UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

3-9-89

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Dimethoate - Qualitative Risk Assessment, Dietary Studies in Mice and Rats caswell no.358

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Summary

The qualitative risk assessment of dimethoate, based upon two chronic/oncogenicity dietary studies in $B_6C_3F_1$ mice and Wistar SPF rats resulted in the following statistical outcomes.

Survival - Male mice had no significant mortality with incremental doses of dimethoate. Female mice had a significant dose related mortality trend as well as a significant difference between control and the mid(100 ppm) dose group.

Male rats had no significant mortality with incremental doses of dimethoate. Female rats had a significant dose related trend but no significant differences in the pair-wise comparisons between the controls and any dose level.

Tumors - In male mice, dose related significant trends occurred in (1)lung (adenoma and/or adenocarcinoma); (2)lymphoma; and (3) in the combined group of lymphoma, reticularsarcoma and leukemia tumor rates with incremental doses of dimethoate. In males, the pair-wise comparison of control and the highest (200 ppm) dose resulted in a significant difference for the combined group of lymphoma, reticularsarcoma and leukemia tumor rates. No other statistically significant results were noted.

In female mice, significant dose related trends in liver carcinoma and also in combined liver (adenoma and/or carcinoma) tumors occurred with dose increments of dimethoate. No other significant findings were observed.

In male rats, dose related significant trends occurred in: (1)spleen hemangiosarcomas; (2)spleen - combined hemangioma and hemangiosarcoma, and (3)combined spleen hemangioma, hemangiosarcoma, and skin hemangiosarcoma. In males, the pair-wise comparison of control and the highest (100 ppm) dose resulted in a significant difference in the spleen (hemangioma and hemangisarcoma) and in the combined (spleen and skin - hemangioma and hemangiosarcoma, and lymph - angioma and angiosarcoma) tumors. The other significant difference was in the pair-wise comparison of control and the 5ppm (lowest) dose group for lymph (angiosarcoma) and the combined (spleen and skin - hemangioma and hemangiosarcoma, and lymph - angiosarcoma) tumor rates.

The female rats did not have any biologically significant tumor increases with dose increments of dimethoate.

Background

Two chronic toxicity/oncogenicity dietary studies, one in mice and the other in rats, were used to yield a qualitative risk assessment of dimethoate.

The mouse study was presented by American Cyanamid (accession numbers 265362-265364). It was a 78 week dietary study in $B_6C_3F_1$ mice that included 240 males and 240 females. The animals were assigned to three (25, 100 and 200 ppm) dose levels and a control. They were allocated accordingly by weight, to the following groups:

Table 1. Dimethoate, $B_6C_3F_1$ Mouse Study - Experimental Design of Dietary Study

Dose(ppm)	Number of		Interim Sacrifice	
	males	females	males	females
0	50	50	10	10
25	50	50	10	10
100	50	50	10	10
200	50	50	10	10

Since histopathological results were not available for interim sacrificed mice, statistical analysis was limited to the 50 animals per group/sex part of the study.

The rat study was presented by BASF Aktiengesllschaft, Ludwigshafer/Rhein, FRG. It was a 24 month dietary study in Wistar SPF rats that included 280 males and 280 females. The animals were fed 0, 1, 5, 25 or 100 ppm of dimethoate and were assigned in a random manner to the following groups:

Table 2. Dimethoate, Wistar SPF Rat - Experimental Design of Dietary Study

Dose (ppm)	Main Study		Satellite Study+	
	Male	Female	Male	Female
0	50	50	15	15
1	--	--	20	20
5	50	50	15	15
25	50	50	15	15
100	50	50	15	15

+ used for clinical chemistry, hematology and urinalysis; in addition, only those that died on study were examined histologically.

Survival Anaylsis

In male mice, there was no statistical evidence of dose related mortality either in the trend analysis or in the pair-wise comparisons of control and each dose group (Table 3).

In female mice, there was a statistically significant ($p<.05$) trend in the positive direction for mortality; there was also a significant ($p<.05$) difference between the control and the mid (100 ppm) dose group (Table 4).

