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MEMORANDUM

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: PROPANIL Qualitative Risk Assessment Based On Sprague-Dawley Crl:CD(SD)BR Rat and Crl:CD-1(ICR)BR Mouse Dietary Studies

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Background

A combined chronic toxicity and oncogenicity study in Sprague-Dawley rats was conducted by Huntingdon Research Centre, Ltd., Cambridgeshire, England, for The Propanil Task Force, Sterling, Virginia, and issued July 1, 1994 (Study No. PTF3; MRID No. 433032-01).

The study design allocated groups of 50 rats per sex to dose levels of 0, 200, 600, or 1800 ppm (0, 9.0, 27.7, or 88.0 mg/kg/day for males; 0, 11.5, 38.3, or 145.0 mg/kg/day for females) of Propanil for 104 weeks. An additional 20 rats per sex per dose were designated for interim sacrifice at week 52.

An oncogenicity study in CD-1 mice was conducted by WIL Research Laboratories, Inc., Ashland, Ohio, for The Propanil Task Force, Liberty, Missouri, and issued September 9, 1994 (Study No. WIL-141011; MRID No. 433917-01).

The study design allocated groups of 60 mice per sex to dose levels of 0, 500 or 1000 ppm (0, 74.9, or 150.0 mg/kg/day for males;

0, 88.6, or 174.1 mg/kg/day for females) of Propanil for 104 weeks. An additional 20 mice per sex per dose were designated for interim sacrifice at week 52.

Survival Analyses

The statistical evaluation of mortality indicated a significant decreasing trend with increasing doses of Propanil in male and female rats. Male and female mice showed no significant incremental changes in mortality with increasing doses of Propanil. See Tables 1 and 2 for rat mortality test results, Tables 7 and 8 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 a significant increasing trend at $p < 0.01$, and significant differences in the pair-wise comparisons of the 600 (at $p < 0.05$) and 1800 (at $p < 0.01$) ppm dose groups with the controls, for testes interstitial cell tumors.

Female rats had a significant increasing trend at $p < 0.01$, and a significant difference in the pair-wise comparison of the 1800 ppm dose group with the controls at $p < 0.05$, for liver adenomas.

There were no compound-related tumors observed in male mice.

Female mice had a significant increasing trend at $p < 0.01$, and a significant difference in the pair-wise comparison of the 1000 ppm dose group with the controls at $p < 0.05$, for malignant lymphomas (all sites).

The statistical analyses of the rats were based upon Peto's prevalence test due to a significant decreasing trend for mortality in both sexes. The statistical analysis of the female mice was based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 3 through 6 for rat tumor analysis results. See Table 9 for female mouse tumor analysis results.

Table 1. Propanil - Sprague-Dawley Rat Study

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

Dose (ppm)	<u>Weeks</u>					Total
	1-26	27-52	52 ⁱ	53-78	79-107 ^f	
0	0/70 (0)	2/70 (3)	19/68	6/49 (12)	28/43 (65)	36/51 (71) ^{**n}
200	0/70 (0)	3/70 (4)	19/67	9/48 (19)	22/39 (56)	34/51 (67)
600	0/70 (0)	1/70 (1)	20/69	5/49 (10)	21/44 (48)	27/50 (54)
1800	0/70 (0)	1/70 (1)	20/69	8/49 (16)	11/41 (27)	20/50 (40) ^{**n}

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

ⁱInterim sacrifice at week 52.

^fFinal sacrifice at week 104.

Values in parenthesis indicate 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. Propanil - Sprague-Dawley Rat Study

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

Dose (ppm)	<u>Weeks</u>					Total
	1-26	27-52	52 ⁱ	53-78	79-106 ^f	
0	0/70 (0)	2/70 (3)	20/68	12/48 (25)	17/36 (47)	31/50 (62) ^{**n}
200	0/70 (0)	2/70 (3)	19/68	9/49 (18)	22/40 (55)	33/51 (65)
600	1/70 (1)	1/69 (1)	20/68	9/48 (19)	19/39 (49)	30/50 (60)
1800	0/70 (0)	0/70 (0)	20/70	3/50 (6)	14/47 (30)	17/50 (34) ^{**n}

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

ⁱInterim sacrifice at week 52.

^fFinal sacrifice at week 104.

Values in parenthesis indicate 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. Propanil - Sprague-Dawley Rat Study

Male Testes Interstitial Cell Tumor Rates[†] and
Peto's Prevalence Test Results (p values)

	<u>Dose (ppm)</u>			
	0	200	600	1800
Tumors (%)	3/38 (8)	3/34 (9)	8 ^a /38 (21)	29/40 (72)
p =	0.000 ^{**}	-	0.046 [*]	0.000 ^{**}

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor in an animal that died on study.

