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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Propazine: Qualitative Risk Assessment of Two-Year Chronic Oral Study in female Rats (IRDC Report No.382-007; April 28, 1980). Caswell # 184.

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Summary

Significant survival disparities were found between dose groups in the two-year chronic oral study of female rats feed propazine. Adjusted, time to death with tumor, analyses were performed on All[+] mammary tumors combined, and Malignant[++] mammary tumors combined. Using the Peto Prevalence Method, statistically significant dose related trends were found for both tumor types, and a statistically significant pairwise comparison is found between control and high dose for the All mammary tumor type.


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+ Papillary adenocarcinoma carcinoma and/or fibroadenoma and/or papillary adenoma and/or adenocarcinoma-carcinoma and/or cystadenoma and/or adenoma and/or ductular adenoma.

++ Papillary adenocarcinoma and/or adenocarcinoma-carcinoma.

Background

A regimen of Propazine technical was fed in diet for two years to CD-1 rats (60/sex/dose) at 0, 3, 100, 1000 ppm. Ten additional rats were initiated in the control and high dose groups to provide for an interim sacrifice at 12 and 13 months of study.

Discussion and Analysis

Survival Analyses[1] of the female rats indicated a significant difference between the control and mid dose groups, such that survival was better in the mid dose group. The high dose group had a significantly lower survival experience than the mid dose group, and the lowest survival experience of all groups. To help illustrate these disparities, abbreviated Kaplan-Meier[2] survival probabilities are calculated for aggregate time intervals in Table 1. The last column of Table 1 is the Kaplan-Meier Product Limit calculated by multiplying the survival rate for a given dose across time. The resulting probability is the chance that an animal for a given dose will survive to the end of study. For example, a high dose group animal has only a 43.4% chance of surviving to the end of study.

Dr. Louis Kasza suggested that the mammary tumors are probably not fatal in context and further that the malignant mammary tumors should be analyzed separately.

Since survival disparities exist and the tumors are incidental in context, as indicated above, an adjusted analysis (ie., time to death with tumor) was performed on both All mammary tumors combined and Malignant mammary tumors combined, by the Peto Prevalence Method[3].

The data for each tumor type used the 'ad hoc runs' method to partition the experimental lifespan into successive time intervals having increasing prevalence. Table 2.a and Table 2.b contain the prevalence rates observed for the 'ad hoc ' time intervals. Based on the Peto Prevalence Method there is a significant dose related trend for Malignant mammary tumors combined ($p<.05$) and All mammary tumors combined ($p<.01$), and a significant difference ($p<.01$) between control and high dose group for All mammary tumors combined.

Table 1

Abbreviated Kaplan-Meier Survival
for Female Rat.

| Dose | Week 52 | Week 78 | Week 92 | Final Survivorship | Kaplan-Meier Product Limit |
|---|---|---|---|---|---|
| 0 | 66/69 (95.7) | 48/57 (84.2) | 41/48 (85.4) | 36/41 (87.8) | 0.604 |
| 3 | 58/60 (96.7) | 55/58 (94.8) | 43/55 (78.2) | 37/43 (86.0) | 0.617 |
| 100 | 59/60 (98.3) | 58/59 (98.3) | 51/58 (87.9) | 44/51 (86.3) | 0.733[1] |
| 1000 | 65/68 (95.6) | 49/55 (89.1) | 39/49 (79.6) | 25/39 (64.1) | 0.434[2] |

() Percent
1 Significantly different from control at P<.05 (Gehan-Breslow: Generalized K/W.)
2 Significantly different from mid dose at P<.01 (Gehan-Breslow: Generalized K/W.)

Table 2.a

Prevalence of Malignant Mammary Tumors Combined for Female Rat.

| Dose | Weeks 75a-103 | Week 104 | Final Kill 105 | Total[b] |
|---|---|---|---|---|
| 0 | 2/16 (12.5) | 0/1 (0) | 8/36 (22.2) | 10/53* (18.9) |
| 3 | 4/17 (23.5) | 1/2 (50) | 3/37 (8.1) | 8/56 (14.3) |
| 100 | 1/13 (7.7) | 0/1 (0) | 9/44 (20.5) | 10/58 (17.2) |
| 1000 | 9/26 (34.6) | 1/2 (50) | 10/25 (40) | 20/53 (37.7) |

a First occurrence of tumor.
b The 10 interim sacrifice animals were not examined.
() Percent

Table 2.b

Prevalence of All Mammary tumors Combined for Female Rat.

| Dose | Weeks 55[a]-71 | Weeks 72-86 | Weeks 87-95 | Weeks 96-105 | Final Kill 105 | Total[b] |
|---|---|---|---|---|---|---|
| 0 | 0/4 (0) | 3/10 (30) | 1/3 (33) | 2/4 (50) | 23/36 (63.9) | 29/57** (50.9) |
| 3 | 0/2 (0) | 2/3 (66.7) | 5/10 (50) | 4/6 (66.7) | 17/37 (45.9) | 28/58 (48.3) |
| 100 | 0/1 (0) | 2/3 (66.7) | 2/5 (40) | 4/6 (66.7) | 24/44 (54.5) | 32/59 (54.2) |
| 1000 | 1/1 (100) | 7/12 (58.3) | 4/5 (80) | 9/12 (75) | 21/35 (60) | 42/55** (76.4) |

a First occurrence of tumor.
b The 10 interim sacrifice animals were not examined.
() Percent

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The Peto Prevalence test for dose related trend is indicated on control and for pairwise comparisons on the dose groups with:

** for P<.01
* for P<.05

Bibliography

[1] Thomas, D.G., Breslow, N.E. and Gart, J. (1977) Trend and homogeneity analyses of proportions and life table data. Computers biomed. Res.,10, 373-381.

[2] Kaplan, E.L. and Meier, P. (1958) Non-parametric estimation from incomplete observations. J.AM.stat.Assoc.,53, 457-481.

[3] Peto, R., Pike, M., Day, N., Gray, R., Lee, 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. In: Monographs on the long-term and short-term screening assays for carcinogens: a critical appaisal. IARC Monographs.Supplement 2. Lyon, Franch: Interational Agency for Research on Cancer, pp.311-426.