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

MEMORANDUM March 31, 1999

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Thiophanate-methyl Qualitative Risk Assessment Based On Fischer 344 Rat and CD-1 Mouse Dietary Studies

P.C. Code 102001

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Background

A carcinogenicity and chronic toxicity study in Fischer 344 rats was conducted by Toxicology Institute, Environmental Toxicology Laboratory, Nippon Soda Company, Limited, Kanagawa, Japan, for Nippon Soda Company, Limited, Tokyo, Japan, and issued August 17, 1993 (Study No. 0566; MRID No. 428966-01).

The study design allocated groups of 50 rats per sex to dose levels of 0, 75, 200, 1200, or 6000 ppm of Thiophanate-methyl for 105 weeks. An additional 10 rats per sex per dose were designated for interim sacrifice at week 53.

An carcinogenicity study in CD-1 mice was conducted by WIL Research Laboratories, Inc., Ashland, Ohio, for Nippon Soda Company, Limited, Tokyo, Japan, and issued November 13, 1992 (Study No. WIL-75024; MRID No. 426077-01).

The study design allocated groups of 50 mice per sex to dose levels of 0, 150, 640, 3000, or 7000 ppm of Thiophanate-methyl for 78 weeks. An additional 10 mice per sex per dose were designated for interim sacrifice at week 40.

Survival Analyses

The statistical evaluation of mortality indicated significant increasing trends with increasing doses of Thiophanate-methyl in male rats and male and female mice. Female rats showed no

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significant incremental changes in mortality with increasing doses of Thiophanate-methyl. See Tables 1 and 2 for rat mortality test results and Tables 5 and 6 for mouse mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

Male rats had significant increasing trends in thyroid follicular cell adenomas, carcinomas and adenomas and/or carcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 6000 ppm dose group with the controls for thyroid follicular cell adenomas, and carcinomas, both at $p < 0.05$. There was also a significant difference in the pair-wise comparison of the 6000 ppm dose group with the controls for thyroid follicular cell adenomas and/or carcinomas combined at $p < 0.01$.

Female rats had a significant increasing trend in thyroid follicular cell adenomas at $p < 0.05$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

Male mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 3000 and 7000 ppm dose groups with the controls, for liver adenomas, and adenomas, carcinomas and/or hepatoblastomas combined, all at $p < 0.01$. There was also a significant increasing trend in liver hepatoblastomas at $p < 0.05$.

Female mice had a significant increasing trend, and significant differences in the pair-wise comparisons of the 3000 and 7000 ppm dose group with the controls, for liver adenomas, all at $p < 0.01$. There was also a significant difference in the pair-wise comparison of the 640 ppm dose group with the controls for liver adenomas at $p < 0.05$.

The statistical analyses of the male rats and male and female mice were based upon Peto's Prevalence Test since there were statistically significant positive trends for mortality with increasing doses of Thiophanate-methyl in these groups. The statistical analyses of the female rats were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 3 and 4 for rat tumor analysis results and Tables 7 and 8 for mouse tumor analysis results.

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Table 1. Thiophanate-methyl Fischer 344 Rat Study

Male Mortality Rates[†] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-52	53[i]	53-78	79-106[f]	Total
0	0/60	0/60	10/60	1/50	12/49	13/50 (26)**
75	0/60	0/60	10/60	2/50	14/48	16/50 (32)
200	0/60	0/60	10/60	7/50	17/43	24/50 (48)*
1200	0/60	0/60	10/60	3/50	20/47	23/50 (46)
6000	0/52[a]	0/52	5[b]/52	4/47	41/43	45/47 (96)**

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

[f]Final sacrifice at week 105.

[i]Interim sacrifice at week 53.

[a]Six accidental deaths at week 11, two at week 12, dose 6000 ppm.

[b]Five instead of ten animals were sacrificed at the week 53 interim sacrifice at the 6000 ppm dose due to the eight accidental deaths at weeks 11 and 12.

()Percent.

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 $p < 0.05$. If **, then $p < 0.01$.

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Table 2. Thiophanate-methyl Fischer 344 Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-52	53[i]	53-78	79-106[f]	Total
0	0/60	0/60	10/60	2/50	11/48	13/50 (26)
75	0/60	0/60	10/60	1/50	12/49	13/50 (26)
200	0/60	0/60	10/60	1/50	7/49	8/50 (16)
1200	0/60	0/60	10/60	0/50	12/50	12/50 (24)
6000	0/60	1/60	10/59	1/49	9/48	11/50 (22)

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

[f]Final sacrifice at week 105.

