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PESTICIDES AND TOXIC SUBSTANCES

Subject: Permethrin - Qualitative Risk Assessment,
Two Year Chronic/Oncogenicity Mouse Study

caswell no. 652BB

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Summary

The qualitative risk assessment of the 2 year dietary permethrin study in Charles River CD-1 mice indicated no survival disparities in females with dose levels of 0, 20, 2500, and 5000 ppm. While in male mice with dose levels of 0, 20, 500, and 2000, ppm., there was a significant increasing trend in survival, namely due to the significant difference between the control and the highest dose group.

In female mice, there were significant increasing trends in tumor rates in lung adenomas, lung carcinomas, lung adenomas and/or carcinomas, in liver adenomas and in liver adenomas and/or carcinomas. In the pairwise comparison of tumor rates of controls and the highest dose group, there were significant differences in lung adenomas, lung carcinomas, and lung adenomas and/or carcinomas, in liver adenomas, and liver adenomas and/or carcinomas. The pairwise comparison of tumor rates for controls and the mid dose group resulted in significant differences in lung adenomas, lung adenomas and/or carcinomas, liver adenomas and liver adenomas and/or carcinomas. The pairwise comparison of tumor rates for female controls and the low dose group resulted in significant differences in lung adenomas and in lung adenomas and/or carcinomas.

In male mice, there were significant increasing trends in tumor rates in liver adenomas, ~~and in liver adenomas and/or carcinomas~~. In the pairwise comparison with controls, the tumor rates were significantly different from the high dose group for liver adenomas and liver adenomas and/or carcinomas.

In males, lung tumor and liver carcinoma tumor rates were not appreciably different among the dose levels of permethrin.

Background

A 24 month chronic feeding/oncogenicity study of permethrin in Charles River CD-1 strain mice was conducted by Bio/Dynamics Inc., (project no. 76-1695) for FMC Corporation and reported in October, 1979.

The study design allocated groups of 75 males to a dietary regimen of 0, 20, 500, 2000 ppm and 75 females to 0, 20, 2500, and 5000 ppm of permethrin for two years.

Table 1. Permethrin- Experimental Design of the Mouse Study

Dose(ppm.)	Number of Mice	
	males	females
0	75	75
20	75	75
500	75	—
2000	75	—
2500	—	75
5000	—	75

Survival Analysis

Survival analysis of the study was based upon the application of the computer program of Thomas, Breslow, and Gart.

Female mice had no statistically significant mortality changes with dose increments of permethrin. See Table 3. for details.

Male mice had a statistically significant ($p=.0000$) increasing trend in mortality, chiefly due to a significant ($p=.0018$) difference in mortality in the highest dose group as compared with controls. Both of these significant outcomes were the result of the Gehan-Breslow Generalized K/W test. See Table 2. for details.

Tumor Analysis

For female mice, because of the absence of survival disparities between dose levels of permethrin, tumor data were statistically evaluated by means of the Cochran-Armitage Trend test and also by the Fisher Exact test for pairwise comparison of dose levels with the control.

Significant increasing tumorigenicity occurred in the lungs and liver of the female mice with increasing doses of permethrin.

Female mice had significant trends in lung adenomas, lung carcinomas, and in lung adenomas and/or carcinomas. In addition, all of the 3 tumor types had significant differences in the pairwise comparison of control and the highest (5000 ppm.) dose group. Also lung adenomas and lung adenomas and/or carcinomas had significant differences in the pairwise comparisons of controls with both the low (20 ppm.) and the mid (2500 ppm.) dose groups. See Table 4. for details.

In female mice, liver adenomas and also liver adenomas and/or carcinomas had significantly increasing trends with incremental doses of permethrin. The pairwise comparisons with controls resulted in significant differences in the mid (2500 ppm.) and also the high (5000 ppm.) dose group for both liver adenomas and liver adenomas and/or carcinomas. Liver carcinomas did not increase significantly. See Table 5. for details.

For male mice, because of significant survival differentials among the dose levels of permethrin, tumor data was statistically evaluated for trends and the pairwise comparisons by means of Peto's Prevalence test.

As in female mice, males also had liver and lung tumors. But in males, lung tumors did not significantly increase with dose increments of permethrin. See Table 6. for details.

In male mice liver adenoma tumor rates had significantly increasing trends. The pairwise comparison of controls and each of the 3 (20, 500, 2000 ppm.) dose groups had significant differences in liver adenoma tumor rates. For the combined liver (adenomas and/or carcinomas) tumor rates, there were significant differences between controls and the mid (500 ppm.) and also the high (2000 ppm.) dose group. In male mice just as in females, liver carcinomas were not significantly elevated with incremental doses of permethrin. However in males, the control group had a 24 % tumor rate of liver carcinomas. See Table 7. for details.

References

- Armitage, P. (1955) Tests for Linear Trends in Proportions, Biometrics 11, 375-386.
- Cochran, W.G. (1954) Some Methods for Strengthening the Common χ^2 Test, Biometrics 10, 417-451.
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Table 2. Permethrin, Mouse Study - Male Mortality Rates[†]
and Cox or Generalized K/W Test Results

<u>Dose</u> (ppm)	<u>Weeks</u>					<u>Total</u>
	<u>0-26</u>	<u>27-52</u>	<u>53-78</u>	<u>79-104</u>	<u>105^a</u>	
0	1/75	6/74	17/68	31/51	20/20	55/75 (73)**
20	4/75	6/71	10/65	28/55	27/27	48/75 (64)
500	6/75	4/69	9/65	30/56	26/26	49/75 (65)
2000	5/75	9/70	27/61	22/34	12/12	63/75 (84)**

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

() Percent.

