survival analysis was prepared by the use of the Thomas, Breslow, and Gart Procedure for both male and female mice.

Results of this evaluation indicated that there was a significant ( $p < .001$ ) upward trend in the mortality of male mice completely due to the large number of deaths which occurred in the highest (100 ppm) dose group ( $p = .01$ ) as compared with the controls.

In female mice, increasing doses of methidathion did not result in significant increases in the mortality trend. In fact, the highest proportion of deaths occurred in the female control group. See Table 1. for details.

The histological examinations that were performed on animals that died on the study and from the final sacrifice at 100 weeks revealed significant liver (adenoma and/or carcinoma) tumor formations with dose increments of methidathion in male mice. Even though survival was a problem for the high (100 ppm) dose group, as well as the increasing tumor rates being nonlinear for increasing doses of the chemical, the Cochran-Armitage Trend test and Fisher's Exact test of pairwise comparisons with the control was applied for the statistical evaluation. In this study, Peto's Prevalence test could not be applied because the data on tumors did not lend itself to the construction of their linear increases within any devised set of time intervals as required for this method of statistical evaluation.

The outcomes indicated that there was a statistically significant ( $p < .01$ ) trend in liver tumor (carcinoma and/or adenoma) formations in male mice with dose increments of methidathion. Pairwise comparisons of controls with 50 ppm and of 100 ppm of the chemical exhibited statistically significant ( $p = .009$ ,  $p < .001$  respectively) differences.

The analysis of benign (adenomas) and malignant (carcinomas) tumor formations separately in males indicated that both types, independently had statistically significant ( $p < .01$ ) trends with dose increments of methidathion by the use of the Cochran-Armitage Trend test.

006497

2

006497

Table 1. Methodathion, Mouse Study - Mortality Rates†  
and Cox or Generalize K/W Test Results

A. Males

<u>Dose</u> <u>(ppm)</u>	<u>0-62</u>	<u>63-78</u>	<u>79-88</u>	<u>89-99<sup>a</sup></u>	<u>Total</u>
0	4/50 (8)	7/46 (15)	5/39 (13)	6/34 (18)	22/50 (44)**
3	5/50 (10)	3/45 (7)	3/42 (7)	10/39 (26)	21/50 (42)
10	3/50 (6)	5/47 (11)	1/42 (2)	15/41 (37)	24/50 (48)
50	7/50 (14)	2/43 (5)	8/41 (20)	5/33 (15)	22/50 (44)
100	5/50 (10)	10/45 (22)	5/35 (14)	18/30 (60)	38/50 (76)**

B. Females

<u>Dose</u> <u>(ppm)</u>	<u>0-62</u>	<u>63-78</u>	<u>79-88</u>	<u>89-100<sup>a</sup></u>	<u>Total</u>
0	5/50 (10)	7/45 (16)	7/38 (18)	12/31 (39)	31/50 (62)
3	4/50 (8)	7/46 (15)	5/39 (13)	6/34 (18)	22/50 (44)
10	3/50 (6)	2/47 (4)	5/45 (11)	12/40 (30)	22/50 (44)
50	6/50 (12)	2/46 (4)	8/44 (18)	10/36 (28)	26/50 (52)
100	4/50 (8)	5/46 (11)	1/41 (2)	16/40 (40)	26/50 (52)

† Number of animals died/number of live animals at the beginning of the interval.

(.) = Percent.

<sup>a</sup> Final sacrifice was at 99-100 weeks.

Note: The above selected time intervals are for display purposes only.

Significance of trend analysis denoted at Control.

Significance of pairwise comparison with control denoted at Dose level.

\* p < .05, \*\* p < .01

006497

3

-3-

For the male adenoma tumor rates, the Fisher Exact test of pairwise comparisons with the control resulted in the following significant p values for dose level 10 ppm  $p=.031$ , 50 ppm  $p=.011$ , and 100 ppm  $p<.001$  respectively.

For the male carcinoma tumor rates, the Fisher Exact test of pairwise comparisons with the control only had a significant ( $p=.025$ ) difference with the highest (100 ppm) dose group. See Table 2. for details.

In female mice, liver tumor (carcinoma and/or adenoma) formations did not increase appreciably with dose increments of this chemical. See Table 3. for details.

006497

4

Table 2. Methidathion - Mouse Study, Male Liver Tumor  
(Carcinoma and/or Adenoma) Rates† and Cochran-Armitage  
Trend Test and Fisher's Exact Test Results

<u>Liver Tumor</u>	<u>Dose (ppm)</u>				
	0	3	10	50	100
Carcinoma	8/46 (17)**	6/45 (13)	4/47 (9)	13/43 (30)	17/45 (38)*
Adenoma only	1/46 (2)**	9/45 (20)**	7/47 (15)*	8/43 (19)**	21/45 (47) <sup>a</sup> **
Carcinoma and/or Adenoma	9/46 (20)**	15/45 (33)	11/47 (23)	21/47 (49)**	38/45 (84)**

† Tumor-bearing animals/animals at risk (excludes all animals that died before appearance of the first tumor).

( ) = Percent.

<sup>a</sup> Appearance of first liver tumor - week 63.

Significance of trend analysis denoted at Control.

Significance of pairwise comparison with control denoted at Dose level.

\*  $p < .05$  \*\*  $p < .01$

006497

5

Table 3. Methidathion - Mouse Study, Female Liver Tumor  
(Carcinoma and/or Adenoma) Rates†

<u>Liver Tumor</u>	<u>Dose (ppm)</u>				
	0	3	10	50	100
Carcinoma	2/42 (5)	2/43 (5) <sup>a</sup>	2/46 (4)	2/43 (5)	5/43 (12)
Adenoma only	3/42 (7)	8/43 (19)	3/46 (7)	1/43 (2)	3/43 (7)
Carcinoma and/or Adenoma	5/42 (12)	10/43 (23)	5/46 (11)	3/43 (7)	8/43 (19)

† Tumor-bearing animals/animals at risk (excludes all animals that died before appearance of the first tumor).  
 ( ) = Percent.

<sup>a</sup> Appearance of first liver tumor - week 75.

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- Cox, D.R. (1972) Regression Models and Life Tables  
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