Caswell 8-30-88

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PROPAZINE - Updated Qualitative Risk Assessment from a Rat 2-Year Chronic Oncogenicity Study.
Caswell No. - 184

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SUMMARY:

Propazine was fed to female Sprague-Dawley rats at doses of 0, 3, 100, and 1000 ppm in a 105 week chronic toxicity /oncogenicity study.

For the female rat The 100 ppm dose group had significantly lower mortality than the control and there was a significant increasing linear trend with dose. The incidence of malignant mammary tumors and all mammary tumors combined was significantly increased in the 1000 ppm dose group compared to controls and there was a significant increasing dose-related trend for both analyses. The 3 ppm dose group was significantly increased compared to control for malignant mammary tumors.

BACKGROUND:

This is a re-evaluation of a chronic rat study (see Levy memo dated 4/1/87). There were disparities between the reviewers counts and the companies. The company then had the lab re-evaluate the tumors and clarify some questions. The counts for mammary tumors in the above referenced memo changed from 1 to 2 animals for most dose groups except in the 3 ppm dose for malignant, which changed from 8 to 17.

Propazine was fed to male and female Sprague-Dawley rats at doses of 0, 3, 100, and 1000 ppm in a 105 week chronic toxicity/oncogenicity study. Approximately 5 animals of each sex were sacrificed after 52 weeks and 57 weeks of continuous dosing in the control and 1000 ppm dose group. The study was conducted by IRDC for Ciba-Geigy. The IRDC report number was 382-007. Data was extracted from a final report dated April 28, 1980. Test animals were assigned randomly to the following groups:

Table 1. Experimental Design for Rat Chronic Study

			Time of Sacrifice (weeks)			
Dose	Total Number		52		57 *	
(ppm)	Male	Female	Male	Female	Male	Female
Control	70	70	5	5	5	5
3	60	60				
100	60	60				
1000	70	70	5	5	5	5

* Compound-withdrawal group fed a control diet for 4 weeks and then sacrificed and necropsied (See Dykstra memo dated 6/8/81).

SURVIVAL ANALYSIS:

Ten animals were not examined in the compound withdrawal group in the control and 1000ppm groups and 2 rats from the other two groups. There were actually 61 rats assigned to the 100 ppm group.

For the female rat the 100ppm dose group had significantly lower mortality than the control ($p = 0.0405$) and there was a significant linear trend with dose ($p = 0.0029$) (Table 2). These results essentially agree with the previous Levy memo.

Test for mortality were made using the Thomas, Breslow, and Gart procedure.

TABLE 2. PROPAZINE, RAT Study-- FEMALE Mortality Rates+ and Cox or Generalized K/W Test Results

DOSE(PPM)	WEEK 1-26	27-52	53 a	53-57	57 a	58-78	79-105 a	TOTAL
0.000	1/68 (1)	2/67 (3)	4/4	1/61 (2)	4/4	8/56 (14)	12/48 (25)	24/60 (40) **
3.000	0/60 (0)	2/60 (3)	0/0	2/58 (3)	0/0	1/56 (2)	18/55 (33)	23/60 (38)
100.000	1/61 (2)	0/60 (0)	0/0	0/60 (0)	0/0	1/60 (2)	14/59 (24)	16/61 (26) *
1000.000	3/68 (4)	0/65 (0)	5/5	1/60 (2)	5/5	5/54 (9)	24/49 (49)	33/58 (57)

\+ Number of animals that died during the interval/Number of animals alive at the beginning of the interval.

( ) Per cent

a Interim sacrifice was conducted at 53 and 57 weeks. Final sacrifice occurred at week 105.

Note: Time intervals were selected for display purposes only. Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

TUMOR ANALYSIS:

Since survival disparities exist and the tumors are incidental in context (see Rich Levy Memo dated April 1, 1987), the Peto Prevalence Method for adjusting for differences in time-to-death with tumor was used. Both malignant mammary tumors and all mammary tumors combined were analyzed. The two malignant mammary tumors were 1) papillary adenocarcinoma and carcinoma and 2) carcinoma-adenocarcinoma. The five benign mammary tumors were fibroadenoma, papillary adenoma, cystadenoma, adenoma, and ductular adenoma (Table 3). A table of all combinations of mammary tumors was provided to the reviewer and copies are available to anyone who is interested.

For the female rats, there were no significant pair-wise comparisons with control and no significant trend for adenomas. The incidence of malignant mammary tumors was significantly increased in the 3 ppm and 1000 ppm dose groups compared to controls ($p = 0.0496$ and $p = 0.0028$, respectively). The incidence of all mammary tumors combined was significantly increased in the 1000 ppm dose groups compared to controls ($p = 0.0015$). There was a significant increasing dose-related trend for both analyses ($p = 0.0029$ and $= 0.0015$, respectively).

TABLE 3. PROPAZINE, RAT Study-- FEMALE Mammary Tumor Rates+ and Peto's Prevalence Test Results

DOSE		0.	3.	100.	1000.
Benign		19/53	16/55	22/59 a	20/54
	(%)	(36)	(29)	(37)	(37)
	(p)	0.3292	0.2931	0.5158	0.5292
Malignant		9/56 b	17/55	10/58	21/53 b
	(%)	(16)	(31)	(17)	(40)
	(p)	0.0029**	0.0496 *	0.4708	0.0028 **
Combined Benign and Malignant		28/56	33/55	32/59	41/59
	(%)	(50)	(60)	(54)	(69)
	(p)	0.0015 **	0.3011	0.4575	0.0015 **

\+ Number of tumor bearing animals / number of animals at risk. (Excluding animals that died before the observation of the first tumor).
( ) Per cent

a) First Adenoma (Fibroadenoma) occurred at 71 weeks in dose 1000 ppm.
b) First Carcinoma occurred at 75 weeks in dose 1000 ppm (Papillary adenocarcinoma & carcinoma) and dose 0 (carcinoma, adenocarcinoma).

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * $p < 0.05$ ** $p < 0.01$

REFERENCES:

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