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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Dithiopyr Qualitative Risk Assessment Based On Charles River CD-1 Mouse and Fisher 344 Rat Dietary Studies

Caswell No. 717C

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Summary

The qualitative risk assessment of Dithiopyr was based upon chronic toxicity/oncogenicity studies conducted in Charles River CD-1 mice and Fisher 344 rats. The mice were fed 0, 3, 30, or 300 ppm of Dithiopyr for 78 weeks. The rats were fed 0, 3, 10, 100, or 300 ppm of Dithiopyr for 104 weeks.

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Dithiopyr in male or female mice or rats.

Male mice had a significant dose-related increasing trend in harderian gland adenomas. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

Female mice had significant dose-related increasing trends in hepatocellular adenomas and uterine horn endometrial stromal polyps. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

There were no significant compound-related tumors observed in male rats.

There were no significant dose-related increasing trends or pair-wise comparisons of the dosed groups with the controls in female rats.

Background

A chronic oncogenicity study in Charles River CD-1 mice was conducted by The Institute of Environmental Toxicology, Tokyo, Japan, for Monsanto Japan Limited, Tokyo, Japan, and issued December 4, 1989 (Study No. IET 87-0001/ET-87-8; MRID No. 419906-03).

The study design allocated groups of 50 mice per sex to dose levels of 0, 3, 30, and 300 ppm of Dithiopyr for 78 weeks. An additional 20 mice per sex per dose were designated for interim sacrifice, ten each at weeks 13 and 52.

A chronic toxicity/oncogenicity study in Charles River Fisher 344 rats was conducted by The Institute of Environmental Toxicology, Tokyo, Japan, for Monsanto Japan Limited, Tokyo, Japan, and issued December 4, 1989 (Study No. IET 86-0148/ET-86-361; MRID No. 419906-01).

The study design allocated groups of 50 rats per sex to dose levels of 0, 3, 10, 100, and 300 ppm of Dithiopyr for 105 weeks. An additional 40 rats per sex per dose were designated for interim sacrifice, ten males each at weeks 13, 27, 53, and 79, ten females each at weeks 14, 27, 53, and 79.

Survival Analysis

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Dithiopyr in male or female mice or rats. See Tables 1, 2, 3 and 4 for mortality test results.

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

Tumor Analysis

Male mice had a significant increasing trend in harderian gland adenomas at $p < 0.01$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

Female mice had significant increasing trends in hepatocellular adenomas and uterine horn endometrial stromal polyps, both at $p < 0.05$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

Although a single uterine horn endometrial stromal polyp was observed in an interim sacrifice control group female mouse at week 52, the Statistics Section believes that the 52-week interim sacrifice animals should not be included in this qualitative risk assessment because no other polyps were observed until essentially the end of the study. One polyp was observed in a 3 ppm dose group animal at week 73. All other polyps were observed at terminal sacrifice at week 78.

No significant compound-related tumors were observed in male rats.

There were no significant dose-related increasing trends or pair-wise comparisons of the dosed groups with the controls in female rats.

These statistical analyses were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons due to the relatively small numbers of tumors observed. See Tables 5, 6, and 7 for tumor analysis results.

Table 1. Dithiopyr - Charles River CD-1 Mouse Study

Male Mortality Rates* and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-12	13[i]	13-51	52[i]	52-78[f]	Total
0	0/70	10/70	2/60	10/58	9/48	11/50 (22)
3	0/70	10/70	1/60	10/59	9/49	10/50 (20)
30	0/70	10/70	4/60	10/56	7/46	11/50 (22)
300	0/70	10/70	5/60	10/55	7/45	12/50 (24)

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

[i]Interim sacrifices at weeks 13 and 52.

[f]Final sacrifice at week 78.

( )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 $p < 0.01$.

Table 2. Dithiopyr - Charles River CD-1 Mouse Study

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

	Weeks					
Dose(ppm)	1-12	13[i]	13-51	52[i]	52-78[f]	Total
0	0/70	10/70	4/60	10/56	12/46	16/50 (32)
3	1/70	10/69	5/59	10/54	10/44	16/50 (32)
30	0/70	10/70	5/60	10/55	8/45	13/50 (26)
300	0/70	10/70	5/60	10/55	11/45	16/50 (32)

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

[i]Interim sacrifices at weeks 13 and 52.