In the rat study, no significant differences in survival occurred with incremental doses of dimethoate in males (Table 5). In female rats, there was a significant ($p<.05$) dose related trend but no significant differences in pair-wise comparison between the controls and any dose group (Table 6).

For both the mouse and the rat study, statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analysis

In mice, elevated tumor activity was observed in the liver, lung and hemolymphoreticular system in both sexes with dose increments of dimethoate.

In male mice, since there was no significant dose related survival findings, the Cochran-Armitage Trend test and Fisher's Exact test for pair-wise comparisons with control was used to statistically evaluate the incremental tumor rates in the liver, lung and hemolymphoreticular system.

In males, combined lung (adenoma and/or adenocarcinoma) tumor rates resulted in a significant ($p=.041$) increasing trend with dose increments of dimethoate but no significant differences in the pair-wise comparison of controls and other dose levels (Table 7). In males, a significant ($p=.001$) dose related trend occurred in the increase of lymphomas but there was no significant differences in the pair-wise comparison of controls and any dose level. In the combined tumor group of lymphoma, reticularsarcoma and leukemia, a significantly ($p<.001$) dose related trend occurred and also a significant ($p=.014$) difference in the pair-wise comparison of control and the highest (200 ppm) dose level (Table 8). Liver tumor rates did not significantly change with dose increments of dimethoate (Table 9).

In female mice, because of a significant finding in dose related mortality, the Peto method was first used to detect any significant findings in the tumorgenicity occurrences associated with incremental doses of dimethoate. However the Peto method of analysis with its time component failed to show any results since all of the observed tumors were late occurring ones. Thus, it was appropriate to use the Cochran-Armitage Trend test and Fisher's Exact test for the pair-wise comparisons of controls and dose levels for the female mouse tumor data.

In females mice, a significant ($p<.05$) dose related trend occurred with increases in liver carcinomas and also for combined liver (adenoma and/or carcinoma) tumors (Table 10). There were no other significant results observed in female mice with respect to lung and hemolymphoreticular tumors (Table 11-12).

For male rats, since there were no significant dose related survival findings, the Cochran-Armitage Trend test and Fisher's Exact test for pair-wise comparisns with control was used to statistically evaluate the incremental tumor rates in the spleen, lymph and the skin.

Male rats had significant ($p<.05$) positive dose related trends for the following three categories of tumors: (1) spleen hemangiosarcoma; (2) combined splenic hemangioma/hemangiosarcoma; and (3) combined spleen and skin vascular tumors (i.e. splenic hemangioma, splenic hemangiosarcomas and skin hemangiosarcomas) (Table 13). There was also a significant ($p<.027$) difference in the pair-wise comparison of control and the high (100 ppm) dose group in the spleen (hemangioma and hemangiosarcoma) tumor rates in males (Table 13). The other significant ($p<.05$) differences in the pair-wise comparison with controls occurred in lymph - (angiosarcoma) tumor rates at 5 ppm and for all the combined (spleen and skin - hemagioma & hemagiosarcoma; lymph- (angiosarcoma) at 5 ppm and at 100 ppm (Table 13).

Female rats had no biologically significant tumor increases with dose increments of dimethoate.

Table 3. Dimethoate - Male Mouse Study, Mortality Rates+ and Cox or Generalized K/W Test Results

Dose(ppm)	Week 1-26	27-52	53-78a	Total
0	0/50	0/50	1/50	1/50(2)
25	0/50	0/50	2/50	2/50(4)
100	0/50	0/50	2/50	2/50(4)
200	1/50	0/49	0/49	1/50(2)

+ Number of animals that died during interval/ Number of animals alive at the beginning of the interval.

( ) percent

a Final sacrifice at weeks 79-80

Note: Time intervals were selected for display purposes only. Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 4. Dimethoate - Female Mouse Study, Mortality Rates* and Cox or Generalized K/W Test Results

Dose(ppm)	Week 1-26	27-52	53-78[a]	Total
0	0/50	0/50	0/50	0/50(0)*
25	0/50	0/50	1/50	1/50(2)
100	0/50	1/50	4/49	5/50(10)*
200	1/50	0/49	2/49	3/50(6)

+ Number of animals that died during interval/ Number of animals alive at the beginning of the interval.