^aFinal sacrifice.

Note: The above time intervals are for display purposes only.

Significance of trend denoted at control.

Significance of pairwise comparison with control denoted at dose level.

*p < .05.

**p < .01.

Table 3. Permethrin, Mouse Study - Female Mortality Rates[†]
and Cox or Generalized K/W Test Results

<u>Dose</u> (ppm)	<u>Weeks</u>					<u>Total</u>
	<u>0-26</u>	<u>27-52</u>	<u>53-78</u>	<u>79-104</u>	<u>105^a</u>	
0	3/75	3/72	13/69	34/56	22/22	53/75 (71)
20	1/75	7/74	10/67	23/57	34/34	41/75 (55)
2500	4/75	7/71	13/64	27/51	24/24	51/75 (68)
5000	4/75	5/71	14/66	30/52	22/22	53/75 (71)

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

()Percent.

^aFinal sacrifice.

Note: The above time intervals are for display purposes only.

Significance of trend denoted at control.

Significance of pairwise comparison with control denoted at dose level.

*p < .05.

**p < .01.

Table 4. Permethrin - Mouse Study, Female Lung Tumor Rates[†]
and Cochran-Armitage Trend Test and Fisher Exact
Test Results

Tumor	Dose (ppm)			
	0	20	2500	5000
Adenoma	9/71	17/68	24/68	29/69
(%)	(13)	(25)	(35) ^a	(42)
p =	0.0002**	0.0495*	0.0015**	0.0001**
Carcinoma	6/66	7/62	11/59	15/62
(%)	(9)	(11) ^b	(19)	(24)
p =	0.0047**	0.4519	0.0977	0.0187*
Both	15/71	24/68	35/68	44/69
(%)	(21)	(35)	(52)	(64)
p =	0.0000**	0.0473*	0.0002**	0.0000**

[†]Number of tumor-bearing animals/Number of animals at risk, excluding those that died before observation of the first tumor.

^aFirst adenoma at week 39.

^bFirst carcinoma at week 62.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control
denoted at dose level.

*p < .05.

**p < .01.

Table 5. Permethrin, Mouse Study - Female Liver Tumor Rates[†]
and Cochran-Armitage Trend Test and Fisher Exact
Test Results

Tumor	Dose (ppm)			
	0	20	2500	5000
Adenoma	2/66	4/62	22/63	28/65
(%)	(3)	(6)	(35) ^a	(43)
p =	0.0000**	0.2994	0.0000**	0.0000**
Carcinoma	4/49	3/55	3/49	2/51
(%)	(8)	(5)	(6)	(4)
p =	0.2534	0.4312	0.4938	0.3082
Both	6/66	7/62	25/63	30/65
(%)	(9)	(11)	(40)	(46)
p =	0.0000**	0.4519	0.0000**	0.0000**

[†]Number of tumor-bearing animals that died/Number of animals at risk, excluding those that died before observation of the first tumor.

^aFirst adenoma at week 54.

^bFirst carcinoma at week 81.

Note: Significance of trend denoted at control.

Significance of pairwise comparison with control denoted at dose level.

*p < .05.

**p < .01.

Table 6. Permethrin, Mouse Study - Male Lung Tumor Rates[†]
and Peto Prevalence Test Results

Tumor	Dose (ppm)			
	0	20	2500	5000
Adenoma	16/73	15/71	15/68	17/69
(%)	(22)	(21)	(22) ^a	(25)
p =	0.1175	0.4651	0.4823	0.1707
Carcinoma	7/49	5/52	13/54	4/30
(%)	(14)	(10) ^b	(24)	(13)
p =	0.3989	0.2217	0.1276	0.1722
Both	23/73	20/71	28/68	21/69
(%)	(32)	(28)	(41)	(30)
p =	0.1329	0.3585	0.1535	0.1722

[†]Number of tumor-bearing animals that died/Number of animals at risk, excluding those that died before observation of the first tumor.

^aFirst adenoma at week 25.

^bFirst carcinoma at week 81.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control
denoted at dose level.

*p < .05.

**p < .01.

Table 7. Permethrin, Mouse Study - Male Liver Tumor Rates and Peto Prevalence Test Results

Tumor	Dose (ppm)			
	0	20	500	2000
Adenoma	6/66	17/63	15/63	17/57
(%)	(9)	(27)	(24)	(30) ^a
p =	0.0034**	0.0058**	0.0150*	0.0003**
Carcinoma	16/68	12/64	19/64	8/60
(%)	(24)	(19)	(30) ^b	(13)
p =	0.1797	0.3481	0.1381	0.1819
Both	22/68	29/64	36/64	25/60
(%)	(32)	(45)	(56)	(42)
p =	0.0973	0.0618	0.0083**	0.0215*

†Number of tumor-bearing animals/Number of animals at risk, excluding those that died before observation of the first tumor.

^aFirst adenoma at week 56.

^bFirst carcinoma at week 47.

Note: Significance of trend denoted at control.
Significance of pairwise comparison with control denoted at dose level.

*p < .05.

**p < .01.