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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PROPAZINE - Second 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, there was a significant increasing linear dose-trend with mortality. The incidence of 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. There was a significant increasing dose-related trend for benign tumors.

BACKGROUND:

This is the third evaluation of a chronic rat study (see Levy memo dated 4/1/87 and Nelson memo dated 8/30/88). The sponsor had the lab re-evaluate the tumors and clarify some questions. The counts for mammary tumors decreased by 6 for the malignant tumors and increased by 5 for the benign tumors in the 1000 ppm dose group. There were more animals the last time than this time. Most animals that were not examined for the tumor of interest were not included.

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 57 week animals were not included the sponsors report and hence are not in any analysis. The study was conducted by IRDC for Ciba-Geigy. The IRDC report number was 382-007. Data was extracted from an addendum to the final report dated October 27, 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 there was a significant increasing linear dose-trend with mortality ($p = 0.0037$, Table 2x). Table 2 from the last memo is included. These results disagree with the previous two memos, where the 100ppm dose group had significantly lower mortality than the control group.

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

	WEEK							
DOSE(PPM)	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 $p < 0.01$

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

	WEEK						
DOSE(PPM)	1-26	27-52	53 a	53-57	58-78	79-105 a	TOTAL
0.000	1/63 (2)	2/62 (3)	4/4	0/56 (0)	8/56 (14)	12/48 (25)	23/59 ** (39)
3.000	0/60 (0)	2/60 (3)	0/0	2/58 (3)	1/56 (2)	18/55 (33)	23/60 (38)
100.000	1/60 (2)	0/59 (0)	0/0	0/59 (0)	1/59 (2)	14/58 (24)	16/60 (27)
1000.000	3/63 (5)	0/60 (0)	5/5	1/55 (2)	5/54 (9)	24/49 (49)	33/58 (57)

TUMOR ANALYSIS:

Using the present data set, no pair-wise survival disparities were detected, but there was a statistically significant increasing dose-trend with mortality. Hence the Cochran-Armitage test for trend and the Fisher's exact test for pair-wise differences between control and treated groups was used. The tumors are incidental in context (see Levy Memo dated April 1, 1987). Both malignant mammary tumors and all mammary tumors combined were analyzed. The two malignant mammary tumors papillary carcinoma and adenocarcinoma were combined (Budd memo). The two benign mammary tumors fibroadenoma and adenoma were also combined (Table 3x). Table 3 from the previous memo is included for comparison.

For the female rats, there was a significant increasing trend between benign tumor incidence and dose but there were no significant pair-wise comparisons between the control and dosed groups. The incidence of malignant mammary tumors was not significantly increased in any dosed group compared to controls and there was no significant trend. The incidence of all mammary tumors combined was significantly increased in the 1000 ppm dose group compared to controls ($p = 0.0184$) and there was a significant increasing dose-related trend ($p = 0.0087$).

Historical control incidence of mammary tumors was provided for IRDC's Sprague Dawley Rats. Twenty of the studies were 2-years long. The other 2 lasted 27 or 28 months. There were 22 control groups from studies ended 8/6/76 and 6/26/79. Group size ranged from 41 rats to 150 rats. Adenoma incidence ranged from 2% to 22%. Fibroadenoma incidence ranged from 19% to 60%. Adenocarcinoma rates ranged from 1% to 29%. The incidence of animals with one or more tumors ranged from 33% to 69%. Papillary carcinoma incidence was not included. Since we grouped the tumors a direct comparison can be made only with the animals with one or more tumor incidence. The average combined tumor incidence was 49.9%.

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

DOSE		0.	3.	100.	1000.
Benign		19/56	16/55	22/59 a	20/59
	(%)	(34)	(29)	(37)	(34)
	(p)	0.3696	0.1506	0.4291	0.4006
Malignant		9/56 b	17/55	10/58	21/58 b
	(%)	(16)	(31)	(17)	(36)
	(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).

TABLE 3x. PROPAZINE. RAT Study-- FEMALE Mammary Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

DOSE		0.000	3.000	100.000	1000.000
Benign		19/53	16/55	22/59 a	25/54
	(%)	(36)	(29)	(37)	(46)
		p= 0.0463*	p= 0.2931	p= 0.5158	p= 0.1837
Malignant		9/53 c	17/55	10/58	15/53 c
	(%)	(17)	(31)	(17)	(28)
		p= 0.1876	p= 0.0706	p= 0.5861	p= 0.1228
Combined Benign and Malignant		28/53	33/55	32/59	40/54
	(%)	(53)	(60)	(54)	(74)
		p= 0.0087**	p= 0.2888	p= 0.5161	p= 0.0184*

c) First Carcinoma occurred at 75 weeks in dose 1000 ppm (Papillary carcinoma) and dose 0 (adenocarcinoma).

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

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