[f]Final sacrifice at week 78.

( )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 $p < 0.01$.

Table 3. Dithiopyr - Charles River Fisher 344 Rat Study

Male Mortality Rates* and Cox or Generalized K/W Test Results

	Weeks									
Dose(ppm)	1-12	13[i]	13-26	27[i]	27-52	53[i]	53-78	79[i]	79-105[f]	Total
0	0/90	10/90	0/80	10/80	0/70	10/70	3/60	10/57	3/47	6/50 (12)
3	0/90	10/90	0/80	10/80	1/70	10/69	0/59	10/59	5/49	6/50 (12)
10	0/90	10/90	0/80	10/80	0/70	10/70	2/60	10/58	5/48	7/50 (14)
100	0/90	10/90	0/80	10/80	0/70	10/70	2/60	10/58	7/48	9/50 (18)
300	0/90	10/90	0/80	10/80	1/70	10/69	2/59	10/57	8/47	11/50 (22)

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

[i]Interim sacrifices at weeks 13, 27, 53 and 79.

[f]Final sacrifice at week 105.

( )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 $p < 0.01$.

Table 4. Dithiopyr - Charles River Fisher 344 Rat Study

Female Mortality Rates* and Cox or Generalized K/W Test Results

	Weeks									
Dose(ppm)	1-13	14[i]	14-26	27[i]	27-52	53[i]	53-78	79[i]	79-105[f]	Total
0	0/90	10/90	0/80	10/80	0/70	10/70	2/60	10/58	6/48	8/50 (16)
3	0/90	10/90	0/80	10/80	0/70	10/70	2/60	10/58	10/48	12/50 (24)
10	0/90	10/90	0/80	10/80	0/70	10/70	3/60	10/57	8/47	11/50 (22)
100	0/90	10/90	0/80	10/80	0/70	10/70	1/60	10/59	11/49	12/50 (24)
300	0/90	10/90	0/80	10/80	0/70	10/70	1/60	10/59	6/49	7/50 (14)

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

[i]Interim sacrifices at weeks 14, 27, 53 and 79.

[f]Final sacrifice at week 105.

( )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 $p < 0.01$.

Table 5. Dithiopyr - Charles River CD-1 Mouse Study

Male Harderian Gland Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	3	30	300
Adenomas (%)	5/47 (11)	1/49 (2)	4/45 (9)	10[a]/45 (22)
p =	0.004**	0.093[n]	0.528[n]	0.111

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative change from control.

[a]First adenoma observed at week 64, dose 300 ppm.

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 $p < 0.01$.

Table 6. Dithiopyr - Charles River CD-1 Mouse Study

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

	Dose (ppm)			
	0	3	30	300
Hepatocelular Adenomas (%)	1/46 (2)	0/44 (0)	2/45 (4)	4[a]/45 (9)
p =	0.026*	0.511[n]	0.492	0.174
Endometrial Stromal Polyps (%)	3/46 (7)	2[b]/44 (5)	5/45 (11)	8/45 (18)
p =	0.020*	0.521[n]	0.345	0.092

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative change from control.

[a]First hepatocellular adenoma observed at week 74, dose 300 ppm.

[b]First uterine horn endometrial stromal polyp observed at week 73, dose 3 ppm.

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 $p < 0.01$.

Table 7. Dithiopyr - Charles River Fisher 344 Rat Study

Female Tumor Rates* and Exact Trend Test
and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	3	10	100	300
Mononuclear Cell Leukemias	7/70	9/70	7/70	9/70	13[a]/70
(%)	(10)	(13)	(10)	(13)	(19)
p =	0.055	0.396	0.610	0.396	0.113
Uterine Horn Endometrial Stromal Polyps	10/70	13/70	15/70	7/70	18[b]/70
(%)	(14)	(19)	(21)	(10)	(26)
p =	0.096	0.325	0.189	0.303[n]	0.069

*Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[n]Negative change from control.

[a]First mononuclear cell leukemia observed at week 78, dose 300 ppm.

[b]First uterine horn endometrial stromal polyp observed at week 53, dose 300 ppm.

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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