^aFirst tumor in an animal that died on study observed at week 86, dose 600 ppm.

Note: Interim sacrifice animals are not included in this analysis. There was one testes interstitial cell tumor in an interim sacrifice animal in the 600 ppm dose group.

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. Propanil - Sprague-Dawley Rat Study

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

	<u>Dose (ppm)</u>			
	0	200	600	1800
Adenomas# (%)	1 ^a /36 (3)	0/40 (0)	1/39 (3)	6/47 (13)
p =	0.002 ^{**}	-	-	0.049 [*]

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

#No liver carcinomas were observed in female rats.

^aFirst liver adenoma observed at week 79, dose 0 ppm.

Note: Interim sacrifice animals are not included in this analysis. There were no liver adenomas in any interim sacrifice animals.

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. Propanil - Sprague-Dawley Rat Study

Female Uterine Endometrial Polyp Rates[†] and Peto's Prevalence Test Results (p values)

	<u>Dose (ppm)</u>			
	0	200	600	1800
Endometrial Polyps (%)	3 ^a /38 (8)	0/30# (0)	3/28# (11)	6/47 (13)
p =	0.228	-	0.215	0.247

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor in an animal that died on study.

#Only those animals found dead or sacrificed in extremis, or those with macroscopic findings in the uterus, were examined microscopically in these dose groups.

^aFirst endometrial polyp in an animal that died on study observed at week 75, dose 0 ppm.

Note: Interim sacrifice animals are not included in this analysis. There were 3 endometrial polyps in interim sacrifice animals in the 1800 ppm dose group. See Table 6 for a separate analysis of the interim sacrifice animals.

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. Propanil - Sprague-Dawley Rat Study

Female Uterine Endometrial Polyp Rates[†] and Exact Trend Test and Fisher's Exact Test Results (p values)

INTERIM SACRIFICE ANIMALS ONLY

	<u>Dose (ppm)</u>			
	0	200	600	1800
Endometrial Polyps (%)	0/20 (0)	0/3# (0)	0/2# (0)	3/20 (15)
p =	0.080	1.000	1.000	0.115

[†]Number of tumor bearing animals/Number of animals examined, including ONLY those that were sacrificed at 52 weeks.

#Only those animals found dead or sacrificed in extremis, or those with macroscopic findings in the uterus, were examined microscopically in these dose groups.

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. Propanil - CD-1 Mouse Study

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

Dose (ppm)	<u>Weeks</u>					Total
	1-26	27-52	52 ⁱ	53-78	79-105 ^f	
0	0/80 (0)	3/80 (4)	19/77	15/58 (25)	18/43 (39)	36/61 (59)
500	2/80 (2)	4/78 (5)	17/74	12/57 (20)	18/45 (37)	36/63 (57)
1000	2/80 (2)	3/78 (4)	19/75	7/56 (12)	27/49 (52)	39/61 (64)

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

ⁱInterim sacrifice at week 52.

^fFinal sacrifice at week 104.

() 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 8. Propanil - CD-1 Mouse Study

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

Dose (ppm)	<u>Weeks</u>					Total
	1-26	27-52	53 ⁱ	53-78	79-105 ^f	
0	1/80 (1)	3/79 (4)	19/76	3/57 (5)	24/54 (42)	31/61 (51)
500	2/80 (2)	4/78 (5)	19/74	11/55 (19)	19/44 (40)	36/61 (59)
1000	1/80 (1)	4/79 (5)	19/75	10/56 (17)	24/46 (48)	39/61 (64)

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

ⁱInterim sacrifice at week 53.

^fFinal 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 $p < 0.01$.

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Table 9. Propanil - CD-1 Mouse Study

Female Malignant Lymphoma (All Tissues) Tumor Rates[†] and Exact Trend Test and Fisher's Exact Test Results (p values)

	<u>Dose (ppm)</u>		
	0	500	1000
Malignant Lymphomas (%)	4/78 (5)	4 ^a /78 (5)	13/77 (17)
p =	0.008 ^{**}	0.640	0.017 [*]

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 34.

^aFirst malignant lymphoma observed at week 34, dose 500 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 $p < 0.01$.

References

Cox, D.R. (1972) Regression Models and Life Tables (with discussion). J. Royal Stat. Soc. Ser. B. 34, 187-220.

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