UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 8 - 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Bifenthrin, Mouse Study - Qualitative and Quantitative Risk Assessment of Combined Toxicity and Oncogenicity Study in Mice. Caswell #463F

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Summary:

The potency estimate, Q_1^* of Bifenthrin is 5.4×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents. This estimate is based upon male mouse urinary bladder tumors (Leiomyosarcomas).

There were no significant survival disparities in male or female mice with increasing doses of Bifenthrin. There was a significant dose related trend for bladder tumors in the males and the high dose was significantly different than the controls. There was a significant dose related trend for liver tumors in the males but no significant pairwise trends.

There was no significant dose related trend for lung tumors in females, but the 50ppm, 200ppm, and 600ppm dose groups had significantly higher tumor rates than the controls.

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Background:

This study was conducted at FMC Laboratory on male and female Swiss-Webster mice. Bifenthrin was administered to both sexes at 50ppm, 200ppm, 500ppm, and 600ppm in the diet. There was also a concurrent control group. All groups had 50 animals. (FMC Tox Lab Study No. A83-974).

Mortality Analysis:

There were no survival disparities in male or female mice with increasing doses of Bifenthrin (Table 1). The Thomas, Breslow, and Gart Procedure (1977) was used to analyze the survival data. Neither the male or the female mice had any significant mortality trend with dose and no departure from trend using Cox's test (1972) for life table data. There were no significant pairwise comparisons between the control and any treated group.

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Table 1. Bifenthrin - Mouse Study, Mortality Rates[+] and Cox or Generalized K/W Test Results

B. Males

Dose ppm	WEEKS 0-26	27-52	53-78	79-87[a]	TOTALS
0	1/50	5/49	20/44	10/24	36/50 (72)
50	1/50	4/49	17/45	9/28	31/50 (62)
200	1/50	5/49	10/44	10/34	26/50 (52)
500	4/50	5/46	19/41	9/22	37/50 (74)
600	3/50	3/47	10/44	15/34	31/50 (62)

a Final sacrifice at 87 weeks.

B. Females

Dose ppm	WEEKS 0-26	27-52	53-78	79-92[b]	TOTALS
0	2/50	8/48	10/40	11/30	31/50 (62)
50	5/50	3/45	13/42	16/29	37/50 (74)
200	4/50	3/46	16/43	12/27	35/50 (70)
500	3/50	4/47	15/43	7/28	29/50 (58)
600	4/50	5/46	8/41	14/33	31/50 (62)

+ Number of Animals Died/Number of Live Animals at the beginning of the interval.
( ) Percent
b Final sacrifice was at 92 weeks.

Note - The above survival tables are broken into aggerate time intervals for display purpose only.
Significance of Trend Analysis denoted at Control.
Significance of pairwise comparison with control denoted at Dose level.
$p < .05$ ** $p < .01$

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Tumor Analysis:

For males, urinary bladder tumors (Leiomyosarcomas) and liver tumors (Hepatocellular adenocarcinomas and adenomas) were analyzed . Since there were no survival disparities, the Fisher's Exact Test was used for pairwise comparisons and the Cochran-Armitage Test was used to test for trends. There was a significant trend ($p<.05$) for the bladder tumors (Table 2) and the 600ppm dose was significantly different ($p<.001$) from the controls. There was a significant trend for the liver adenocarcinomas (Table 3, $p<.05$) and the pooled adenoma and adenomacarcinoma ($p<.05$) data, but adenoma alone was not significant. There were no significant pairwise comparisons when treated groups were tested against controls for the liver tumors.

At the suggestion of Byron Backus (Reviewer), lung bronchioalveolar adenomas and adenocarcinomas for the females (Table 4) were combined. Since there were no survival disparities, the Fisher's Exact Test was used for pairwise comparisons and the Cochran-Armitage Test was used to test for trends. The pairwise comparisons showed significantly elevated tumor incidence for the 50ppm group ($p=.007$), the 200ppm group ($p=.033$) and the 600 ppm group ($p=.02$). The test for trend was not significant.

Dose-Response Review:

Since mortality in the mouse study was not significantly impaired with increasing doses of bifenthrin, the potency estimate Q_1^* was obtained through the use of K. Crumps Multi-Stage commputer program (1986). The bladder tumor data for male mice was used to estimate the dose-response effect. The resulting potency estimates in parts per million of bifenthrin were converted to mg/kg/day for animals by using Lehman's Tables and then to human equivalents by use of the interspecies surface area adjustment as recommended by EPA Cancer Guidelines.

The resultant potency estimate for the mouse was 4.04×10^{-3} $[mg/kg/day]^{-1}$ and in human equivalents was 5.4×10^{-2} $[mg/kg/day]^{-1}$.

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Table 2. Bifenthrin - Mouse Study, Males Urinary Bladder Tumor (Leiomyosarcomas) Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

Dose ppm	0	50	200	500	600
	2/46	6/48	8/48	7/45	14/45
	(4)**	(12)	(17)	(16)	(31)**

+ Tumor Bearing Animals/ Animals at Risk.

Note - Significance of Trend Analysis denoted at Control;
Significance of pairwise comparison with control denoted at Dose level.
* p < .05 ** p < .01

Table 3. Bifenthrin - Mouse Study, Males Liver Tumor (Hepatocellular Adenocarcinomas and Adenomas) Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

Dose ppm	0	50	200	500	600
Adeno-carcinoma	0/24* (0)	0/28 (0)	1/35 (3)	2/24 (8)	2/34 (6)
Adenoma	2/41 (5)	2/43 (5)	3/43 (7)	2/39 (5)	5/40 (12)
Adenoma & Adeno-carcinoma	2/41* (5)	2/43 (5)	4/43 (9)	4/39 (10)	7/40 (18)

+ Tumor Bearing Animals/ Animals at Risk.

Note - Significance of Trend Analysis denoted at Control;
Significance of pairwise comparison with control denoted at Dose level.
* p < .05 ** p < .01

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Table 4. Bifenthrin - Mouse Study, Females Lung Bronchioalveolar Adenocarcinoma and Adenoma Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results

Dose ppm	0	50	200	500	600
	14/49 (29)	26/47** (55)	23/47* (49)	19/47 (40)	23/45* (51)

+ Tumor Bearing Animals/ Animals at Risk.

Note - Significance of Trend Analysis denoted at Control; Significance of pairwise comparison with control denoted at Dose level.

* $p < .05$ ** $p < .01$

Bibliography:

Thomas, D G, N Breslow, and J J Gart, Trend and Homogeneity Analyses of Proportions and Life Table Data, Computers and Biomedical Research 10, 373-381, 1977.

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

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