( ) Final sacrifice for control, weeks 77-80, and for 25, 100 and 200 ppm., weeks 79-80.

Note: Time intervals selected for display purposes only. Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 5. Dimethoate Male Rat Study, Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose(ppm)	Week 1-26	27-52	53-78	79-104[a]	Total
0	1/65	0/64	4/64	10/60	15/65 (23)
5	0/65	2/65	1/63	10/62	13/65 (20)
25	1/65	1/64	0/63	15/63	17/65 (26)
100	1/65	2/64	4/62	12/58	19/65 (29)

[+] Number of animals that died during interval/ Number of animals alive at the beginning of the interval.

( ) percent

a Final sacrifice for control, 5, and 25 ppm at weeks 105-107, and for 100 ppm at weeks 105-106.

Note: Time intervals selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 6. Dimethoate - Female Rat Study, Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose(ppm)	Week 1-26	27-52	53-78	79-104[a]	Total
0	0/65	0/65	1/65	18/64	19/65 (29)*
5	0/65	1/65	2/64	17/62	20/65 (31)
25	0/65	0/65	3/65	19/62	22/65 (34)
100	0/65	1/65	3/64	25/61	29/65 (45)

[+] Number of animals that died during interval/ Number of animals alive at the beginning of the interval.

( ) percent

a Final sacrifice at weeks 105-106.

Note: Time intervals selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 7. Dimethoate - Male Mice Bronchoalveolar Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

	Dose(ppm)			
Tumor	0	25.00	100.00	200.00
Adenoma	2/50 (4)	4/50 (8)	0/50 (0)	6[a]/49 (12)
p=	0.100	0.339	0.248	0.128
Adeno-carcinoma	0/50 (0)	0/50 (0)	3[b]/50 (6)	1/49 (2)
p=	0.123	1.000	0.121	0.495
Combined Tumors	2/50 (4)	4/50 (8)	3/50 (6)	7/49 (14)
p=	0.041*	0.339	0.500	0.075

+ Number of tumor bearing animals/ Number of animals at risk (excluding those that died before 52 weeks).

( ) percent

a First adenoma observed at week 79.
b First adenocarcinoma obserevd at week 79.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 8. Dimethoate - Male Mice, Hemolymphoreticular Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results

	Dose(ppm)			
Tumors	0	25.00	100.00	200.00
Reticular-sarcoma	0/50 (0)	1[a]/50 (2)	0/50 (0)	1/49 (2)
p=	0.283	0.500	1.000	0.495
Lymphoma	1/50 (2)	0/50 (0)	1/50 (2)	6[b]/49 (12)
p=	0.001**	0.500	0.752	0.053
Leukemia	0/50 (0)	0/50 (0)	0/50 (0)	1[c]/49 (2)
p=	0.059	1.000	1.000	0.495
Combined Tumors	1/50 (2)	1/50 (2)	1/50 (2)	8/49 (16)
p=	0.001**	0.752	0.752	0.014*

[+] Number of tumor bearing animals/ Number of animals at risk (excluding those that died before 52 weeks).

( ) percent

a First reticularsarcoma observed at week 79.
b First lymphoma observed at week 79.
c First leukemia observed at week 80.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 9. Dimethoate - Male Mice, Hepatocellular Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

	Dose(ppm)			
Tumor	0	25.00	100.00	200.00
Adenoma	6/50 (12)	7/50 (14)	8/50 (16)	8[a]/49 (16)
p=	0.274	0.500	0.387	0.371
Carcinoma	11[b]/50 (22)	12/50 (24)	10/50 (20)	7/49 (14)
p=	0.114	0.500	0.500	0.232
Combined Tumors	17/50 (34)	19/50 (38)	18/50 (36)	15/49 (31)
p=	0.2923	0.418	0.500	0.442

+ Number of tumor bearing animals/ Number of animals at risk (excluding those that died before 52 weeks).

