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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: BAYTAN - Qualitative Risk Assessment of Two-year Chronic Toxicity/Oncogenicity Study in Female Mice - Caswell # 74A.

FROM: C.J. Nelson, Statistician cjnelson 8-7-87
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: George Ghali, Ph.D.
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Richard Levy, M.P.H.,Leader-Biostatistics Team
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C) Richard Levy 8-7-87

and

for Reto Engler, Ph.D., Chief E. Rinde
Scientific Mission Support Staff
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Summary:

A survival analysis of a 24 month combined chronic oral toxicity/oncogenicity study in female CF_1/W74 mice at levels of 125, 500, and 2000 ppm revealed no significant mortality trend and no significant pairwise comparisons between control and dosed groups. In the tumor analyses however, there was a significant dose-response trend for liver carcinomas and/or adenomas, and adenomas only. Hyperplastic lesions also had a significant trend. The incidence of liver adenomas at the high dose were significantly greater than the control group. The study was conducted by Bayer AG Laboratory for Mobay Chemical Corporation and reported in 1982.

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Background:

A 24 month combined chronic oral toxicity/oncogenicity study in male and female $CF_1/W74$ mice at levels of 125, 500, and 2000 ppm was conducted by Bayer AG Laboratory for Mobay Chemical Corporation and reported in 1982. There were 50 male and female mice at each dose group.

Data Analysis:

Because no data were provided for male mice lesions, only female mice were evaluated. There were no pairwise differences in survival and no significant trend using a time adjusted survival analyses (Thomas, Breslow, Gart) on the data shown in Table 1.

Since there were no survival problems, the Cochran-Armitage test for dose related trends and the Fisher's Exact test for pairwise differences was used to analyze the liver lesion data (Table 2 and Table 3). Animals that died before 52 weeks were excluded from the analysis on the premise that it may take about one year for the lesion of interest to appear.

There were no significant pairwise differences in liver carcinoma incidence between the control and dosed groups and no significant trend. Liver adenomas for the high dose females was significantly different ($p=.017$) from the control and there was a significantly increasing trend ($p=.0025$) with increasing dose. There was a significantly increasing dose-response trend for both liver hyperplasia ($p=.0325$) and combined liver carcinoma and/or adenoma ($p=.0115$). However, no significant pairwise comparisons between control and any dosed group were detected.

Two mice had both an adenoma and hyperplasia but are listed with the adenoma only group. In other words all animals with any of these liver lesions are counted in one of the categories and thus are in mutually exclusive categories.

Historical control data was provided for thirteen different studies on the same strain of mouse between 1976 and 1980. Only one of the studies was run at the same lab in 1977. In this study the control rate for adenomas was 5.1% (3/59) and the control rate for carcinomas was 3.4% (2/59). For the thirteen studies the pooled adenoma rate was 3.6% (24/661) and the pooled carcinoma rate was 2.0% (13/661). The tenth and ninetieth percentiles of the 13 studies was approximately 0% and 6% for adenomas respectively and 0% and 4% for carcinomas. For the combined adenoma and/or carcinoma the tenth percentile was approximately 2% and the ninetieth percentile was approximately 10%. There was no information on hyperplasia. It was impossible to determine which animals may have had both an adenoma and a carcinoma. Hence the combined estimates are a worst case. In

any event, the control animals in this study with adenoma (0%), carcinoma (2.3%), or adenoma and/or carcinoma (2.3%) are in close agreement with the historical controls and there is no need to adjust any of the analyses.

Bibliography:

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

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

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

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.

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Table 1 BAYTAN - Female Mice Mortality Rates+ and Cox or Generalized K/W Analysis Test Results

Dose (ppm)	WEEKS 0-26	27-52	53-78	79-105	Sacrif	Total[a)]
0	1/50	2/49	10/47	21/37	16	34/50 (68)
125	1/50	6/49	9/43	18/34	16	34/50 (68)
500	1/50	1/49	9/48	22/39	17	33/50 (66)
2000	0/50	2/50	11/48	18/37	19	31/50 (62)

\+ Number of rats that died/number of rats alive at the beginning of the interval. () Percent.
a) Final sacrifice at 106 weeks.

Note: The above time intervals were selected for display purposes only. Significance of trend analysis denoted at Control. Significance of pairwise comparison between control and dosed groups denoted at Dose level. ** p < .01 and * p < .05.

Table 2 BAYTAN - Female Mice Liver Tumor Rates+ and Trend or Fisher's Exact Test Results.

Dose (ppm)	0	125	500	2000
Carcinoma and/or Adenoma[a)]	1/43* (2)	0/40 (0)	5/45 (11)	6/47 (13)
Carcinoma[a)]	1/43 (2)	0/40 (0)	1/45 (2)	0/47 (0)
Adenoma Only[b)]	0/43** (0)	0/40 (0)	4/45 (9)	6/47* (13)

\+ Number of tumor bearing animals/ number of animals at risk (excludes all animals that died before the first year)
a) First carcinoma appeared at week 87 (day 613) at 500ppm.
b) First adenoma appeared at week 71 (day 501) at 2000 ppm.

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

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Table 3 BAYTAN - Female Mice Hyperplasia Rates[+] and Trend or Fisher's Exact Test Results.

Dose (ppm)	0	125	500	2000
Hyperplasia Only[a)]	2/43*	1/40	1/45	5/47
	(5)	(2)	(2)	(11)

+ Number of non-neoplastic lesion bearing animals/ number of animals at risk (excludes all animals that died before the first year)

a) First hyperplastic lesion appeared at week 71 (day 501) at 2000 ppm.

Note: Significance of trend analysis denoted at Control. Significance of pairwise comparison between control and dosed groups denoted at Dose level. ** $p < .01$ and * $p < .05$.