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

006950

Subject: Tetramethrin (Neopynamin) – Qualitative Risk Assessment, Two Year Dietary Rat Studies – Charles River CD (1974 and 1981) and Long Evans (1981)

caswell no. 844

From: Bernice Fisher, Biostatistician   *Bernice Fisher* 10/20/88
         Science Support Section
         Science Analysis and Coordination Branch, HED (TS-769C)

To: William Dykstra, Toxicologist
         Review Section I
         Toxicology Branch I, HED (TS-769C)

Thru: Richard Levy, M.P.H., Senior Scientist (Biostatistics)   *[signature]*
         Science Analysis and Coordination Branch, HED (TS-769C)   10-20-88
                        and
         John A. Quest, Ph.D., Head   *John A. Quest* 10/20/88
         Science Support Section
         Science Analysis and Cordination Branch, HED (TS-769C)

Summary

The qualitative risk assessment of two year dietary studies of Charles River CD (Sprague Dawley derived), 1974, 1981 and Long Evans, 1981 male rats indicated no significant survival trends with dose increments of tetramethrin in any of the three groups. However there was a survival disparity in the Charles River CD, 1974 study, between the low dose and control.

Dose levels of tetramethrin in the Charles River CD rat study for 1974 consisted of 0, 1000, 3000, and 5000 ppm. Dose groups of tetramethrin in the Charles River CD, 1981 and the Long Evans, 1981 rat studies were 0, 200, 1000, and 5000 ppm.

Testicular interstitial cell adenomas exhibited significant increasing trends in all the three studies with dose increments of tetramethrin.

The pairwise comparison of control and the highest dose group of these adenomas in all three studies, were found to be significantly different. The pairwise comparison of control and the mid dose level in the 1974 Charles River CD rat study resulted in a significant difference also for these interstitial cell adenomas.

Background

Hazleton Labs conducted three rat feeding studies for Sumitomo Chemical Company. In the first one (1974), tetramethrin was fed to F_0 generation Charles River CD (Sprague Dawley derived) rats, 120 males and 120 females, one week prior to breeding and then contiued for an additional 104 weeks in the F_1 generation of pups. Selected were 50 male and female F_1 pups for dose levels of 1000, 3000, and 5000 ppm of tetramethrin. The controls were 60 F_1 pups of each sex. The only positive effect reported in this F_1 generation study was in males – increases in testicular interstitial cell andenomas with dose increments of tetramethrin.

Hazleton then conducted two other studies in 1981, similar in design to the tne 1974 F_1 generation study, in order to reassess this finding. In the 1981 studies, male F_1 offspring of two strains – Charles River CD (Sprague Dawley derived) and Long Evans Hood – were selected at random with no more than three male pups per litter as the sample to have the histopathological examinations. The dose levels of tetramethrin in these two studies were 0, 200, 1000, and 5000 ppm. Each group contained 50 males.

Table 1. Tetramethrin – Experimental Designs of the Rat Studies, F_1 Generation Males

Dose	Long Evans		Charles River CD			
	1981		1974		1981	
ppm	total	interim sacrifice	total	interim sacrifice	total	interim sacrifice
0	50	-	60	10	50	-
200	50	-	—		50	-
1000	50	-	50		50	-
3000	—		50	10	—	
5000	50	-	50	10	50	-

Survival Analysis

Mortality trends were not found to be significant in any of the three rat studies. Only one pairwise comparison with controls and the 1000 ppm. dose group in the Charles River CD study, 1974 resulted in a significant ($p < .05$) increase in deaths.

The statistical analysis of survival was based upon the Thomas, Breslow, and Gart computer program. See Tables 2., 3., and 4. for details.

Tumor Analysis

In the absence of a statistically significant difference in survival with dose increments of tetramethrin in two of the three studies, the evaluation of testicular interstitial cell adenoma in rats was made by use of the Cochran-Armitage Trend test (one-sided) and the Fisher Exact test for the pairwise comparisons of control with each dose level.

For the evaluation of the interstitial cell adenomas in the third study - Charles River CD, 1974 - with a mortality problem, Peto's Prevelence test was used.

In each of the three studies, significantly ($p < .01$) increasing interstitial adenoma trends occurred in the male rats with dose increments of tetramethrin. In addition, the pairwise comparison of controls and the highest (5000 ppm.) dose group in each of the three studies, resulted in significant differences - for 1974 Charles River CD and 1981 Long Evans, $p < .01$ and for 1981 Charles River CD, $p < .05$. For the 1974 Charles River CD rats, the pairwise comparison of control and the mid (3000 ppm.) dose also resulted in a significant ($p < .01$) difference. See Tables 5. and 6. for details.