( ) percent

a First adenoma observed at week 79.
b First carcinoma observed at week 66.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 10. Dimethoate - Female Mice, Hepatocellular Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results

	Dose(ppm)			
Tumor	0	25.00	100.00	200.00
Adenoma	5[a]/50 (10)	4/50 (8)	3/49 (6)	8/49 (16)
p=	0.118	0.500	0.369	0.264
Carcinoma	0/50 (0)	0/50 (0)	1/49 (2)	2[b]/49 (4)
p=	0.025*	1.000	0.495	0.242
Combined Tumors	5/50 (10)	4/50 (8)	4/49 (8)	10/49 (20)
p=	0.031*	0.500	0.513	0.122

[+] Number of tumor bearing animals/ Number of animals at risk (excluding those that died before 52 weeks).

( ) percent

a First adenoma obsered at week 78.
b First carcinoma observed at week 79.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 11. Diomethoate - Female Mice, Bronchoalveolar Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results

	Dose(ppm)			
Tumors	0	25.00	100.00	200.00
Adenoma	0/50 (0)	0/50 (0)	0/49 (0)	1[a]/49 (2)
p=	0.060	1.000	1.000	0.495
Adeno-carcinoma	0/50	0/50	0/49	0/49

[+] Number of tumor bearing animal/ Number of animals at risk (excluding those that died before 52 weeks).

( ) percent

a First adenoma observed at week 80.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 12. Dimethoate - Female Mice, Hemolymphoreticular Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results

	Dose(ppm)			
Tumors	0	25.00	100.00	200.00
Reticular-sarcoma	0/50 (0)	2/50 (4)	1[a]/49 (2)	2/49 (4)
p=	0.198	0.248	0.495	0.242
Lymphoma	6[b]/50 (12)	8/50 (16)	4/49 (8)	6/49 (12)
p=	0.354	0.387	0.383	0.606
Leukemia	3/50 (6)	4/50 (8)	7[c]/49 (14)	4/49 (8)
p=	0.319	0.500	0.151	0.489
Combined Tumors	9/50 (18)	14/50 (28)	12/49 (24)	12/49 (24)
p=	0.362	0.171	0.294	0.294

[+] Number of tumor bearing animals/ Number of animals at risk (excluding those that died before 52 weeks).

( ) percent

a First reticularsarcoma observed at week 64.
b First lymphoma observed at week 77.
c First leukemia observed at week 67.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 13. Dimethoate - Male Rats, Spleen, Lymph and Skin Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

Individual Tumor	Dose(ppm) 0	5.00	25.00	100.00
Spleen				
Hemangioma	0/54	1/49	0/54	1[a]/53
	(0)	(2)	(0)	(2)
p=	0.247	0.476	1.000	0.495
Hemagiosarcoma	0/54	2/49	1/54	4[b]/53
	(0)	(2)	(2)	(8)
p=	0.023*	0.224	0.500	0.057
Lymph				
Angioma	0/54	0/49	1[c]/53	0/52
	(0)	(0)	(2)	(0)
p=	0.415	1.000	0.495	1.000
Angiosarcoma	0/54	4[d]/49	2/53	2/52
	(0)	(8)	(4)	(4)
p=	0.446	0.048*	0.243	0.238
Skin				
Hemagiosarcoma	1[e]/54	0/49	0/54	0/53
	(2)	(0)	(0)	(0)

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a first spleen hemangioma at week 105

b first spleen hemangiosarcoma at week 93

c first lymph angioma at week 103

d first lymph angiosarcoma at week 94

e first skin hemangiosarcoma at week 76

Table 13 continued

Combined Tumors	Dose(ppm) 0	5.00	25.00	100.00
Spleen - (Hemangioma & Hemangiosarcoma)	0/54 (0)	3/49 (6)	1/54 (2)	5/53 (9)
p=	0.018*	0.104	0.500	0.027*
Spleen & Skin - (Hemangioma & Hemangiosarcoma)	1/54 (2)	3/49 (6)	1/54 (2)	5/53 (9)
p=	0.042*	0.273	0.752	0.098
Lymph - (Angiomas and Angiosarcoma)	0/54 (0)	4/49 (8)	3/53 (6)	2/52 (4)
p=	0.467	0.048*	0.118	0.238
All Tumors	1/54 (2)	7/49 (14)	4/54 (7)	7/53 (13)
p=	0.101	0.021*	0.182	0.028*

+ Number of tumor bearing animals/ Number of animals at risk (excluding animals that died before 52 weeks).

( ) percent

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

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