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OFFICE OF
PREVENTION, PESTICIDES AND
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Subject: Phosmet (Imidan Technical,T-10719), B6C3F1 Mouse Oncogenicity study, 4/81-5/83 - Qualitative Risk Assessment Revised, January,1994

Caswell no.543

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The re-evaluation of the qualitative risk assessment of Phosmet was based upon a study of oncogenicity in B6C3F1 mice (4/81-5/83). The mice were fed 0, 5, 25 and 100 ppm of Phosmet (Imidan) for 2 years.

At this time, it was expedient to review and re-evaluate the original individual animal data in order to revise the qualitative risk assessment according to current HED methodology. The current statistical analysis did not change conclusions that were previously reported (Imidan Technical (T-10719)-Qualitative Analysis of Mouse Oncogenicity Study, B.Fisher-2/86). That is, that there was no significant differential mortality with increasing doses of phosmet in both male and female mice. Also that the liver tumor (adenoma and/or carcinoma) rates had a significantly ($p<.01$) increasing trend with dose increments of Phosmet in both sexes of mice. Male mice had a statistically significant ($p=.019$) difference in the comparison of controls and

the high dose (100 ppm) level in the liver tumor rates and the females had a borderline (p=.066) difference in the same dose level comparisons of these tumor rates.

It was additionally noted in this review that the female mice had a significantly (p=.007) increasing trend in mammary gland adenocarcinomas.

The statistical analysis of tumor rates was based upon the Exact Trend test and Fisher's Exact test for pair-wise comparisons of controls and each dose group for the females since there was no statistical evidence of differential mortality with increasing doses of Phosmet (Imidan).

However, in the male mice, there was an early onset of tumors that was observed first in the ten interim sacrificed animals (0/10, 1/10, 2/10, and 3/10 with doses of 0, 5, 25 and 100 ppm). Therefore these data were included with the rest of the liver tumors that occurred in the lifetime study for the statistical evaluations. Thus, the evaluation of tumor rate changes was based on the Peto's Prevalence Test methods to adjust for the different lengths of survival.

Table 1. Phosmet (Imidan) - B6C3F1 Mouse Study, Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-52	52[a]	53-78	79-105[b]	Total
0	1/60	10/10	0/49	3/49	4/50(8)
5	0/60	10/10	0/50	7/50	7/50(14)
25	0/60	10/10	0/50	10/50	10/50(20)
100	0/60	10/10	0/50	8/50	8/50(16)

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

( ) percent

a Interim sacrifice at week 52.
b Final sacrifice at week 105.

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 2. Phosmet (Imidan) -B6C3F1 Mouse Study, Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-52	52[a]	53-78	79- 105[b]	Total
0	1/60	10/10	1/49	12/48	14/50(28)
5	0/60	10/10	1/50	14/49	15/50(30)
25	2/60	10/10	1/48	8/47	11/50(22)
100	0/60	10/10	0/50	13/50	13/50(26)

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

( ) percent

a Interim sacrifice at week 52.
b Final sacrifice at week 105.

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 3. Phosmet(Imidan) - B6C3F1 Male Mice, Liver Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0	5	25	100
Liver Tumors				
Adenomas (%)	10/59 (17)	10[a]/60 (17)	12/60 (20)	21/60 (35)
p=	0.002**	0.437	0.245	0.008**
Carcinomas (%)	13/59 (22)	11/60 (18)	11[b]/60 (18)	14/60 (23)
p=	0.364	0.815(n)	0.843(n)	0.599
Both (%)	23/59 (39)	21/60 (35)	23/60 (38)	35/60 (58)
p=	0.002**	0.727(n)	0.585(n)	0.019*

[+] 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 52, dose 5 ppm.
b First carcinoma observed at week 52, dose 25 ppm.

n Negative change from control.

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 4. Phosmet(Imidan) - B6C3F1 Female Mice, Liver Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	5	25	100
Liver Tumors				
Adenomas (%)	5/49 (10)	4/50 (8)	5[a]/48 (10)	9/50 (18)
p=	0.061	0.487(n)	0.617	0.205
Carcinomas (%)	5[b]/49 (10)	4/50 (8)	3/48 (6)	9/50 (18)
p=	0.046*	0.487(n)	0.369(n)	0.205
Both (%)	10/49 (20)	8/50 (16)	8/48 (17)	18/50 (36)
p=	0.007**	0.379(n)	0.416(n)	0.066

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53 or were sacrificed at week 52.

a First adenoma observed at week 93, dose 25 ppm.
b First carcinoma observed at week 78, dose 0.

n Negative change from control.

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 5. Phosmet(Imidan) -B6C3F1 Female Mice, Mammary Gland Adenocarcinoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	5	25	100
Mammary Gland Adenocarcinomas (%)	1/49 (2)	0/50 (0)	1/48 (2)	5[a]/50 (10)
p=	0.007**	0.495(n)	0.747	0.107

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53 or were sacrificed at week 52.

a First tumor observed at week 92, dose 100 ppm.

n Negative change from control.

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 $p<.01$.