[i]Interim sacrifice at week 53.

()Percent.

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 $p < 0.05$. If **, then $p < 0.01$.

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Table 3. Thiophanate-methyl Fischer 344 Rat Study

Male Thyroid Follicular Cell Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	75	200	1200	6000
Adenomas (%)	1/50 (2)	0/46 (0)	0/45 (0)	3/47 (6)	12[a]/44 (27)
p =	0.000**	-	-	0.309	0.014*
Carcinomas (%)	0/47 (0)	0/44 (0)	0/42 (0)	0/47 (0)	3[b]/27 (11)
p =	0.002**	-	-	-	0.011*
Combined (%)	1/50 (2)	0/46 (0)	0/45 (0)	3/47 (6)	14[c]/44 (32)
p =	0.000**	-	-	0.309	0.001**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

[a]First adenoma observed at week 53, dose 1200 ppm, in an interim sacrifice animal. Interim sacrifice animals have been excluded from this analysis. Second adenoma observed at week 78, dose 6000 ppm.

[b]First carcinoma observed at week 86, dose 6000 ppm.

[c]One animal in the 6000 ppm dose group had both an adenoma and a carcinoma.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 4. Thiophanate-methyl Fischer 344 Rat Study

Female Thyroid Follicular Cell Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	75	200	1200	6000
Adenomas[f] (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)	2[a]/49 (4)
p =	0.031*	1.000	1.000	0.500	0.242

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First adenoma observed at week 92, dose 6000 ppm.

[f]No carcinomas were observed.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 5. Thiophanate-methyl CD-1 Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-20	21-40	40[i]	41-60	61-80[f]	Total
0	0/60	0/60	10/60	2/50	8/48	10/50 (20)**
150	0/60	0/60	10/60	2/50	8[a]/47	10/49 (20)
640	0/60	2/60	10/58	2/48	10/46	14/50 (28)
3000	0/60	0/60	10/60	6/50	10/44	16/50 (32)
7000	1/60	3/59	10/56	5/46	15/41	24/50 (48)**

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

[f]Final sacrifice at week 78.

[i]Interim sacrifice at week 40.

[a]One accidental death at week 68, dose 150 ppm.

()Percent.

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 $p < 0.05$. If **, then $p < 0.01$.

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Table 6. Thiophanate-methyl CD-1 Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-20	21-40	40[i]	41-60	61-79[f]	Total
0	1/60	1/59	10/58	1/48	9/47	12/50 (24)**
150	0/60	1/60	10/59	5/49	7/44	13/50 (26)
640	0/60	2/60	10/58	2/48	11/46	15/50 (30)
3000	0/60	0/60	10/60	3/50	14/47	17/50 (34)
7000	0/60	1/60	10/59	7/49	15/42	23/50 (46)*

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

[f]Final sacrifice at week 79.

[i]Interim sacrifice at week 40.

()Percent.

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 $p < 0.05$. If **, then $p < 0.01$.

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Table 7. Thiophanate-methyl CD-1 Mouse Study

Male Liver Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	150	640	3000	7000
Adenomas (%)	4/47 (9)	8/46 (17)	7/47 (15)	19/45 (42)	24[a]/42 (57)
p =	0.000**	0.098	0.123	0.000**	0.000**
Carcinomas[b] (%)	0/40 (0)	0/39 (0)	1/36 (3)	0/34 (0)	1/26 (4)
p =	0.118	-	0.146	-	0.107
Hepato-blastomas (%)	0/40 (0)	0/39 (0)	0/36 (0)	0/34 (0)	1[c]/26 (4)
p =	0.016*	-	-	-	0.107
Combined (%)	4/47 (9)	8/46 (17)	8/47 (17)	19/45 (42)	24[d]/42 (57)
p =	0.000**	0.098	0.074	0.000**	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

[a]First adenoma observed at week 59, dose 7000 ppm.
[b]First carcinomas observed at week 80, simultaneously at 640 and 7000 ppm, in final sacrifice animals.
[c]First hepatoblastoma observed at week 80, dose 7000 ppm.
[d]One animal in the 7000 ppm dose group had an adenoma, a carcinoma and a hepatoblastoma.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 8. Thiophanate-methyl CD-1 Mouse Study

Female Liver Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	150	640	3000	7000
Adenomas[f] (%)	0/43 (0)	0/39 (0)	3/38 (8)	8/34 (24)	18[a]/32 (56)
p =	0.000**	-	0.034*	0.001**	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

[a]First adenoma observed at week 74, dose 7000 ppm.

[f]No carcinomas were observed.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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References

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