-4-

Table 2. Tetramethrin - Charles River CD (Sprague Dawley derived), 1974
Rat Study - Male Mortality Rates[+] and Cox or
Generalized K/W Test Results

Dose (ppm)	Week					
	1-26	27-52	52[a]	53-78	79-105	Total
0	0/60	1/60	10/10	5/49	11/44	17/50 (34)
1000	0/50	1/50	10/10	6/39	16/33	23/40 (57)[*]
3000	0/50	0/50	10/10	3/40	10/37	13/40 (32)
5000	0/50	1/50	10/10	2/39	15/37	18/40 (45)

[+] Number of Deaths during Interval / Number of Animals Alive at Beginning of Interval

( ) percent

a Interim Sacrifice at week 52

Note: Above Time Intervals were Selected for Display Purposes Only.

Significance of trend denoted at Control.
Significance of pairwise comparison with control denoted at Dose level.
[**] p<.01 and [*] p<.05

4

Table 3. Tetramethrin - Charles River CD (Sprague Dawley derived), 1981
Rat Study - Male Morality Rates[+] and Cox or
Generalized K/W Test Results

Dose (ppm)	1-26	27-52	Week 53-78	79-105	Total
0	1/50	2/49	6/47	11/41	20/50 (40)
200	1/50	1/49	3/48	19/45	24/50 (48)
1000	0/49[a]	1/49	8/48	14/40	23/49 (47)
5000	2/50	3/48	5/45	11/40	21/50 (42)

[+] Number of Deaths during Interval/ Number of Animals Alive at Beginning of Interval

( ) percent

a Final Sacrifice

b animal missing -week 79

Note: Above Time Intervals were Selected for Display Purposes Only.

Significance of trend denoted at Control.
Significance of pairwise comparison with control denoted at Dose level.
** $p<.01$ and * $p<.05$

Table 4. Tetramethrin - Long Evans , 1981 Rat Study -
Male Mortality Rates[+] and Cox or
Generalized K/W Test Results

Dose (ppm)	1-26	27-52	53-78	Week 79-104	Total
0	0/49[a]	2/49	5/47	5/42	12/49 (24)
200	0/49[b]	1/49	4/48	7/44	12/49 (24)
1000	1/49[c]	2/48	3/46	9/43	15/49 (31)
5000	0/49[d]	0/49	3/49	12/46	15/49 (31)

[+] Number of Deaths during Interval / Number of Animals Alive at Beginning of Interval

( ) percent

a animal missing - week 65
b animal missing - week 79
c animal missing - week 97
d animal missing - week 92

Note: Above Time Intervals were Selected for Display Purposes Only.

Significance of trend denoted at Control.
Significance of pairwise comparison with control denoted at Dose level.
[**] $p < .01$ and [*] $p < .05$

Table 5. Teramethrin — Rat Study, Charles River CD (1974) —
Male Interstitial Cell Adenoma Rates[+]
and Peto Prevalence Test Results (p values)

Testicular Interstitial Cell Adenoma	Dose (ppm)			
	0	1000	3000	5000
Charles River CD - 1974 (percent)	2/42 (5)	3/30 (10)	9/36 (25)	14/35 (40)[a]
p =	0.0000[**]	0.1313	0.0034[**]	0.0000[**]

[+] Number of Tumor Bearing Animals / Number of Animals at Risk, Excluding Those that Died Before Observation of the First Tumor.

a First adenoma at week 83

Note: Significance of Trend denoted at Control.
Significance of pairwise comparison with control denoted at Dose level.
[**] $p < .01$ and   [*] $p < .05$

7

-8-

Table 6. Tetramethrin – Rat Studies, Charles River CD and Long Evans
(1981) – Male Interstitial Cell Adenoma Rates[+]
and Cocnran-Armitage Trend Test and Fisher's
Exact Test Results (p values)

Testicular Interstitial Cell Adenoma	Dose(ppm)			
	0	200	1000	5000
Charles River CD – 1981 (percent) p =	7/39 (18) 0.0006**	7/40 (17) 0.5951	3/40 (7) 0.1451	16/39 (41)[a] 0.0229*
Long Evans 1981 (percent) p =	4/42 (10) 0.0000**	3/44 (7) 0.4736	4/39 (10) 0.6011	22/43 (51)[b] 0.0000**

+ Number of Tumor Bearing Animals / Number of Animals at Risk, Excluding
Those that Died Before Observation of the First Tumor.

a First adenoma at week 88
b First adenoma at week 89

Note: Significance of trend denoted at Control.
     Significance of pairwise comparison with control denoted at Dose level.
          ** p<.01 and * p<.05

006950

References

Armitage, P. (1955) Tests for Linear Trends in Proportions, Biometrics 11, 375-386.

Cochran, W.G. (1954) Some Methods for Strengthening the Common X^2 Test, Biometrics 10, 417-451.

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

Peto, R., Pike, M., Day, N., Gray, P., Parish S., Peto, J., Richard, S., and Wahrendorf, J. (1980) Guidelines for Simple, Sensitive, Significant Tests for Carcinogenic Effects in Long-Term Animal Experiments. - Monographs on the Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal. IARC Monographs. Supplement 2. Lyon, France: International Agency on Research on Cancer, 311-426.

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