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JUN 11 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cypermethrin, Mouse Study Females Qualitative Risk
Assessment - Reevaluation With Historical Controls

Caswell No. 271DD

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THRU: Richard Levy, M.P.H., Leader - Biostatistician Team
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and

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Background

A long-term feeding study, 97 weeks for males and 101 weeks for females, consisting of five groups of 70 male and 70 female, Swiss strain mice, was conducted by ICI Central Toxicology Laboratory (June 1982). The administered dose levels of cypermethrin were 0 (2 concurrent controls), 100, 400, and 1600 ppm. From the study group, 8 to 10 animals were selected for an interim sacrifice at 52 weeks.

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At the suggestion of Dr. Doherty, survival and the lung neoplasms (carcinomas and/or adenomas), in female mice, were used for the qualitative reevaluation of cypermethrin. In addition, Dr. Doherty submitted historical control data (see attachment) from seven studies. However, only five out of the group were pertinent, since in the other two, a dietary route of administering cypermethrin, was not used.

Data Analysis

The two concurrent control groups of female mice were combined because they had similar survival patterns (tested by the Thomas, Breslow and Gart computer program) and no significant difference in the lung tumor rates (Fisher's Exact test).

Survival in the female mice was not significantly impaired with increasing doses of cypermethrin (Thomas, Breslow and Gart computer program). See table 1. for survival summary.

The Cochran-Armitage test for trend was used on the observed lung tumor data and on a Tarone (1982) modification of the concurrent control data (table 2). The modified data adjusts the concurrent control based on historical control data. In both cases, the results indicated that there was a significant ($p < .01$) increase in tumor rates with increasing doses of cypermethrin. This outcome occurred both for the carcinoma and/or adenoma groups and the adenoma alone data set. Since there were only three carcinomas (two in the controls and one in the mid-dose group), the adenoma data group had the greater weight in determining the significant trend of tumors with dose increments of cypermethrin.

In the pairwise comparisons, only the high (1600 ppm) dose groups versus the controls, evaluated by Fisher's Exact test, produced significant differences. For carcinoma and/or adenoma group, $p = .013$ (raw data) and $p = .016$ (modified data); and for the adenoma only group, $p = .005$ (raw data) and $p = .004$ (modified data). See Table 2 for details. The modified data made little difference in the trend test or the Fisher exact test.

Attachment

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CypermethrinTable 1. Cypermethrin, Mouse Study - Females
Mortality Rates⁺

<u>Dose</u>	<u>Weeks</u>					
ppm	0-51	52-53 ^a	53-78	79-99	100-102	Total ^b
0	17/139	0/18	29/104	51/75	6/24	105/121 (87)
100	10/70	0/10	19/50	19/31	1/12	49/60 (82)
400	10/70	0/10	15/50	22/35	1/13	48/60 (80)
1600	13/70	0/11	13/46	25/33	1/8	52/59 (88)

⁺ Number of Deaths/Number of Animals Alive at Beginning
of Time Period

^a Interim Planned Kill - weeks 52 and 53

^b Excludes Interim Planned Kills

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Table 2. Cypermethrin, Mouse Study - Females
Lung Tumor Rates⁺ and
Cochran-Armitage Trend Test and Fisher
Exact Test Results

A. Lung Tumor Rates⁺
(Carcinoma and/or Adenoma)

Dose	Weeks				Tarone Modified
ppm	46 ^a -78	79-99	100-102	Total	
0	4/52	5/51	3/24	12/127 ^b (9)**	16/156 (10)**
100	1/33	3/19	2/12	6/64 (9)	6/64 (9)
400	3/29	5/22	0/13	8/64 (13)	8/64 (13)
1600	3/28	7/25	4/8	14/61 (23)*	14/61 (23)*

B. Lung Tumor Rates⁺
(Adenomas only)

Dose	Weeks				Tarone Modified
ppm	46-78 ^a	79-99	100-102	Total	
0	3/52	4/51	3/24	10/127 ^b (8)**	13/157 (8)**
100	1/33	3/19	2/12	6/64 (9)	6/64 (9)
400	2/29	5/22	0/13	7/64 (11)	7/64 (11)
1600	3/28	7/25	4/8	14/61 (23)**	14/61 (23)**

+ Number of Tumor-Bearing Animals/Number of Animals Examined
() Percent

^a Appearance of first tumor (week 46 - adenomas)

^b Excludes animals that were examined, but died before the appearance of the first tumor in the study

Note: The above time intervals are for display 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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References

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(with discussion). 9. Roy. Stat. Soc. Ser. B 34,
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- Tarone, R.E. (1982) The Use of Historical Control Information
in Testing for a Trend in Proportions. Biometrics 38,
215-220.
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- Thomas, D.G.; Breslow, N.; Gart, J.J. (1977) Trend and
Homogeneity Analyses of Proportions and Life Table Data.
Computers and Biomedical Research. 10, 373-381.

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MEMORANDUM

SUBJECT: Cypermethrin: Historical control data for the mouse oncogenicity study.

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FROM: John Doherty *John Doherty* 3/26/87
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TO: Richard Levy, Leader
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Attached is a report from the ICI Corporation summarizing the historical control data from several studies on the incidences of lung neoplasms. This information is relevant to the statistical assessment of cypermethrin.

As per the suggestion of Mr. Burnam, the report is being forwarded to you for inclusion in the revised statistical assessment of increased lung tumor incidences in the cypermethrin mouse oncogenicity study. It is our understanding that models for statistical evaluation currently in use within Toxicology Branch incorporate historical control data in the overall assessment.

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Cypermethrin toxicology review

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