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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chlorothalonil Qualitative Risk Assessment Based On Fischer 344 Rat Dietary Study

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Background

An oncogenicity study in Fischer 344 rats was conducted by International Research and Development Corporation, Mattawan, Michigan, for Fermenta ASC Corporation, Mentor, Ohio, and issued June 7, 1989 (Study No. 1102-84-0103-TX-007; MRID No. 412505-02).

The study design allocated groups of 55 rats per sex to dose levels of 0, 1.5, 3.5, 15, or 175 mg/kg/day of Chlorothalonil for 30 months. An additional 10 rats per sex per dose were designated for interim sacrifice at week 52. Because of dietary binding at low levels, the lowest two dose groups were mixed with higher levels of Chlorothalonil, resulting in dose groups of 2 and 4 mg/kg/day, instead of the intended 1.5 and 3.5 mg/kg/day dose groups, respectively. Due to high mortality, the study was terminated at week 111 for males in the first four dose groups, week 99 for males in the high dose group, and week 125 for females.

Survival Analyses

The statistical evaluation of mortality indicated significant increasing trends for mortality in both male and female rats with increasing doses of Chlorothalonil. See Tables 1 and 2 for 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, and significant differences in the pair-wise comparisons of the 175 mg/kg/day dose group with the controls, for kidney tubular adenomas and adenomas and/or carcinomas combined, and stomach squamous cell papillomas, all at $p < 0.01$. There was a significant increasing trend at $p < 0.01$ and a significant difference in the pair-wise comparison of the 175 mg/kg/day dose group with the controls at $p < 0.05$ for kidney tubular carcinomas. There was a significant difference in the pair-wise comparison of the 15 mg/kg/day dose group with the controls for kidney tubular adenomas and/or carcinomas combined at $p < 0.05$. There was a significant difference in the pair-wise comparison of the 4 mg/kg/day dose group with the controls for stomach squamous cell papillomas at $p < 0.05$.

Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 175 mg/kg/day dose group with the controls, for kidney tubular adenomas, carcinomas, and adenomas and/or carcinomas combined, and stomach squamous cell papillomas and/or carcinomas combined, all at $p < 0.01$. There was a significant increasing trend, and a significant difference in the pair-wise comparisons of the 175 mg/kg/day dose group with the controls, for stomach squamous cell papillomas, both at $p < 0.05$. There was a significant increasing trend in stomach squamous cell carcinomas at $p < 0.01$.

The statistical analyses of both the male and female rats were based upon Peto's Prevalence Test since there were statistically significant positive trends for mortality in both sexes with increasing doses of Chlorothalonil. See Tables 3 through 6 for tumor analysis results.

Table 1. Chlorothalonil - Fischer 344 Rat Study

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

Dose (mg/kg/day)	Weeks 1-26	27-52	52[i]	53-78	79-111[f]	Total
0	0/65	0/65	10/65	1/55	22/54	23/55 (42)**
2	0/65	1/65	10/64	0/54	21/54	22/55 (40)
4	0/65	1/65	10/64	2/54	19/52	22/55 (40)
15	0/65	1/65	10/64	2/54	31/52	34/55 (62)
175	0/65	0/65	10/65	4/55	40/51	44/55 (80)**

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

[i]Interim sacrifice at week 52.

[f]Final sacrifice at week 111 for 0, 2, 4, and 15 mg/kg/day dose groups; final sacrifice at week 99 for 175 mg/kg/day dose group.

( )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. Chlorothalonil - Fischer 344 Rat Study

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

Dose (mg/kg/day)	Weeks 1-26	27-52	52[i]	53-78	79-126[f]	Total
0	0/65	0/65	10/65	1/55	30/54	31/55 (56)**
2	0/65	1/65	10/64	1/54	25/53	27/55 (49)
4	0/65	0/65	10/65	4/55	32/51	36/55 (65)
15	0/65	2/65	10/63	1/53	32/52	35/55 (64)
175	0/65	0/65	10/65	2/55	43/53	45/55 (82)*

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

[i]Interim sacrifice at week 52.

[f]Final sacrifice at week 125.

( )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. Chlorothalonil - Fischer 344 Rat Study

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

	Dose (mg/kg/day)				
	0	2	4	15	175
Adenoma (%)	1/54 (2)	1/54 (2)	1/54 (2)	3/53 (6)	17[a]/54 (31)
p =	0.000**	-	-	0.102	0.000**
Carcinoma (%)	0/54 (0)	0/54 (0)	0/50 (0)	1/52 (2)	7[b]/48 (15)
p =	0.000**	-	-	0.109	0.011*
Combined (%)	1/54 (2)	1/54 (2)	1/54 (2)	4/53 (8)	23[c]/54 (43)
p =	0.000**	-	-	0.045*	0.000**

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

[a]First adenoma observed at week 71, dose 175 mg/kg/day.

[b]First carcinoma observed at week 83, dose 175 mg/kg/day.

[c]One animal in the 175 mg/kg/day dose group had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in this analysis.
One animal in the 175 mg/kg/day dose group of the interim sacrifice group had an adenoma.

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. Chlorothalonil - Fischer 344 Rat Study

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

	Dose (mg/kg/day)				
	0	2	4	15	175
Papilloma (%)	0/54 (0)	0/54 (0)	3/49 (6)	2/52 (4)	5[a]/46 (11)
p =	0.000**	-	0.042*	0.076	0.001**

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

[a]First papilloma observed at week 85, dose 175 mg/kg/day.

Note: Interim sacrifice animals are not included in this analysis.

No animals in the interim sacrifice group had papillomas.

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. Chlorothalonil - Fischer 344 Rat Study

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

	Dose (mg/kg/day)				
	0	2	4	15	175
Adenoma (%)	0/54 (0)	0/53 (0)	0/51 (0)	0/52 (0)	24[a]/53 (45)
p =	0.000**	-	-	-	0.000**
Carcinoma (%)	0/39 (0)	0/39 (0)	0/33 (0)	0/35 (0)	11[b]/35 (31)
p =	0.000**	-	-	-	0.000**
Combined (%)	0/54 (0)	0/53 (0)	0/51 (0)	0/52 (0)	32[c]/53 (60)
p =	0.000**	-	-	-	0.000**

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

[a]First adenoma observed at week 79, dose 175 mg/kg/day.

[b]First carcinoma observed at week 111, dose 175 mg/kg/day.

[c]Three animals in the 175 mg/kg/day dose group had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in this analysis.
No animals in the interim sacrifice group had adenomas or carcinomas.

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. Chlorothalonil - Fischer 344 Rat Study

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

	Dose (mg/kg/day)				
	0	2	4	15	175
Papilloma (%)	1/44 (2)	1/45 (2)	2/47 (4)	4/41 (10)	7[a]/46 (15)
p =	0.011*	0.404	0.168	0.095	0.020*
Carcinoma (%)	1/54 (2)	0/53 (0)	0/52 (0)	1/52 (2)	3[b]/54 (6)
p =	0.007**	-	-	-	0.094
Combined (%)	1[c]/54 (2)	1/53 (2)	2/52 (4)	5/52 (10)	9[c]/54 (17)
p =	0.001**	0.404	0.168	0.060	0.003**

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

[a]First papilloma observed at week 99, dose 175 mg/kg/day.

[b]First carcinoma observed at week 75, dose 175 mg/kg/day.

[c]One animal in each of the 0 and 175 mg/kg/day dose groups had both an adenoma and a carcinoma.

Note: Interim sacrifice animals are not included in this analysis.
No animals in the interim sacrifice group had papillomas or carcinomas.

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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